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Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD) (Review)

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[Intervention Review]

Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD)

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ABSTRACT

Background

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed and treated psychiatric disorders in childhood. Typically, children and adolescents with ADHD find it difficult to pay attention and they are hyperactive and impulsive. Methylphenidate is the psychostimulant most often prescribed, but the evidence on benefits and harms is uncertain. This is an update of our comprehensive systematic review on benefits and harms published in 2015.

Objectives

To assess the beneficial and harmful effects of methylphenidate for children and adolescents with ADHD.

Search methods

We searched CENTRAL, MEDLINE, Embase, three other databases and two trials registers up to March 2022. In addition, we checked reference lists and requested published and unpublished data from manufacturers of methylphenidate.

Selection criteria

We included all randomised clinical trials (RCTs) comparing methylphenidate versus placebo or no intervention in children and adolescents aged 18 years and younger with a diagnosis of ADHD. The search was not limited by publication year or language, but trial inclusion required that 75% or more of participants had a normal intellectual quotient (IQ > 70). We assessed two primary outcomes, ADHD symptoms and serious adverse events, and three secondary outcomes, adverse events considered non-serious, general behaviour, and quality of life.

Data collection and analysis

Two review authors independently conducted data extraction and risk of bias assessment for each trial. Six review authors including two review authors from the original publication participated in the update in 2022. We used standard Cochrane methodological procedures. Data from parallel-group trials and first-period data from cross-over trials formed the basis of our primary analyses. We undertook separate analyses using end-of-last period data from cross-over trials. We used Trial Sequential Analyses (TSA) to control for type I (5%) and type II (20%) errors, and we assessed and downgraded evidence according to the GRADE approach.

Main results

We included 212 trials (16,302 participants randomised); 55 parallel-group trials (8104 participants randomised), and 156 cross-over trials (8033 participants randomised) as well as one trial with a parallel phase (114 participants randomised) and a cross-over phase (165 participants randomised). The mean age of participants was 9.8 years ranging from 3 to 18 years (two trials from 3 to 21 years). The male-female ratio was 3:1. Most trials were carried out in high-income countries, and 86/212 included trials (41%) were funded or partly funded by the pharmaceutical industry. Methylphenidate treatment duration ranged from 1 to 425 days, with a mean duration of 28.8 days. Trials compared methylphenidate with placebo (200 trials) and with no intervention (12 trials). Only 165/212 trials included usable data on one or more outcomes from 14,271 participants.

Of the 212 trials, we assessed 191 at high risk of bias and 21 at low risk of bias. If, however, deblinding of methylphenidate due to typical adverse events is considered, then all 212 trials were at high risk of bias.

Primary outcomes: methylphenidate versus placebo or no intervention may improve teacher-rated ADHD symptoms (standardised mean difference (SMD) −0.74, 95% confidence interval (CI) −0.88 to −0.61; I^2 = 38%; 21 trials; 1728 participants; very low-certainty evidence). This corresponds to a mean difference (MD) of −10.58 (95% CI −12.58 to −8.72) on the ADHD Rating Scale (ADHD-RS; range 0 to 72 points). The minimal clinically relevant difference is considered to be a change of 6.6 points on the ADHD-RS. Methylphenidate may not affect serious adverse events (risk ratio (RR) 0.80, 95% CI 0.39 to 1.67; I^2 = 0%; 26 trials, 3673 participants; very low-certainty evidence). The TSA-adjusted intervention effect was RR 0.91 (CI 0.31 to 2.68).

Secondary outcomes: methylphenidate may cause more adverse events considered non-serious versus placebo or no intervention (RR 1.23, 95% CI 1.11 to 1.37; I^2 = 72%; 35 trials 5342 participants; very low-certainty evidence). The TSA-adjusted intervention effect was RR 1.22 (CI 1.08 to 1.43). Methylphenidate may improve teacher-rated general behaviour versus placebo (SMD −0.62, 95% CI −0.91 to −0.33; I^2 = 68%; 7 trials 792 participants; very low-certainty evidence), but may not affect quality of life (SMD 0.40, 95% CI −0.03 to 0.83; I^2 = 81%; 4 trials, 608 participants; very low-certainty evidence).

Authors' conclusions

The majority of our conclusions from the 2015 version of this review still apply. Our updated meta-analyses suggest that methylphenidate versus placebo or no-intervention may improve teacher-rated ADHD symptoms and general behaviour in children and adolescents with ADHD. There may be no effects on serious adverse events and quality of life. Methylphenidate may be associated with an increased risk of adverse events considered non-serious, such as sleep problems and decreased appetite. However, the certainty of the evidence for all outcomes is very low and therefore the true magnitude of effects remain unclear.

Due to the frequency of non-serious adverse events associated with methylphenidate, the blinding of participants and outcome assessors is particularly challenging. To accommodate this challenge, an active placebo should be sought and utilised. It may be difficult to find such a drug, but identifying a substance that could mimic the easily recognised adverse effects of methylphenidate would avert the unblinding that detrimentally affects current randomised trials.

Future systematic reviews should investigate the subgroups of patients with ADHD that may benefit most and least from methylphenidate. This could be done with individual participant data to investigate predictors and modifiers like age, comorbidity, and ADHD subtypes.

PLAIN LANGUAGE SUMMARY

Is methylphenidate an effective treatment for children and adolescents with attention deficit hyperactivity disorder (ADHD) and does it cause unwanted effects?

Key messages

- Methylphenidate might reduce hyperactivity and impulsivity and might help children to concentrate. Methylphenidate might also help to improve general behaviour, but does not seem to affect quality of life.

- Methylphenidate does not seem to increase the risk of serious (life-threatening) unwanted effects when used for periods of up to six months. However, it is associated with an increased risk of non-serious unwanted effects like sleeping problems and decreased appetite.

- Future studies should focus more on reporting unwanted effects and should take place over longer periods of time.

What is attention deficit hyperactivity disorder (ADHD)?

ADHD is one of the most commonly diagnosed and treated childhood psychiatric disorders. Children with ADHD find it hard to concentrate. They are often hyperactive (fidgety, unable to sit still for long periods) and impulsive (doing things without stopping to think). ADHD can make it difficult for children to do well at school, because they find it hard to follow instructions and to concentrate. Their behavioural problems can interfere with their ability to get on well with family and friends, and they often get into more trouble than other children.

How is ADHD treated?

Methylphenidate (for example, Ritalin) is the medication most often prescribed to children and adolescents with ADHD. Methylphenidate is a stimulant that helps to increase activity in parts of the brain, such as those involved with concentration. Methylphenidate can be taken as a tablet or given as a skin patch. It can be formulated to have an immediate effect, or be delivered slowly, over a period of hours. Methylphenidate may cause unwanted effects, such as headaches, stomachaches and problems sleeping. It sometimes causes serious unwanted effects like heart problems, hallucinations, or facial 'tics' (twitches).

What did we want to find out?

We wanted to find out if methylphenidate improves children's ADHD symptoms (attention, hyperactivity) based mainly on teachers' ratings using various scales, and whether it causes serious unwanted effects, like death, hospitalisation, or disability. We were also interested in less serious unwanted effects like sleep problems and loss of appetite, and its effects on children's general behaviour and quality of life.

What did we do?

We searched for studies that investigated the use of methylphenidate in children and adolescents with ADHD. Participants in the studies had to be aged 18 years or younger and have a diagnosis of ADHD. They could have other disorders or illnesses and be taking other medication or undergoing behavioural treatments. They had to have a normal IQ (intelligence quotient). Studies could compare methylphenidate with placebo (something designed to look and taste the same as methylphenidate but with no active ingredient) or no treatment. Participants had to be randomly chosen to receive methylphenidate or not. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 212 studies with 16,302 children or adolescents with ADHD. Most of the trials compared methylphenidate with placebo. Most studies were small with around 70 children, with an average age of 10 years (ages ranged from 3 to 18 years). Most studies were short, lasting an average of around a month; the shortest study lasted just one day and the longest 425 days. Most studies were in the USA.

Based on teachers' ratings, compared with placebo or no treatment, methylphenidate:

- may improve ADHD symptoms (21 studies, 1728 children)

- may make no difference to serious unwanted effects (26 studies, 3673 participants)

- may cause more non-serious unwanted effects (35 studies, 5342 participants)

- may improve general behaviour (7 trials 792 participants)

- may not affect quality of life (4 trials, 608 participants)

Limitations of the evidence

Our confidence in the results of the review is limited for several reasons. It was often possible for people in the studies to know which treatment the children were taking, which could influence the results. The reporting of the results was not complete in many studies and for some outcomes the results varied across studies. Studies were small and they used different scales for measuring symptoms. And most of the studies only lasted for a short period of time, making it impossible to assess the long-term effects of methylphenidate. Around 41% of studies were funded or partly funded by the pharmaceutical industry.

How up to date is this evidence?

This is an update of a review conducted in 2015. The evidence is current to March 2022.

Summary of findings 1. Methylphenidate compared with placebo or no intervention for children and adolescents with ADHD

Methylphenidate compared with placebo or no intervention for ADHD

Patient or population: children and adolescents (up to and including 18 years of age) with ADHD
Settings: outpatient clinic, inpatient hospital ward and summer school
Intervention: methylphenidate
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no intervention	Methylphenidate				
ADHD symptoms: all parallel-group trials and first-period cross-over trials ADHD Rating Scale (teacher-rated) Average trial duration: 68.7 days		Mean ADHD symptom score in the intervention groups corresponds to a mean difference of −10.58 (95% CI −12.58 to −8.72) on ADHD Rating Scale	**SMD** **−0.74** (−0.88 to −0.61)	1728 (21 trials)	⊕⊖⊖⊖ **Very low**[a,b]	The analysis was conducted on a standardised scale with data from studies that used different teacher-rated scales of symptoms (Conners' Teacher Rating Scale (CTRS), Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale, The Swanson, Nolan and Pelham (SNAP) Scale - Teacher, Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)). We translated the effect size on to the ADHD Rating Scale from the SMD.
Proportion of participants with one or more serious adverse events	**Trial population**		**RR 0.80** (0.39 to 1.67)	3673 (26 trials)	⊕⊖⊖⊖ **Verylow**[a,c]	TSA RIS = 9349 TSA showed a RR of 0.91 (TSA-adjusted CI 0.31 to 2.68)
	8 per 1000	**6 per 1000** (5 less to 5 more)				
Proportion of participants with one or more adverse events considered non-serious	**Trial population**		**RR 1.23** (1.11 to 1.37)	5342 (35 trials)	⊕⊖⊖⊖ **Verylow**[a,b]	TSA RIS = 9139 TSA showed a RR of 1.22 (TSA-adjusted CI 1.08 to 1.43)
	437 per 1000	**538 per 1000** (348 less to 162 more)				

General behaviour: all parallel-group trials and first-period cross-over trials General behaviour rating scales (teacher-rated)		Mean general behaviour score in the intervention groups was **0.62 standard mean deviations lower** (95% CI 0.91 lower to 0.33 lower)	**SMD −0.62** (−0.91 to −0.33)	792 (7 trials)	⊕⊖⊖⊖ **Very low**[a,b,d]
Quality of life (parent-rated)		Mean quality-of-life score in the intervention groups corresponds to a mean difference of 4.94 (95% CI −0.37 to 10.25) on the Child Health Questionnaire	**SMD 0.40** (−0.03 to 0.83)	608 (4 trials)	⊕⊖⊖⊖ **Verylow**[a,b,c,e]

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ADHD: attention deficit hyperactivity disorder; **CI:** confidence interval; **RIS**: required information size; **RR**: risk ratio; **SMD:** standardised mean difference; **TSA:** Trial Sequential Analysis

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two levels due to high risk of bias (systematic errors causing overestimation of benefits and underestimation of harms) in several risk of bias domains, including lack of sufficient blinding and selective outcome reporting (many of the included trials did not report on this outcome).
[b]Downgraded one level due to inconsistency: moderate statistical heterogeneity.
[c]Downgraded two levels due to imprecision: wide confidence intervals and/or the accrued number of participants was below 50% of the diversity-adjusted required information size (DARIS) in Trial Sequential Analysis.
[d]Downgraded one level due to indirectness: children's general behaviour was assessed by different types of rating scales with different focus on behaviour.
[e] Downgraded one level due to indirectness: children's quality of life was assessed by their parents.

BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed and treated developmental psychiatric disorders (Scahill 2000). It is acknowledged to be a complex heterogenous neurodevelopmental condition with no known cure (Buitelaar 2022). Many clinicians and academics see pharmacological treatments as being effective and safe but there is "considerable individual variability" of treatment response, dose needed, and tolerability (Buitelaar 2022).

The prevalence of ADHD in children and adolescents is estimated to be 3% to 5% (Polanczyk 2007), depending on the classification system used, with boys two to four times more likely to be diagnosed than girls (Schmidt 2009). Individuals with ADHD exhibit difficulties with attentional and cognitive functions including problem-solving, planning, maintaining flexibility and orientation, sustaining attention, inhibiting responses, and sustaining working memory (Pasini 2007; Sergeant 2003). They also experience difficulties in managing affects, for example, motivational delay and mood dysregulation (Castellanos 2006; Nigg 2005; Schmidt 2009). The diagnosis of ADHD has become more aligned between the *American Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5; APA 2013), and the World Health Organization's (WHO) *International Classification of Diseases* (ICD), 11th Edition (ICD-11; WHO 2019). The ICD-11 was adopted in 2019, and came into effect in January 2022.

Both the DSM-5 and the ICD-11 base diagnoses on several inattentive and hyperactive-impulsive symptoms being present before the age of 12 years, and causing impairment of functioning in several settings. There are also 'predominantly inattentive', 'predominantly hyperactive/impulsive' and 'combined' presentations in both systems (APA 2013; WHO 2019).

ADHD is increasingly recognised as a psychiatric disorder that extends into adulthood and occurs with high heterogeneity and comorbidity with other psychiatric disorders (Schmidt 2009). The Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) trial identified one or more co-occurring conditions in almost 40% of participants (MTA 1999a). These included oppositional defiant disorder, conduct disorder, depression, anxiety, tics, learning difficulties and cognitive deficits (Jensen 2001; Kadesjö 2001). Some argue that ADHD should be "considered not only a neurodevelopmental disorder, but also a persistent and complex condition, with detrimental consequences for quality of life in adulthood" (Di Lorenzo 2021, p. 283).

Rising rates of ADHD diagnoses, possible harm to children resulting from drug treatment (Zito 2000), and variation in prevalence estimates are matters of increasing concern (Moffit 2007; Polanczyk 2014). The need for a validated diagnostic test to confirm the clinical diagnosis of ADHD has given rise to a debate about its validity as a diagnosis (Timimi 2004). Professional and national bodies have developed guidelines on assessment, diagnosis and treatment of ADHD in an attempt to ensure that high standards are maintained in diagnostic and therapeutic practice (American Academy of Pediatrics 2011; CADDRA 2011; NICE 2018; Pliszka 2007a; SIGN 2009). Psychosocial interventions, such as parent management training, are recommended in the first instance for younger children and for those with mild to moderate symptoms (American Academy of Pediatrics 2011; NICE 2018; Pliszka 2007a), whereas stimulants (given alone or in combination with psychosocial interventions) are recommended for children with more severe ADHD (American Academy of Pediatrics 2011; CADDRA 2011; NICE 2018).

Description of the intervention

Methylphenidate, lisdexamphetamine/dexamphetamine, atomoxetine (a non-stimulant selective noradrenaline reuptake inhibitor) and guanfacine (an alpha-2 agonist) are recommended medical treatments for children, aged five years and above, and adolescents with ADHD, when psychoeducation and environmental modification have been implemented and reviewed, according to the NICE guidelines 2018 (NICE 2018). Furthermore, research suggests that the combination of behaviour therapy (e.g. behavioural parent training, school consultation, direct contingency management) and pharmacotherapy might benefit children with ADHD (Gilmore 2001; MTA 1999a).

Globally, methylphenidate has been used for longer than 50 years for the treatment of children with ADHD (Kadesjö 2002; NICE 2018). It has been part of driving innovation in controlled-release technologies and new formulations. However, it has also contributed to concerns of pharmaceutical cognitive enhancement as well as created debate on pharmaceutical sales techniques in medicine, driven by high and possibly still increasing prescription rates (Wenthur 2016). In Europe, around 3% to 5% of children and adolescents have a prescription for methylphenidate (Bachmann 2017; Hodgkins 2013; Schubert 2010; Trecenõ 2012; Zoëga 2011) and in the USA approximately 8% of children and adolescents under 15 years of age have a prescription of methylphenidate (Akinbami 2011). However, USA statistics reported a trend of reduction in 2019 (Drug Usage Statistics 2013-2019).

Pharmacological treatment with methylphenidate of children and adolescents with ADHD is reported to have a beneficial effect of reducing the major symptoms of hyperactivity, impulsivity, and inattention. It is licensed for the treatment of children aged six years and older with ADHD (Kanjwal 2012), but is recommended by the NICE guideline as off-label use from the age of five years (NICE 2018). Before starting medication for ADHD, a baseline assessment is necessary; the ADHD criteria must be reviewed, mental health and social circumstances considered and a review of physical health including a cardiovascular assessment with cardiological history, heart rate, and blood pressure should be conducted. If positive cardiovascular history or a co-existing condition is being treated with a medicine that may pose an increased cardiac risk, electrocardiogram (ECG) is recommended (NICE 2018). Individual parent-training programmes for parents and carers of children and young people with ADHD and symptoms of oppositional defiant disorder or conduct disorder must likewise be considered (NICE 2018).

Different releases (immediate, sustained, or extended-release) and formulations (oral or transdermal) of methylphenidate are available and it is important to individualise the treatment to optimise effect and minimise adverse events (Childress 2019). Response of treatment is individual and intervention dose can vary significantly between children with some responding to relatively low dosages while others require larger doses to achieve the same effect (Stevenson 1989). Therefore, it is important that the dose

of methylphenidate is titrated to an optimal level that maximises therapeutic benefits while producing minimal adverse events. Immediate-release formulations of methylphenidate are usually initiated at 5 mg once or twice daily then titrated weekly by 5 mg to 10 mg daily, divided into two or three doses until effects are noted and adverse effects are tolerable. The dose can range from 5 mg to 60 mg methylphenidate, 1.4 mg/kg daily administered in two to three doses (BNF 2020; Pliszka 2007a). Under specialist supervision, the dose may be increased to 2.1 mg/kg daily in two to three doses (maximum 90 mg daily). Modified-release formulations are initiated with 18 mg once daily and increased up to a maximum of 54 mg.

Immediate-release methylphenidate has a bioavailability of 11% to 53% and an approximate duration of two to four hours with a peak blood concentration after two hours and a half-life of two hours. Sustained-release and extended-release formulations of methylphenidate have a duration of action of three to eight hours and eight to 12 hours, respectively (Kimko 1999; NICE 2018).

Studies have indicated impairments in children's height and weight during treatment with methylphenidate (Schachar 1997a; Swanson 2004b; Swanson 2009). McCarthy and colleagues' study using the 'German Health Interview and Examination Survey for Children and Adolescents' (KiGGS) database found that methylphenidate use in boys with ADHD was associated with low body mass index (BMI) but were "unable to confirm that methylphenidate use is also associated with low height (≤3rd percentile) and changes in blood pressure" (McCarthy 2018).

Monitoring of height, weight, heart rate, blood pressure, and adverse events, as well as encouraging adherence for effective treatment, are suggested. Medication-free periods are recommended to reassess the treatment efficacy on ADHD symptoms (Kidd 2000; NICE 2018). Adverse effects of methylphenidate are common and dose-dependent (Rossi 2010; Storebø 2018b). In a large Cochrane Review of observational studies, more than half (51.3%) of participants being treated with methylphenidate experienced one or more adverse events considered non-serious such as headache, sleep difficulties, abdominal pain, decreased appetite, anxiety, and sadness (Storebø 2018b). Furthermore, 16% discontinued methylphenidate due to 'unknown' reasons and another 6% due to adverse events considered non-serious (Storebø 2018b).

Serious adverse events such as psychosis, mood disorders (Block 1998; Cherland 1999; MTA 1999a), serious cardiovascular events, and sudden unexplained death have also been reported (Cooper 2011; Habel 2011), but methylphenidate does not seem to increase serious adverse events in randomised clinical trials (Storebø 2015a). It must however be taken into consideration that this meta-analysis was considerably underpowered and not able to draw firm conclusions (Storebø 2015a).

As a stimulant, methylphenidate carries the risk of addiction, and the nonmedical use has been reported to vary from 5% to 35% (Clemow 2014), with a peak risk at ages estimated to be between 16 and 19 years, and a new user rate of 0.7% to 0.8% per year (Austic 2015). Conversely, methylphenidate has been correlated with the reduction of harmful outcomes such as reducing emergency department visits (Dalsgaard 2015), reducing criminality (Lichtenstein 2012), reducing transport accidents (Chang 2017), and having a protective effect on abuse of other substances (Chang 2014).

How the intervention might work

The pharmacodynamics of methylphenidate have been extensively investigated in animal and human studies with brain imaging and chemistry studies, yet they remain uncertain. It is presumed that the effects of methylphenidate on ADHD symptoms are related to its effects on dopaminergic and noradrenergic neurotransmissions within the central nervous system (Engert 2008). Methylphenidate is assumed to act by inhibiting catecholamine reuptake, primarily as a dopamine-norepinephrine re-uptake inhibitor, modulating levels of dopamine and, to a lesser extent, levels of norepinephrine (Heal 2006; Iversen 2006).

Methylphenidate binds to and blocks dopamine and norepinephrine transporters (Heal 2006; Iversen 2006), and increased concentrations of dopamine and norepinephrine in the synaptic cleft lead to escalated neurotransmission. On average, methylphenidate elicits a 3 to 4 times increase in dopamine and norepinephrine in the striatum and prefrontal cortex (Hodgkins 2013), which is responsible for executive functions and produces effects such as increased alertness, reduced fatigue, and improved attention.

Methylphenidate is thought to activate self-regulated control processes to ameliorate what are believed to be the core neurofunctional problems of ADHD (Barkley 1977a; Schulz 2012; Solanto 1998). Evidence suggests that symptom control is strongly related to functional improvement (Biederman 2003a; Cox 2004a; Swanson 2004a).

Studies indicate that methylphenidate is effective for treating both the core symptoms of ADHD (inattention, hyperactivity, and impulsivity) and aggression (Connor 2002), since children can manage their impulsivity better (Barkley 1981; Barkley 1989a; Shaw 2012). Barkley noted differences in response to methylphenidate between ADHD inattentive and combined subtypes: children with the inattentive subtype were judged to have a less favourable response to methylphenidate than those diagnosed with the combined presentation (Barkley 1991b). Some children and adolescents may become less responsive to methylphenidate treatment over time (Molina 2009). However, magnetic resonance imaging studies suggest that long-term treatment with ADHD stimulants may decrease abnormalities in the brain structure and function found in patients with ADHD (Frodl 2012; Spencer 2013).

Why it is important to do this review

During the past 20 years, several systematic reviews and narrative reviews have investigated the efficacy of methylphenidate for ADHD (with or without meta-analysis). Fifteen reviews have pooled results on methylphenidate treatment for children and adolescents with ADHD (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Reichow 2013; Schachter 2001; Van der Oord 2008). However, none of these were conducted as Cochrane systematic reviews. Most of them did not adhere to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a), nor the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati 2009; Moher 2015). None of

these reviews had a peer-reviewed protocol published before the analyses were conducted. Thirteen did not undertake subgroup analyses examining the effects of comorbidity on treatment effects (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; Maia 2014; Punja 2013; Schachter 2001; Van der Oord 2008). Some did not control for treatment effects by ADHD subtype (Bloch 2009; Charach 2013; Faraone 2002; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Schachter 2001; Van der Oord 2008). Others did not consider effects according to the dose of methylphenidate (Charach 2011; Charach 2013; Faraone 2006; Faraone 2009; Hanwella 2011; Kambeitz 2014; Maia 2014; Punja 2013; Reichow 2013; Van der Oord 2008). As for the outcomes, most meta-analyses pooled data from parents, teachers and independent assessors (Bloch 2009; Charach 2011; Charach 2013; Hanwella 2011; Kambeitz 2014; King 2006; Reichow 2013), and did not separate outcome measures for inattention and hyperactivity/impulsivity (Bloch 2009; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Hanwella 2011; Kambeitz 2014; Van der Oord 2008). Moreover, most previous reviews only investigated the effects of methylphenidate on symptoms of ADHD; review authors did not present data on spontaneous adverse events (Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; Maia 2014; Van der Oord 2008), nor on adverse events, as measured by rating scales (Bloch 2009; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Reichow 2013; Schachter 2001; Van der Oord 2008), and they did not try to explain why such information was not provided. Finally, these reviews did not systematically assess the risk of random errors, risk of bias, or trial quality (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Van der Oord 2008). These shortcomings plus other methodological limitations including potential bias in excluding non-English language publications (Charach 2013; Faraone 2010; Punja 2013; Van der Oord 2008), and not searching the principal major international databases nor reporting search terms clearly (Bloch 2009; Faraone 2002; Kambeitz 2014; Reichow 2013), may have compromised data collection, consequently calling the results of these previous meta-analyses into question.

The first version of this systematic review was published in 2015 (Storebø 2015a). In this version, we reported that methylphenidate may improve teacher-reported ADHD symptoms, teacher-reported general behaviour, and parent-reported quality of life among children and adolescents diagnosed with ADHD. We also underlined that the low quality of the evidence meant that we could not be certain of the magnitude of the effects. There was evidence that methylphenidate is associated with an increased risk of adverse events considered non-serious, such as sleep problems and decreased appetite. We did not have evidence that methylphenidate increased the risk of serious adverse events, but this was unclear due to underreporting of serious adverse events (Storebø 2015a). We received many critical responses which were published as articles and letters to editors as well as blog comments. Six comments were received on the BMJ version of this review (Storebø 2015b). An editorial by Mina Fazel commenting on the article in the BMJ was also published alongside the review article (Fazel 2015). Mina Fazel recognised that our review was a comprehensive and rigorous Cochrane systematic review and meta-analysis of the use of methylphenidate in young people with ADHD. She underlined the need for more research as she concluded: "The slow progress of ADHD research and limited evidence base for treatments are in stark contrast with the hallmarks of the disorder itself, with its high prevalence and broad symptomology" (Fazel 2015). A short version of the review was also published in JAMA in 2016 (Storebø 2016b), followed by a commenting editorial by Philip Shaw who concluded: "Sometimes in medicine, the best available data are imperfect. Such imperfections do not render the data unusable; rather, the limitations can be weighed by physicians and other health care professionals, and by families as they decide how best to help a child struggling with ADHD. Psychostimulants improve ADHD symptoms and quality of life. This meta-analysis highlights the complexities in quantifying this benefit." (Shaw 2016 p. 1954). Philip Shaw wrote that in a meta-analysis of methylphenidate for adults with ADHD (Epstein 2014), the trial biases were similar to those in our review and that the bias assessment seemed to be very subjective (Shaw 2016). The review by Epstein and colleagues (Epstein 2016), was withdrawn from the Cochrane Library on 26 May 2016 due to several methodological problems including erroneous risk of bias assessment (Boesen 2017; Storebø 2015b [pers comm]).

Several critical comments on our 2015 review from different authors were published in blog posts, articles and letters to editors (Hollis 2016; Banaschewski 2016a; Banaschewski 2016b; Hoekstra 2016; Romanos 2016). All these comments and our responses are listed with references in the 2015 published version of this review (Storebø 2015a). The critical points raised focused on our certainty assessment, including our use of the vested interest risk of bias domain, concerns that blinding may be affected by easily recognisable adverse events, concerns that we erroneously included too many non-eligible trials (such as cross-over trials and trials with add-on treatment to methylphenidate), and that we had errors in the data extracted. We showed in several response articles and letters to editors that our trial selection was not flawed and that our data collection and interpretation of data in most aspects was systematic and sound (Storebø 2016a; Storebø 2016c; Storebø 2016d; Storebø 2016e; Storebø 2016f; Storebø 2018a). We answered all criticism, but in one case our response to a critical editorial (Gerlach 2017), in the Journal ADHD Attention Deficit and Hyperactivity Disorders was declined by the editor. In addition, we have argued that our assessment of quality and our conclusion were not misleading (Storebø 2016c; Storebø 2016d; Storebø 2016e; Storebø 2016f; Storebø 2018a). We agreed that minor errors were present in the review, yet we were still able to show that the effects were negligible and that these minor errors did not affect our conclusions (Storebø 2016c; Storebø 2016d; Storebø 2016e; Storebø 2016f; Storebø 2018a). We stated that the evidence for the use of methylphenidate in children and adolescents with ADHD was flawed (Storebø 2016c; Storebø 2016d; Storebø 2016e; Storebø 2016f; Storebø 2018a).

In 2018 an application for including methylphenidate on the 21st update of the WHO's List of Essential Medicines was rejected due to concerns regarding the quality of the evidence for benefits and harms (Storebø 2021). An extended research team made a comparable application in 2020 for the 22nd update of the list. The decision of the committee was — for the second time — not to include methylphenidate on the WHO Model List of Essential Medicines due to low quality of evidence, lack of data after 12 weeks, and adverse effects of concern (Pereira Ribeiro 2022). The committee also stressed that "evidence of the effectiveness and

safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration, outcomes of the revision of the of the Mental Health Gap Action Programme (mhGAP) Guideline for Mental, Neurological and Substance use Disorders, and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings would be informative for any future consideration for inclusion of methylphenidate on the Model Lists" (WHO 2021 p. 538).

We have published an overview article where we found 24 eligible systematic reviews and meta-analyses published after the 2015 version of the current review (Ribeiro 2021). The results showed that the evidence was uncertain due to the low quality of evidence. There was also an underreporting of adverse events in randomised clinical trials. We concluded that there is uncertain evidence to support that methylphenidate is beneficial in treating children and adolescents with ADHD. (Ribeiro 2021).

In October 2021 the European ADHD Guidelines Group (EAGG) published an overview article summarising the current evidence and identified methodological issues and gaps in the current evidence (Coghill 2021). The authors of this article were mostly the same authors that had published the many critical comments to our 2015 version of this review. They wrote in this article: "We have summarized the current evidence and identified several methodological issues and gaps in the current evidence that we believe are important for clinicians to consider when evaluating the evidence and making treatment decisions. These include understanding potential impact of bias such as inadequate blinding and selection bias on study outcomes; the relative lack of high-quality data comparing different treatments and assessing long-term effectiveness, adverse effects and safety for both pharmacological and non-pharmacological treatments; and the problems associated with observational studies, including those based on large national registries and comparing treatments with each other" (Coghill 2021).

Combined, this indicates a need to update this systematic review on the benefits and harms of methylphenidate for children and adolescents with ADHD and that this should continue to be done until more solid evidence for the recommendation about the use of methylphenidate for children and adolescents with ADHD can be established. Given the mounting concerns regarding the increasing use of methylphenidate in children younger than six years, it is vital that researchers explore the risks versus benefits of treatment in this younger population (US FDA 2011). Although stimulant medications may have a favourable risk-benefit profile, they might carry potential risks of both serious and non-serious adverse events.

To expand our understanding of adverse events, particularly where these are rare or take time to become apparent, we felt it necessary to bolster the limited data from randomised clinical trials (RCTs) by including data from non-randomised studies (Storebø 2015a). Our Cochrane systematic review from 2018 focused on the harms of methylphenidate treatment in children and adolescents with ADHD (Storebø 2018b). This review included 260 non-randomised studies: four patient-controlled studies, seven comparative cohort studies, 177 cohort studies, two cross-sectional studies, and 70 patient reports, including over 2.2 million participants. In contrast to our 2015 review based on RCTs (Storebø 2015a), methylphenidate compared to no intervention significantly increased the risk of serious adverse events in comparative studies (risk ratio (RR) 1.36, 95% confidence interval (CI), 1.17 to 1.58; 2 trials; 72,005 participants). Serious adverse events included psychotic disorders, arrhythmia, seizures, and hypertension. Approximately half (51.2%) of participants experienced one or more non-serious adverse event (95% CI 41.2 to 61.1%; 49 trials; 13,978 participants). These were sleep difficulties (17.9%), decreased appetite (31.1%), and abdominal pain (10.7%). Furthermore, 16.2% (95% CI 13.0 to 19.9%; 57 trials, 8340 participants) discontinued methylphenidate because of 'unknown' reasons and 6.20% (95% CI 4.90 to 8.00%; 37 trials; 7142 participants) because of non-serious adverse events. We assessed most included studies as having critical risk of bias. The GRADE quality rating of the certainty of evidence was very low. Some studies indicated that methylphenidate can decrease children's normal growth rate (Schachar 1997b; Swanson 2004a; Swanson 2009). Given the unclear evidence in this field and the need for better data, we, therefore, conducted the present update of this systematic review of the benefits and harms of methylphenidate for children and adolescents with ADHD in RCTs while adhering to the Cochrane guidance (Higgins 2022a), and to the PRISMA guidelines (Liberati 2009; Moher 2015).

OBJECTIVES

To assess the beneficial and harmful effects of methylphenidate for children and adolescents with ADHD.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of methylphenidate for the treatment of children and adolescents with ADHD. We included trials irrespective of language, publication year, publication type or publication status.

Types of participants

Children and adolescents aged 18 years and younger with a diagnosis of ADHD, according to the DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994), and DSM-5 (APA 2013), or with a diagnosis of hyperkinetic disorders according to the ICD-9, ICD-10 (WHO 1992), and ICD-11 (WHO 2019) . We included participants with ADHD with or without comorbid conditions such as conduct or oppositional disorders, tics, depression, attachment disorders or anxiety disorders. Trials eligible for inclusion were those in which at least 75% of participants were aged 18 years or younger, and the mean age of the trial population was 18 years or younger. We also required that at least 75% of participants had a normal intellectual quotient (IQ > 70).

Types of interventions

Methylphenidate, administered at any dosage or in any formulation, versus placebo or no intervention.

We permitted co-interventions if the experimental and control intervention groups received the co-interventions similarly. In some trials that included co-interventions in both groups, such as a behavioral intervention combined with methylphenidate versus a behavioral intervention, we considered these as methylphenidate versus no intervention. We did not permit polypharmacy as a co-intervention in only one of the intervention groups.

Types of outcome measures

Primary outcomes

- ADHD symptoms (attention, hyperactivity and impulsivity), measured over the short term (within six months) and over the long term (longer than six months) by psychometric instruments or by observations of behaviour, using, for example, Conners' Teacher Rating Scales (Conners 1998a; Conners 2008). Raters could be teachers, independent assessors, or parents. We chose to report the results of teacher-rated outcomes as the primary outcome (see Results).
- Number of serious adverse events. We defined a serious adverse event as any event that led to death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, or as any important medical event that may have jeopardised the patient's life or that required intervention for prevention. We considered all other adverse events to be considered non-serious (ICH 1996).

Secondary outcomes

- Non-serious adverse events. We assessed all adverse events, including, for example, growth retardation and cardiological, neurological and gastrointestinal events, as described in *ICH* (International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use) *Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1)* (ICH 1996).
- General behaviour in school and at home, as rated by psychometric instruments such as the Child Behaviour Checklist (CBCL; Achenbach 1991), measured over the short term (within six months) and over the long term (longer than six months). Raters could be teachers, independent assessors, or parents. We chose to report the results of teacher-rated outcomes as primary outcomes (see Results).
- Quality of life, as measured by psychometric instruments such as the Child Health Questionnaire (CHQ; Landgraf 1998). Raters could be teachers, the children, independent assessors, or parents.

Search methods for identification of studies

Electronic searches

We ran the first literature searches in October 2011 and updated them in November 2012, March 2014, between 26 February and 10 March 2015 and most recently 11 January 2021 and 25 March 2022. We searched the following sources.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 1; part of the Cochrane Library, which includes the Specialised Register of the Cochrane Developmental, Psychosocial and Learning Problems Group), searched 25 March 2022
- MEDLINE Ovid (1946 to current), searched 25 March 2022
- Embase Ovid (1980 to current), searched 25 March 2022
- CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1980 to current), searched 25 March 2022
- PsycINFO Ovid (1806 to current), searched 25 March 2022
- Epistemonikos (www.epistemonikos.org/) searched 25 March 2022
- Conference Proceedings Citation Index - Science (CPCI-S) and Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SS&H) (Web of Science; 1990 to 25 March 2022)
- ClinicalTrials.gov (ClinicalTrials.gov), searched 25 March 2022
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; who.int/ictrp/en), searched 25 March 2022
- Networked Digital Library of Theses and Dissertations (NDLTD; ndltd.org), searched 29 November 2022)
- DART Europe E-Theses Portal (www.dart-europe.eu/basic-search.php), searched 28 November 2022)
- Theses Canada (library-archives.canada.ca/eng/services/services-libraries/theses/Pages/theses-canada.aspx), searched 29 November 2022
- Worldcat (worldcat.org), searched 28 November 2022

The search strategy for each database is shown in Appendix 1. We used a broad strategy to capture trials on efficacy and trials on adverse events. To overcome poor indexing and abstracting, we listed individual brand names within the search strategies. We did not limit searches by language, year of publication or type or status of the publication. We sought translation of relevant sections of non-English language articles.

Searching other resources

To find additional relevant trials not identified by electronic searches, we checked the bibliographic references of identified review articles, meta-analyses and a selection of included trials. Furthermore, we requested published and unpublished data from pharmaceutical companies manufacturing methylphenidate, including Takeda Pharmaceuticals, Medice (represented in Denmark by HB Pharma), Janssen-Cilag, Novartis, Rhodes Pharmaceuticals, Ironshore Pharmaceuticals and Pfiizer (Appendix 2). We also requested data from unpublished trials from experts in the field.

Data collection and analysis

We conducted this review according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a), and performed analyses using Review Manager 5 (RevMan 5; Review Manager 2020).

Selection of studies

In this update of the Storebø 2015a review, seven review authors (OJS, HEC, JPS, JPR, MROS, PDR, CMLH) worked together in groups of two and independently screened titles and abstracts of all publications obtained from the literature searches. We obtained full-text papers for any abstract/title that might match our inclusion criteria and assessed them against our listed inclusion criteria. We discussed disagreements, and if we were unable to reach agreement or consensus, we consulted a third review author (OJS).

Data extraction and management

In this update of the Storebø 2015a review, working together in groups of two, six review authors extracted data (MROS, CMLH, JPR, JPS, MS, OJS). We resolved disagreements by discussion and we used an arbiter if required. When data were incomplete, or when data provided in published trial reports were unclear, we contacted

trial authors to ask for clarification of missing information. We contacted the authors of all cross-over trials to obtain first-period data on ADHD symptoms.

We developed data extraction forms a priori. After performing data extraction pilots, we updated these forms to accommodate the extraction of more detailed data and to facilitate standardised approaches to data extraction among review authors. All data extractors used these extraction forms (see Appendix 3; Appendix 4).

Six review authors (MS, HEC, JPR, JPS, MROS and OJS) entered data into RevMan 5 (Review Manager 2020).

Assessment of risk of bias in included studies

For each included trial, data extractors (MROS, CMLH, JPR, JPS, MS, OJS) independently evaluated risk of bias domains (listed below), resolving disagreements by discussion. For each domain, we assigned each trial to one of the following three categories: low risk of bias, unclear (uncertain) risk of bias or high risk of bias, according to guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Given the risk of overestimation of beneficial intervention effects and underestimation of harmful intervention effects in RCTs with unclear or inadequate methodological quality (Kjaergard 2001; Lundh 2012; Lundh 2018; Moher 1998; Savović 2012a; Savović 2012b; Savovic 2018; Schulz 1995; Wood 2008), we assessed the influence of risk of bias on our results (see Subgroup analysis and investigation of heterogeneity). Risk of bias components were as follows: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other potential sources of bias. We defined low risk of bias trials as trials that had low risk of bias in all domains. We considered trials with one or more unclear or high risk of bias domains as trials with high risk of bias.

Measures of treatment effect

We defined the treatment effect as an improvement in ADHD symptoms, general behaviour and quality of life.

Dichotomous data

We summarised dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We calculated the risk difference (RD).

Continuous data

If all trials used the same measure of a given continuous outcome in a meta-analysis, we calculated mean differences (MDs) with 95% CIs. If trials used different measures, we calculated standardised mean differences (SMDs) with 95% CIs. If trials did not report means and standard deviations but did report other values (e.g. *t*-tests, P values), we transformed these into standard deviations.

For primary analyses of teacher-rated ADHD symptoms, teacher-rated general behaviour and quality of life, we transformed SMDs into MDs on the following scales to assess whether results exceeded the minimal clinically relevant difference: ADHD Rating Scale (ADHD-RS; DuPaul 1991a), Conners' Global Index (CGI; Conners 1998a), and Child Health Questionnaire (CHQ; Landgraf 1998). We transformed SMDs into MDs on the ADHD-RS by using the SD 14.3 from Riggs 2011, on the CGI by using the SD 5.79 from Greenhill 2002, and on the CHQ by using the SD 12.35 from Newcorn 2008. We identified a minimal clinically relevant difference (MIREDIF) of 6.6 points on the ADHD-RS, ranging from 0 to 72 points, based on a trial by Zhang 2005, and a MIREDIF of 7.0 points on the CHQ, ranging from 0 to 100 points, based on a trial by Rentz 2005. We could find no references describing a MIREDIF on the CGI (range 0 to 30 points).

Unit of analysis issues

Many ADHD trials use cross-over methods. We aimed to obtain data from the first period of these trials and to pool these data with data from parallel-group trials, as they are similar (Curtin 2002). We requested these data from trial authors if they were not available in the published report. When we were not able to obtain first-period data from cross-over trials, we established another group comprising only end-of-last-period data. Our original intention was to adjust for the effect of the unit of analysis error in cross-over trials by conducting a covariate analysis, but data were insufficient for this. As cross-over trials are more prone to bias from carry-over effects, period effects and unit of analysis errors (Curtin 2002), we conducted a subgroup analysis to compare these two groups. We tested for the possibility of a carry-over effect and a period effect (Subgroup analysis and investigation of heterogeneity). We found similar treatment effects in the two groups and no significant subgroup differences. However, we noted considerable heterogeneity, and so we presented the results of the analyses separately (Effects of interventions). In a methods article, we investigated the risk of carry-over effect and unit of analysis error due to period effects comparing parallel-group trials, the first period of cross-over trials and the end of the last period of cross-over trials and found no signs of period effects or carry-over effects in cross-over trials assessing methylphenidate for children and adolescents with ADHD (Krogh 2019).

For dichotomous outcomes in cross-over trials, we were unable to adjust the variance to account for the correlation coefficient as advised by Elbourne 2002 due to insufficient information or to estimate the RR using the marginal probabilities as recommended by Becker 1993. Consequently, we used end-of-last-period data for estimating RRs. As these effect estimates are prone to potential bias, we performed a sensitivity analysis by removing these trials to assess the robustness of the pooled results.

We used endpoint data when these were reported or could be obtained from trial authors. However, when RCTs reported only 'change scores', we pooled these with scores from the end of intervention (da Costa 2013). We used only endpoint standard deviations in the trials with 'change scores'. We explored whether inclusion of change data affected the outcomes by performing a sensitivity analysis (see Sensitivity analysis).

Dealing with missing data

We obtained missing data by contacting trial authors. When we were not able to obtain missing data, we conducted analyses using available (incomplete) data. Although some trials reported that they used intention-to-treat (ITT) analyses, data were missing for many primary outcomes (Hollis 1999). We could not use 'best-case scenario' and 'worst-case scenario' analyses on our assessment of benefit as there were no dichotomous outcomes. Also, we decided not to use 'best-case scenario' and 'worst-case scenario' analyses in our assessment of adverse events because we evaluated these analyses to be imprecise due to the high number of trials not

reporting adverse events, and due to the high number of dropouts in the trials reporting adverse events.

Assessment of heterogeneity

We identified three types of heterogeneity: clinical, methodological and statistical. Clinical heterogeneity reflects variability among participants, interventions and outcomes of trials; methodological heterogeneity reflects variability in the trial designs; and statistical heterogeneity reflects differences in effect estimates between trials. We assessed clinical heterogeneity by comparing differences in trial populations, interventions and outcomes, and we evaluated methodological heterogeneity by comparing the trial designs. We identified potential reasons for clinical and methodological heterogeneity by examining individual trial characteristics and subgroups. Furthermore, we observed statistical heterogeneity in trials both by visual inspection of a forest plot and by use of a standard Chi^2 test value with a significance level of α (alpha) = 0.1. We examined the I^2 statistic (Higgins 2003). We judged values between 0% and 40% to indicate little heterogeneity, between 30% and 60% to indicate moderate heterogeneity, between 50% and 90% to indicate substantial heterogeneity, and between 75% and 100% to indicate considerable heterogeneity (Deeks 2022).

Assessment of reporting biases

We followed the recommendations for reporting bias, including publication bias and outcome reporting bias, provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2022). We drew funnel plots (estimated differences in treatment effects against their standard error) and performed Egger's statistical test for small-study effects; asymmetry could be due to publication bias or could indicate genuine heterogeneity between small and large trials (Page 2022). We did not visually inspect the funnel plot if fewer than 10 trials were included in the meta-analysis, in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2022). We compared results extracted from published journal reports to results obtained from other sources (including correspondence) as a direct test for publication bias.

Data synthesis

We performed statistical analyses as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). We synthesised data statistically when clinical heterogeneity was not excessive (e.g. variability in participant characteristics was minimal). Furthermore, we included and analysed trials undertaken in any configuration or setting (e.g. in groups, at home, or at a centre).

We used the inverse variance method, which gives greater weight to larger trials, to generate more precise estimates. For some adverse events we combined dichotomous and continuous data using the generic inverse variance method. We synthesised data using change-from-baseline scores or endpoint data. If data were available for several intervals, we used the longest period assessed. We used the fixed-effect and random-effects models in all meta-analyses, however, we reported the results of the random-effects model when we included more than one trial in the meta-analysis. This approach gives greater weight to smaller trials. Statistical significance did not change when we applied a fixed-effect model (Jakobsen 2014). We performed separate meta-analyses for three types of raters (teachers, independent assessors, and parents) for data from parallel-group trials combined with data from the first period of cross-over trials and data from the end of the last period from cross-over trials.

ADHD symptom scales describe the severity of inattention, hyperactivity and impulsivity at home and at school; high scores indicate severe ADHD. We judged that, in spite of the diversity of psychometric instruments, they could be used for our outcomes, and we integrated different types of scales into the analyses. We used MDs if all trials used the same measure and SMDs when different trials used different outcome measures for the same construct.

When separate measures of hyperactivity, impulsivity and inattention were available, we used combined scores. When symptoms were measured and reported at different time points during the day (after ingestion of medication or placebo), we used the time point closest to noon.

Three types of raters, teachers, independent assessors and parents measured two outcomes — ADHD symptoms and general behaviour. We considered these data as showing different outcomes. We presented the results of teacher-rated measures as the primary outcome because symptoms of ADHD are more readily detectable in the school setting (Hartman 2007).

For children weighing 25 kg or less, the maximum recommended dose of methylphenidate is 30 mg/day compared to 60 mg/day for children weighing more than 25 kg. After careful consideration, we renamed the high-dose group as 'moderate/high' dose because doses are not always 'high' in heavier children. When trials reported data for different doses, we used data for the dose that we defined as moderate/high (> 20 mg/day) in our primary analyses.

We summarised adverse event data as RRs with 95% CIs for dichotomous outcomes. For the purposes of this review, we used only dichotomous outcomes that reflected the number of participants affected by the event per the total number of participants.

Diversity-adjusted required information size and Trial Sequential Analysis

Trial Sequential Analysis is a method that combines the required information size (RIS) for a meta-analysis with the threshold for statistical significance to quantify the statistical reliability of data in a cumulative meta-analysis, with P value thresholds controlled for sparse data and repetitive testing of accumulating data (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2017).

Comparable to the a priori sample size estimation provided in a single RCT, a meta-analysis should include a RIS at least as large as the sample size of an adequately powered single trial to reduce the risk of random error. A Trial Sequential Analysis calculates the RIS in a meta-analysis and provides trial sequential monitoring boundaries with an adjusted P value.

When new trials emerge, multiple analyses of accumulating data lead to repeated significance testing and hence introduce multiplicity. Use of conventional P values exacerbates the risk of random error (Berkey 1996; Lau 1995; Wetterslev 2017). Meta-analyses not reaching the RIS are analysed with trial sequential monitoring boundaries analogous to interim monitoring boundaries in a single trial (Wetterslev 2008; Wetterslev 2017).

If a Trial Sequential Analysis does not result in significant findings (no Z-curve crossing the trial sequential monitoring boundaries) before the RIS has been reached, the conclusion should be that more trials are needed to reject or accept an intervention effect that was used to calculate the required sample size, or when the cumulated Z-curve enters the futility area, the anticipated intervention effect should be rejected.

For calculations with the Trial Sequential Analysis programme, we included trials with zero events by substituting 0.25 for zero (CTU 2022; Thorlund 2011).

For the outcomes 'total serious adverse events' and 'total non-serious adverse events', we calculated the a priori diversity-adjusted required information size (DARIS; i.e. number of participants in the meta-analysis required to detect or reject a specific intervention effect) and performed a Trial Sequential Analysis for these outcomes based on the following assumptions (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009).

- Proportion of participants in the control group with adverse events
- Relative risk reduction of 20% (25% on 'total serious adverse events')
- Type I error of 5%
- Type II error of 20%
- Observed diversity of the meta-analysis

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses of teacher-rated ADHD symptoms (primary outcome) to test the robustness of this estimate.

- Age of participants (trials with participants aged 2 to 6 years compared to trials with participants aged 7 to 11 years compared to trials with participants aged 12 to 18 years)
- Sex (boys compared to girls)
- Comorbidity (children with comorbid disorders compared to children without comorbid disorders)
- Type of ADHD (participants with predominantly inattentive subtype compared to participants with predominantly combined subtype)

After learning about other factors that may affect the effects of methylphenidate, we performed the following additional post hoc subgroup analyses on teacher-rated ADHD symptoms to test the robustness of the estimate.

- Types of scales (e.g. Conners' Teacher Rating Scale (CTRS; Conners 1998a), compared to Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale (Swanson 2006)
- Dose of methylphenidate (low dose (≤ 20 mg/day or ≤ 0.6 mg/kg/day) compared to moderate or high dose (> 20 mg/day or > 0.6 mg/kg/day)).
- Duration of treatment (short-term trials (≤ 6 months) compared to long-term trials (> 6 months))
- Trial design (parallel-group trials compared to cross-over trials (first-period data and end-of-last-period data))
- Medication status before randomisation (medication naive (> 80% of included participants were medication naive) compared to not medication naive (< 20% of included participants were medication naive))
- Risk of bias (trials at low risk of bias compared to trials at high risk of bias)
- Enrichment trials. Enrichment trials (trials that excluded methylphenidate non-responders, placebo responders, and/or participants who had adverse events due to the medication before randomisation) compared to trials without enrichment
- Vested interest ((conflict of interest regarding funding) trials at either high or unclear risk of vested interest compared to trials at low risk of vested interest). Our assessment of vested interest for the individual studies can be seen in Table 1.
- Type of control group (trials with placebo control group compared to trials with no-intervention control group)

Sensitivity analysis

We conducted sensitivity analyses to determine whether findings were sensitive to the following.

- Decisions made during the review process, such as our assessment of clinical heterogeneity (listed below)
- Combined 'change scores' and 'endpoint data' in the meta-analyses
- Random-effects and fixed-effect model meta-an lyses

No sufficiently well-designed method has been used to combine the results of trials at high risk of bias and trials at low risk of bias (Higgins 2022a). We performed sensitivity analyses by grouping together trials with similar classifications of bias, as described above, and investigated the impact on intervention effects.

We excluded the following trials from the sensitivity analyses.

- IQ under 70 (Oesterheld 1998; Pearson 2013; Smith 1998; Taylor 1987)
- Change scores (Carlson 2007; Findling 2008; Kollins 2021; McCracken 2016; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Tucker 2009)
- Older than 18 years of age (Green 2011; Szobot 2008)

Summary of findings and assessment of the certainty of the evidence

We constructed a summary of findings table in which to document all review outcomes. Two review authors (HEC and OJS) assessed the evidence using the GRADE approach. The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Considerations are due to within-trial risk of bias; directness of the evidence; heterogeneity of the data; precision of effect estimates; and risk of publication bias (Guyatt 2011; Schünemann 2022). When possible, that is, when the MD or the RR was available, we used the results from the Trial Sequential Analysis as the rating for imprecision (Jakobsen 2014). We downgraded imprecision in GRADE by two levels if the accrued number of participants was below 50% of the DARIS, and one level if between 50% and 100% of the DARIS (Korang 2020). We did not downgrade for imprecision if the cumulative Z-curve crossed the monitoring boundaries for benefit, harm, futility,

or the DARIS (Korang 2020). We reported two primary outcomes (teacher-rated ADHD symptoms and serious adverse events) and three secondary outcomes (non-serious adverse events, teacher-rated general behaviour, and quality of life) at end of treatment in Summary of findings 1.

RESULTS

Description of studies

For more information, please see Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies, as well as Table 2 for an overview of study characteristics and Table 3 for an overview of key inclusion and exclusion criteria.

Results of the search

An overview of the searches can be seen in Figure 1.

Figure 1.

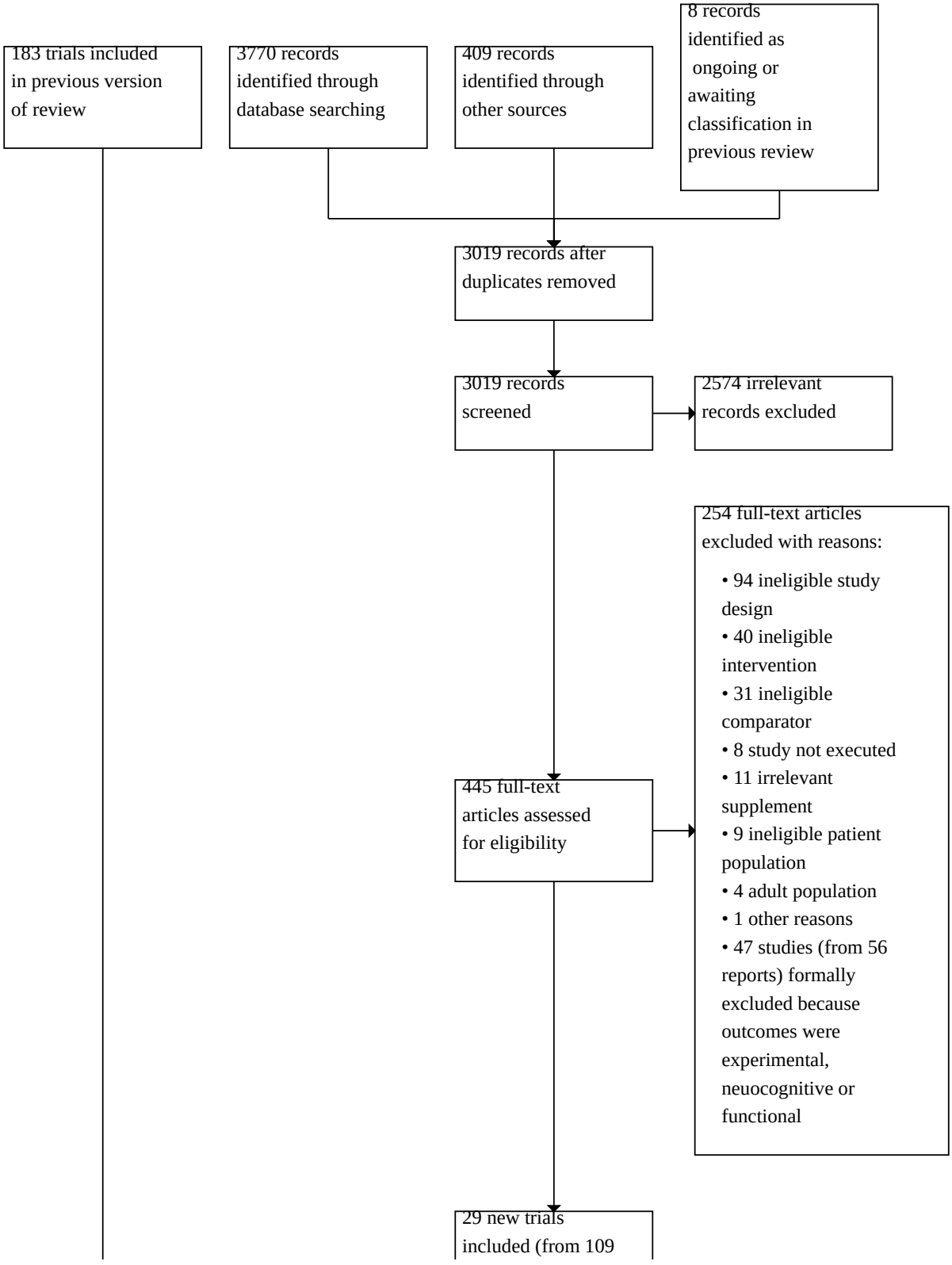
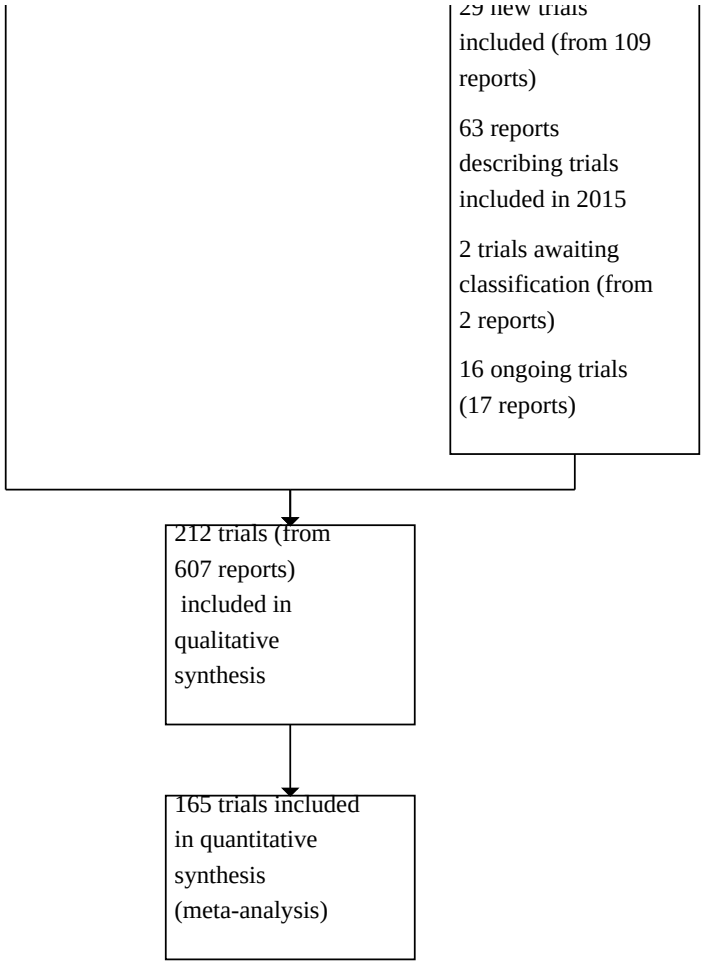


Figure 1. (Continued)



We carried out electronic searches over six periods. The four searches that took place from October 2011 to February 2015 are described in detail in the previous version of this review (Storebø 2015a). All searches from the previous version of the review resulted in 183 included trials (from 433 reports), one study (from one report) awaiting classification, and five ongoing trials (from six reports).

Searches up to January 2021 produced an additional 2244 records after duplicates were removed (3132 initial records). Searches up to March 2022 produced an additional 285 records after duplicates were removed (401 initial records). Searches for dissertations up to December 2022 resulted in an additional 100 records after duplicates were removed (237 initial records). We identified an additional 347 records after duplicates were removed (409 initial records) by reading through the reference lists of other reviews on ADHD and stimulant therapy published since 2015, and by corresponding with study authors of included studies and with pharmaceutical companies. We also looked through all included studies from all searches to look for protocols or trial registrations that were not already included, which resulted in 35 of the 347 records. We rescreened studies awaiting classification and ongoing studies from the previous version of the review (eight reports).

During 2021 we contacted authors of 24 of the new included trials twice for supplemental information and data; nine responded and we received data from seven trials. Additionally, we contacted two authors of studies included during the latest search in March 2022 only once but they did not respond in due time to be applied to this review.

For the searches in 2021 and 2022 we excluded non-randomised studies during screening, focusing only on RCTs. From 3019 screened records we excluded 2574 clearly irrelevant reports on the basis of titles and abstract. We retrieved the full texts of the remaining 445 reports, which we assessed for eligibility. They were all accessible in English. We excluded 254 full-text reports and identified two studies as awaiting classification (from 2 reports; see Characteristics of studies awaiting classification) and 16 trials as ongoing (from 17 reports; see Characteristics of ongoing studies). We included 172 reports of which 109 described 29 new RCTs, while 63 reports were added to the trials included in the previous version of the review. Additional information about all included trials can be found in the Characteristics of included studies tables.

Included studies

We included a total of 212 trials (from 607 reports) in this review (Figure 1). Of these, 55 are parallel-group trials (from 222 reports) and 156 are cross-over trials (from 359 reports). One study (24 reports) includes a parallel phase as well as a cross-over phase, thus we used data from this study in the parallel trial analyses as well as the cross-over trial analyses (Kollins 2006 (PATS)). A total of 165 trials (14,271 participants) provided usable data for the quantitative analyses. An overview of key demographics for all included trials can be seen in Table 2, and the distribution of key inclusion and exclusion criteria across the trials is available in Table 3 .

Included parallel-group trials

Including Kollins 2006 (PATS), we included 56 parallel-group trials described in 244 reports. Fifty trials (7895 participants) provided usable data for the quantitative analyses.

Duration

Most trials (n = 51) were short-term (< 6 months in duration). Only four were long-term trials (conducted for ≥ 6 months; Barragán 2017; Jensen 1999 (MTA); Perez-Alvarez 2009; Schachar 1997a). The duration of one trial was unclear, but lasted somewhere between three to five months (Tannock 2018). The mean duration of the methylphenidate intervention across 56 trials was 67.1 days (range 1 to 425 days).

Location

Thirty-five of the 56 trials (including Kollins 2006 (PATS)), were conducted in the USA. Three trials were conducted in the USA and Canada (Biederman 2003b; Jensen 1999 (MTA); Weiss 2021); one in the USA, Canada and Australia (Findling 2006); and one in the USA, Canada, Taiwan, Mexico and Puerto Rico (Lin 2014). Three trials each were conducted in Canada (Butter 1983; Schachar 1997a; Tannock 2018), and the Netherlands (Matthijssen 2019; Schrantee 2016; Van der Meere 1999a). Two trials each were conducted in Brazil (Martins 2004; Szobot 2004), Israel (Green 2011; Jacobi-Polishook 2009). Single trials were conducted in Mexico (Barragán 2017), New Zealand (Heriot 2008), Germany (Lehmkuhl 2002), and Norway (Duric 2012). One trial was conducted in Germany, Sweden, Spain, Hungary, France, UK, Italy, Belgium, Poland, and the Netherlands (Coghill 2013).

The location of one trial was not clear (Firestone 1981).

Setting

All but the following 10 trials were conducted in outpatient clinics. One was carried out in an outpatient as well as inpatient setting (Green 2011), two were carried out in a naturalistic classroom setting (Biederman 2003b; Greenhill 2006), four in a laboratory classroom (Childress 2017; Childress 2020a; Childress 2020b; Kollins 2021), one in a research unit at a hospital (Schachar 1997a), and two provided no information on setting (Brown 1985; McCracken 2016).

Participants

The 56 trials included a total of 8218 participants with a boy-to-girl ratio of 3:1 (with the percentage of girls ranging from 0% to 41% (mean across studies 23.8%)). All participants were between 3 and 20 years of age (mean 9.9 years).

Thirty-nine trials described the percentage of methylphenidate-naive participants (range 0% to 100%; mean 51.6%).

Thirty-seven trials described the proportion of participants with combined subtype ADHD (range 25% to 100%; mean 69.9%); 33 trials reported the proportion of participants with hyperactive subtype (range 0% to 56%; mean 4.5%) and 34 trials revealed the proportion with inattentive subtype (range 0% to 72.9%; mean 25.8%).

Six trials excluded children and adolescents with any psychiatric comorbidity (Findling 2010; Greenhill 2002; Greenhill 2006; Perez-Alvarez 2009; Tucker 2009; Wigal 2017). Eleven trials clearly stated what comorbidities were or could be included, (Duric 2012; Green 2011; Jensen 1999 (MTA); Lehmkuhl 2002; Pliszka 2000; Riggs 2011; Schachar 1997a; Szobot 2004; Tourette's Syndrome Study Group 2002; Van der Meere 1999a; Wolraich 2001), and 21 trials excluded psychiatric comorbidities to some extent. Thirteen of the trials only allowed the psychiatric comorbidities oppositional defiant disorder, conduct disorder, socially aggressive, or disturbance in social behavior (Carlson 2007; Findling 2008; Heriot 2008; Horn 1991; Ialongo 1994; Lin 2014; Martins 2004; McCracken 2016; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Tannock 2018). One only included participants with oppositional defiant disorder or conduct disorder but there was no information on the presence of other psychiatric comorbidities (Connor 2000). For two trials there was no limit to psychiatric comorbidities (Coghill 2013; Kollins 2006 (PATS)). Two trials stated nothing about the inclusion or exclusion of comorbidities or their prevalence among participants (Butter 1983; NCT00409708). Opositional defiant disorder was the most commonly reported comorbidity (prevalence clearly reported for 19 trials, range 8.2% to 53%; mean 35.1%), followed by conduct disorder (prevalence clearly reported for 11 trials, range 2% to 32.3%; mean 11.2%). Three trials reported oppositional defiant disorder and conduct disorder together (range 57.6% to 100%) (Connor 2000; Martins 2004; Szobot 2004), therefore we could not use them for the calculated mean.

Nine trials specifically excluded participants taking other medications (Carlson 2007; Childress 2017; Heriot 2008; Ialongo 1994; Jacobi-Polishook 2009; Kollins 2006 (PATS); Perez-Alvarez 2009; Tucker 2009; Wigal 2017), and 35 trials specified the exclusion or inclusion of some medications. Four trials had comedication as part of the intervention (Carlson 2007; Connor 2000; McCracken 2016; Riggs 2011). No information on comedication was available for 16 of the trials.

Some form of co-therapy was part of the intervention in 10 of the trials (Brown 1985; Firestone 1981; Heriot 2008; Horn 1991; Jensen 1999 (MTA); NCT00409708; Palumbo 2008; Perez-Alvarez 2009; Riggs 2011; Tucker 2009). Two trials had a therapy phase prior to medication (Childress 2020c; Kollins 2006 (PATS)), and five trials specified limitations to therapy during the study (Biederman 2003b; Childress 2009; Greenhill 2006; Matthijssen 2019; NCT02293655). Nothing was stated about co-therapy for the remaining 39 trials.

Interventions

Twenty-nine trials used extended- and modified-release methylphenidate. Two trials used immediate- and extended-release methylphenidate (Findling 2006; Wolraich 2001). One trial used transdermal methylphenidate patches (Findling 2010), and

one trial used both transdermal patches and extended-release methylphenidate (Findling 2008). The type used in four trials was unclear (Butter 1983; Horn 1991; Ialongo 1994; Schrantee 2016). The remaining 19 trials used immediate-release methylphenidate.

The method of reporting the dosage of methylphenidate varied considerably between trials, but the overall daily dose ranged from 5 mg to 68 mg with a mean reported total daily dose of 34.4 mg/day or 0.78 mg/kg/day. The average dose of any type of modified- or extended-release methylphenidate was 44.2 mg, and the average dose of immediate-release methylphenidate was 23.0 mg.

Forty-eight trials used placebo as control, and eight used no intervention as control (Barragán 2017; Brown 1985; Duric 2012; Heriot 2008; Jensen 1999 (MTA); NCT00409708; Perez-Alvarez 2009; Tucker 2009).

Eight trials used clonidine (Connor 2000; Palumbo 2008; Tourette's Syndrome Study Group 2002), omega 3/6 (Barragán 2017), atomoxetine (Carlson 2007), guanfacine (McCracken 2016), or lisdexamphetamine (Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose)), as a co-intervention in both the intervention and control groups. Three trials used parent training (Firestone 1981; Heriot 2008; Schachar 1997a), two used cognitive-behavioural therapy (Brown 1985; Riggs 2011), and six used other behavioural therapies (Duric 2012; Horn 1991; Jensen 1999 (MTA); NCT00409708; Perez-Alvarez 2009; Tucker 2009), as co-interventions for the intervention and control groups. One trial used neurofeedback as co-intervention in both the intervention and control group (Duric 2012).

Included cross-over trials

We included 157 cross-over trials (including Kollins 2006 (PATS)), described in 383 reports. Of these, 116 trials (6490 participants) provided usable data for the quantitative analyses

Seventy-five trials were described in a single publication. Sixteen trials yielded five or more publications. One trial, that ran until 2020 is reported across the greatest number of publications per trial, with 27 publications all reporting preliminary data with a varying number of participants across reports (Bhat 2020).

Duration

Three cross-over trials did not report duration (Kelly 1989; Sunohara 1999; Tannock 1993). The remaining 154 cross-over trials had a duration of less than six months.

The duration of methylphenidate treatment, including all periods of methylphenidate at any dose for the individual participant, without counting the duration of the placebo intervention, ranged between 1 and 56 days with a mean of 15.2 days.

Location

A total of 109 trials were carried out in the USA; 21 in Canada; and one in both the USA and Canada (Quinn 2004). Six trials were conducted in Israel (Kritchman 2019; Lufi 1997; Lufi 2007; Moshe 2012; Tirosh 1993a; Tirosh 1993b); five in Germany (Bliznakova 2007; Döpfner 2004; Konrad 2004; Konrad 2005; Schulz 2010); five in the Netherlands (Buitelaar 1995; Flapper 2008; Kortekaas-Rijlaarsdam 2017; Lijffijt 2006; Overtoom 2003); two each in the UK (Coghill 2007; Taylor 1987), Norway (Ramtvedt 2013; Zeiner 1999), and Brazil (Szobot 2008; Zeni 2009); and one each in Australia (Nikles 2006), Iran (Soleimani 2017), and Taiwan (Huang 2021). One trial did not specify the country of origin (Hicks 1985).

Setting

Twenty-one trials were completed as a part of summer treatment programmes or summer schools. Nine trials were conducted in inpatient wards (Brown 1991; Carlson 1995; Gonzalez-Heydrich 2010; Kent 1995; Konrad 2005; Pelham 1993a; Pelham 2002; Solanto 2009; Wallace 1994), and seven in both outpatient clinics and inpatient wards (Garfinkel 1983; Hicks 1985; Kaplan 1990; Kolko 1999; Konrad 2004; Tannock 1992; Wallander 1987). Sixteen trials were conducted in a laboratory classroom setting and one in a naturalistic school setting (Ullmann 1986). Six trials did not report the setting (Bliznakova 2007; CRIT124US02; Pliszka 2007; Stoner 1994; Ullmann 1985; Urman 1995). All remaining trials were conducted in outpatient clinics only.

Participants

The 157 cross-over trials included a total of 8198 participants (range 1 to 430 per trial; mean 52.2). The percentage of girls ranged from 0% in 30 trials to 100% in one trial (CRIT124US02); (mean across the 149 studies that reported ratio; 18.7%, equivalent to a boy-to-girl ratio of 7:2). All participants were between 4 and 21 years of age (mean 9.7 years). Sixteen trials did not report average age; however, all of these trials reported age range (Ahmann 1993; Carlson 1995; Coghill 2007; Corkum 2008; Gadow 1990; Kent 1999; Klorman 1990; Leddy 2009; NCT02039908; Pelham 1989; Quinn 2004; Rapport 1987; Solanto 2009; Sumner 2010).

A total of 97 trials described the percentage of methylphenidate-naive participants included (range 0% to 100%; mean 52.7%). In 29 trials, all participants were methylphenidate-naive. Thirty trials only included participants previously treated with methylphenidate.

Eighty-one trials described the proportion of participants with combined ADHD subtype (range 0% to 100%; mean 70.3%), 73 trials reported the proportion with hyperactive subtype (range 0% to 100%; mean 7.8%) and 74 trials reported the proportion with inattentive subtype (range 0% to 73.7%; mean 21.6%).

Fifteen trials excluded children with any psychiatric comorbdity (Flapper 2008; Garfinkel 1983; Huang 2021; Lufi 1997; Moshe 2012; Muniz 2008; Quinn 2004; Schachar 2008; Soleimani 2017; Swanson 1998; Swanson 2002a; Tirosh 1993a; Tirosh 1993b; Wilens 2008; Wilkison 1995). Forty-six trials clearly stated what comorbidities were or could be included and 22 trials excluded psychiatric comorbidities to some extent. Thirty-eight of the trials only allowed the psychiatric comorbidities oppositional defiant disorder, conduct disorder, socially aggressive or disturbance in social behaviour. For five trials there was no limit to psychiatric comorbidities (Cox 2006; Gadow 2011; Kent 1999; Kollins 2006 (PATS); Symons 2007). Thirty-three stated nothing about the inclusion or exclusion of comorbidities or their prevalence among participants.

Opposotional defiant disorder was the most commonly reported comorbidity (prevalence clearly reported for 67 trials, range 1.36% to 100%; mean 43.2%), followed by conduct disorder (prevalence clearly reported for 56 trials, range 2.9% to 100%; mean 24%). Six trials reported oppositional defiant disorder and conduct disorder together (range 57.6 to 100%) therefore we could not use them

for the calculated mean (Carlson 1995; Döpfner 2004; Gorman 2006; Hale 2011; Pelham 2011; Tannock 1995a). Six trials reported participants with Tourette's syndrome (range 2.7% to 100%; mean 67%; Castellanos 1997; Coghill 2007; Gadow 1995; Gadow 2007; Gadow 2011; Kent 1999). One trial only included participants with epilepsy (Gonzalez-Heydrich 2010), one trial only included participants with cerebral palsy (Symons 2007), and two trials only included participants with bipolar disorder or borderline personality (Findling 2007; Zeni 2009). Twenty-eight trials reported prevalence of participants with comorbid anxiety (range 2.7% 46% mean 20.8%).

Twenty-seven trials specifically excluded participants taking other medications, and 48 trials specified the exclusion or inclusion of some medications. Six trials had comedication as part of the intervention (Carlson 1995; Findling 2007; Gonzalez-Heydrich 2010; Kaplan 1990; Szobot 2008; Zeni 2009). No information on comedication was available for 82 of the trials.

Some form of co-therapy was part of the intervention in five of the trials (Döpfner 2004; Fabiano 2007; Kolko 1999; Pelham 2014; Waxmonsky 2008). One trial had a therapy phase prior to medication (Kollins 2006 (PATS)), and six trials specified limitations to therapy during the study (Brams 2012; Froehlich 2018; Lufi 1997; Muniz 2008; Silva 2006; Silva 2008). The remaining 145 trials stated nothing about co-therapy.

Interventions

Thirty-two of the trials used extended- and modified-release methylphenidate and 83 of the trials used immediate-release methylphenidate. Nine trials used both immediate- and extended-release methylphenidate (Döpfner 2004; Johnston 1988; Fitzpatrick 1992a; Pearson 2013; Pelham 1990a; Pelham 2001a; Schachar 2008; Swanson 2002b; Wigal 2003), four trials used two different types of extended-release methylphenidate (Lopez 2003; Schulz 2010; Silva 2005a; Swanson 2004b), one trial used three different types of extended-release methylphenidate (NCT02536105), and five trials used transdermal methylphenidate patches (McGough 2006; Pelham 2005; Pelham 2011; Wilens 2008; Wilens 2010). It was unclear what type of methylphenidate the remaining 28 trials used.

The method of reporting the dose of methylphenidate varied considerably between trials, and the dose administered to participants was unclear for 20 trials. Overall daily dose ranged from 4 mg to 72 mg, with a mean reported total daily dose of 24.6 mg or 0.77 mg/kg/day. Doses of immediate-release methylphenidate ranged from 4 mg to 50 mg, with a mean reported total daily dose of 21.4 mg or 0.8 mg/kg. Doses of extended-release methylphenidate ranged from 15 mg to 72 mg, with a mean reported total daily dose of 35.2 mg or 1.1 mg/kg. The duration of methylphenidate treatment ranged from 1 to 56 days, with an average duration of 15.2 days.

All trials used a placebo as a control.

In six trials, participants received some kind of comedication in both the intervention and control groups (antidepressant: Carlson 1995; divalproex sodium: Findling 2007; continuation of stable antiepileptic medication: Gonzalez-Heydrich 2010; diphenhydramine 50 mg: Kaplan 1990; marijuana and/or cocaine: Szobot 2008; an antipsychotic: Zeni 2009).

In five trials some form of therapy was part of the intervention in both the intervention and control groups (Döpfner 2004; Fabiano 2007; Kolko 1999; Pelham 2014; Waxmonsky 2008).

Outcomes

Some psychometric ADHD instruments measured the total score for ADHD symptoms, whereas others assessed only specific symptom domains of ADHD (e.g. inattention, hyperactivity, impulsivity). We categorised all scales into five subgroups: ADHD symptoms; serious adverse events; non-serious adverse events; general behaviour; and quality of life. Some psychometric instruments are abbreviated versions or revised versions, but all have been validated.

ADHD symptoms

Conners' questionnaires were the most frequently used measures of ADHD symptoms; more than 30 different versions measured core symptoms of ADHD (normative data are generally well intercorrelated in revised versions; Goyette 1978).

Table 4 presents the list of all measures that the included trials used to assess ADHD symptoms. This list primarily refers to original articles describing the psychometric properties of measurement scales, but in a few cases, we refer to trials describing the use of a specific measurement scale.

Serious and non-serious adverse events

Trials used rating scales or spontaneous reports to measure adverse events, or they were recorded by investigators at regular interviews or visits, or both. Some trials included physical examinations or paraclinical examinations, or both, such as blood testing, electrocardiogram, blood pressure reading, measurement of heart rate and assessment of weight and height. We recorded serious adverse events in accordance with the ICH classification (ICH 1996). However, when in doubt, we asked trial authors which classification or definition they had used in their trial.

Some trials combined all of the above modes of measurement; others used a single measure such as spontaneous reports or rating scales. Sixty-eight trials employed rating scales; the Barkley Side Effect Rating Scale (SERS) was used most frequently (Barkley 1990).

Other scales used included the Significant Adverse Event Reviews Questionnaire (SAERS; Barkley 1990; Zeni 2009), the Pittsburgh Side Effect Rating Scale (PSERS; Pelham 1993b; Pelham 2005a) and Subject's Treatment Emergent Symptom Scale (STESS; Guy 1976a).

For the purpose of measuring specific adverse events, some trials used rating scales such as Paediatric Sleep Questionnaire (PSQ; Chervin 2000), Sleep Disturbances Scale for Children (SDSC; Bruni 1996), Children's Sleep Habits Questionnaire (CSHQ; Owens 2000), Childrens' Depression Rating Scale (CDRS-R; Poznanski 1983), The Colombia Suicide Severity Rating Scale (C-SSRS, Posner 2011), Young Mania Rating Scale (YMRS; Young 1978), Yale Global Tic Severity Scale (YGTSS; Leckman 1989), Tic Symptom Self Report Scale (TSSR; Leckman 1988), and the Massachusetts General Hospital (MGH) Abuse and Diversion Questionnaire (Wilens 2006a).

General behaviour

Trials used many different scales to assess general behaviour. These scales have different foci, such as aggression or oppositional behaviour, but all describe participants' behaviour and the

influence of methylphenidate. Higher scores on general behaviour symptom scales signify better outcomes.

Table 5 presents the list of all measures used to assess general behaviour. This list refers primarily to the original articles describing the psychometric properties of measurement scales used to measure general behaviour in the included trials. In a few cases, we refer to trials that describe the use of a specific measurement scale.

Quality of life

Seven scales measured quality of life in relation to both ADHD and life in general. For all scales, higher values equated to better health. Only four could be used in meta-analyses: Child Health Questionnaire (CHQ; Landgraf 1998); Children's Global Assessment Scale (CGAS; Shaffer 1983); Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP-CE: PRF; Riley 2004); and The Parent- and Child-rated Revised Questionnaire for Children and Adolescents to record health-related quality of life (KINDL-R; Ravens-Sieberer 1998).

See Table 6 for additional information on the types of rating scales used to assess the quality of life in the included trials.

Excluded studies

In the previous review we excluded 691 full-text reports for reasons reported in Storebø 2015a [https://revman.cochrane.org/#/70070502150950261O/dashboard/htmlCompare/current/4.36.11?version1WithProductionChanges=false&version2WithProductionChanges=false#REF-Storeb_x00f8_-2015a]. For this update, we excluded an additional 254 full-text reports, which were ineligible for the following reasons: ineligible study design (94 reports), ineligible intervention (40 reports), ineligible comparator (31 reports), study not executed (8 reports), irrelevant supplement (11 reports), ineligible population (13 reports), other reasons (1 report).

The remaining 47 trials (from 56 reports) initially seemed to meet our eligibility criteria but on closer inspection did not, because they examined the impact of methylphenidate on very specific domains that were outside the focus of this review such as motor co-ordination, reaction time, memory tasks, and reading skills. We added these to the Characteristics of excluded studies [https://revman.cochrane.org/#/70070502150950261O/dashboard/htmlCompare/current/4.36.11?version1WithProductionChanges=false&version2WithProductionChanges=fals which now lists 125 trials. For more information on these trials, please see Characteristics of excluded studies.

Studies awaiting classification

Two trials (Drtílková 1997; Wang 2020), are currently awaiting classification for various reasons. Drtílková 1997 required translation from the Czech language into English, which we were unable to procure within the time frame of working with the update of this review. The other trial Wang 2020 was unavailable to us with all institutional library IDs in our possession. We contacted the trial authors in an attempt to retrieve their report or further information on outcome data but did not receive any reply. For further details on each trial see Studies awaiting classification.

Ongoing trials

We included 16 ongoing trials assessing methylphenidate for children and adolescents with ADHD but for which outcome data have not yet been made available. Ten trials have a parallel design (ChiCTR1800014945; EUCTR2007-004664-46-NL; EUCTR2008-001291-71-DE; IRCT138804132000N2; IRCT201701131556N94; IRCT20190317043079N; NCT00414921; NCT00485550; NCT02807870; Verlaet 2017), and six have a cross-over design (EUCTR2008-004425-42-NL; EUCTR2020-003660-11-NL; Müller 2021; NCT00141050; NCT00254878; NCT00446537). See Ongoing studies for further information regarding each trial.

Risk of bias in included studies

We assessed the risk of bias of each included trial using the Cochrane risk of bias tool (RoB 1; Higgins 2011). A summary of our assessment is displayed in Figure 2 and Figure 3. One trial, Kollins 2006 (PATS), includes a parallel as well as a cross-over phase and accounts for a low risk of bias trial among both parallel and cross-over trials. As shown, we assessed 13 of the 157 cross-over trials (8.3%) and nine of the 56 included parallel-group trials (16.1%) at low risk of bias in all domains apart from blinding. However, even the 21 trials (here, counting Kollins 2006 (PATS) as a single trial) likely had breaks in their blinding due to prevalent adverse events due to methylphenidate (see below). We assessed the remaining 191 trials (90.1%) at high risk of bias. Accordingly, we judged all 212 trials to be trials at high risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

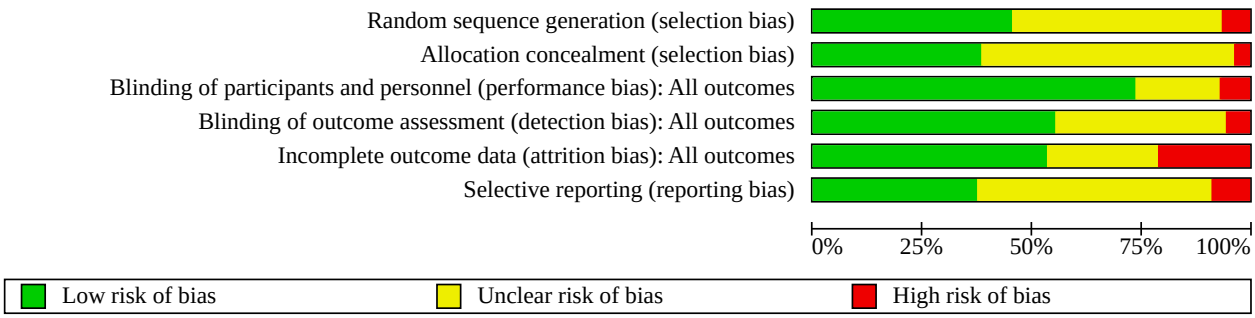
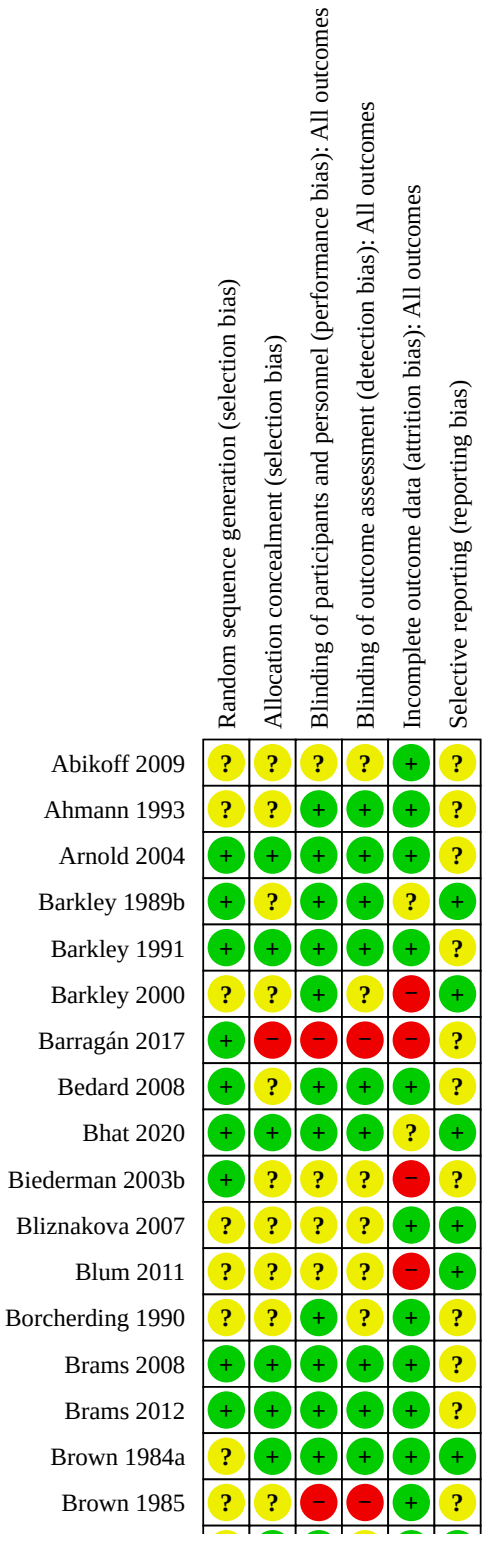


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial



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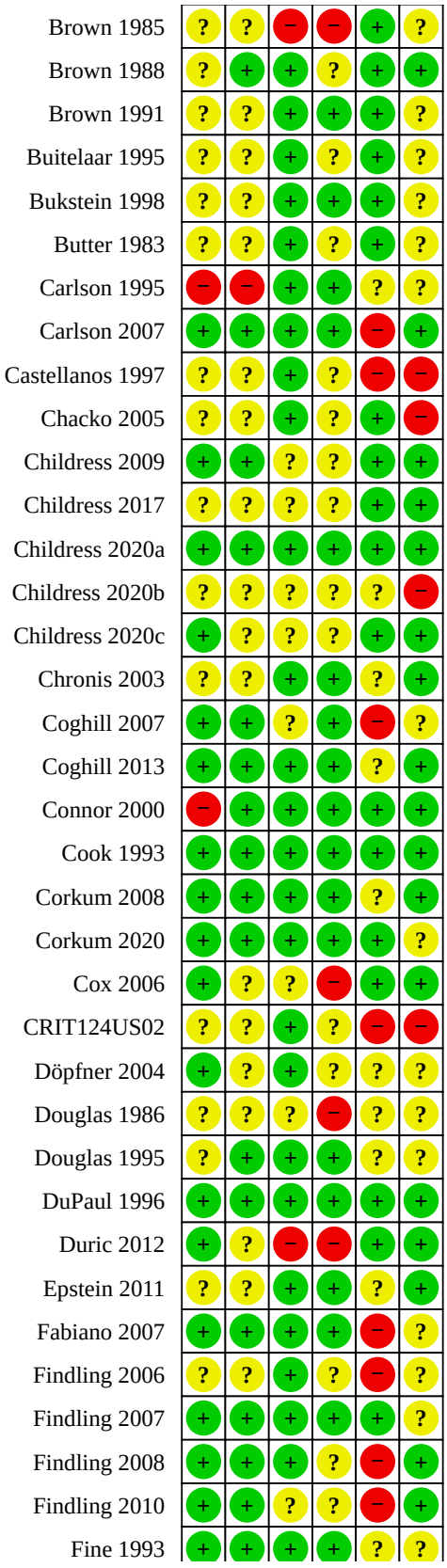

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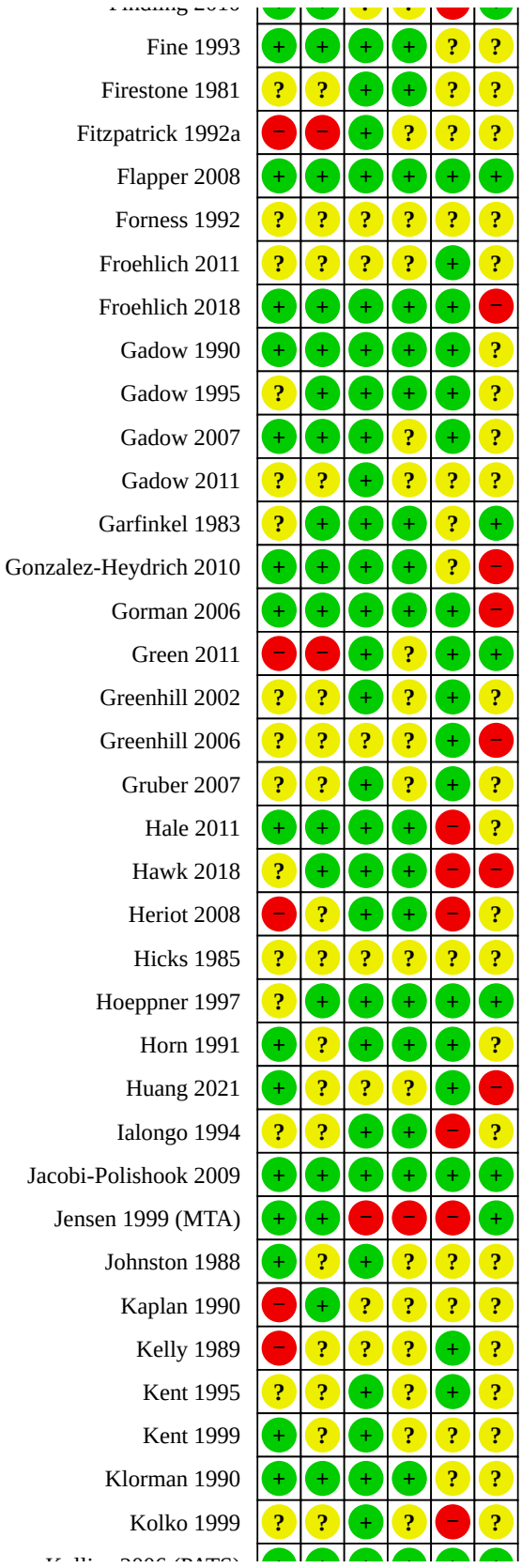

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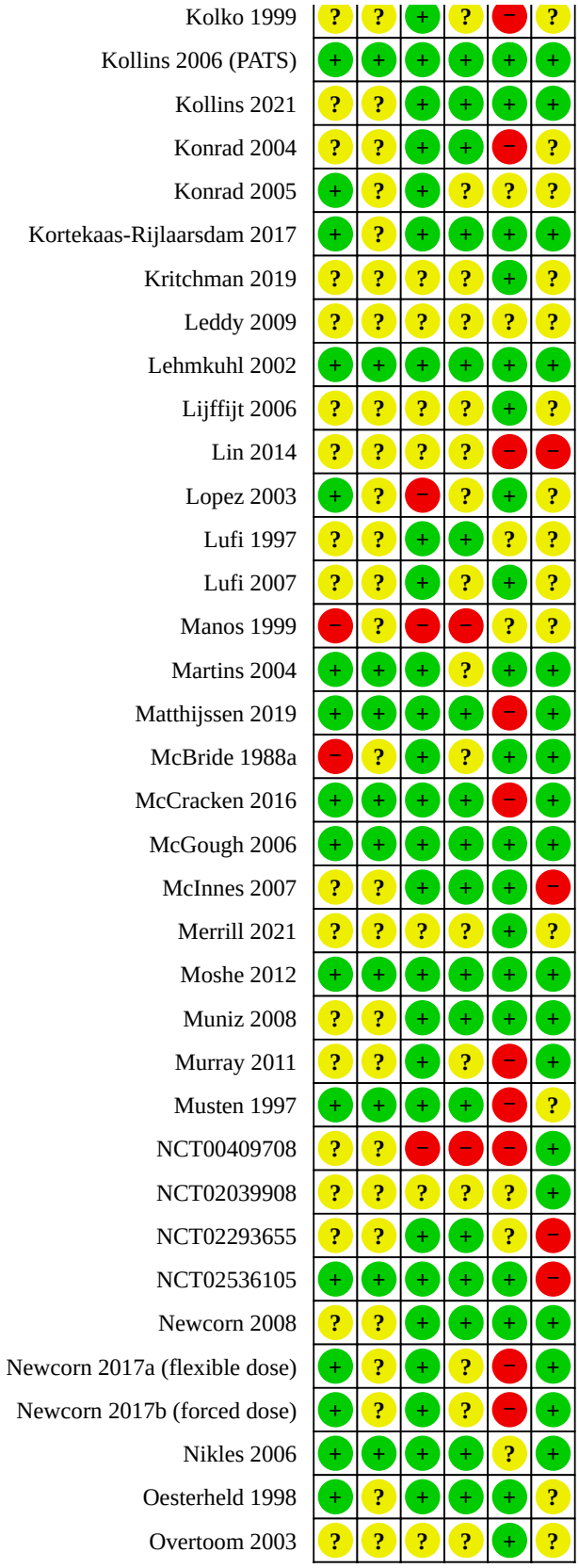


Figure 3. (Continued)

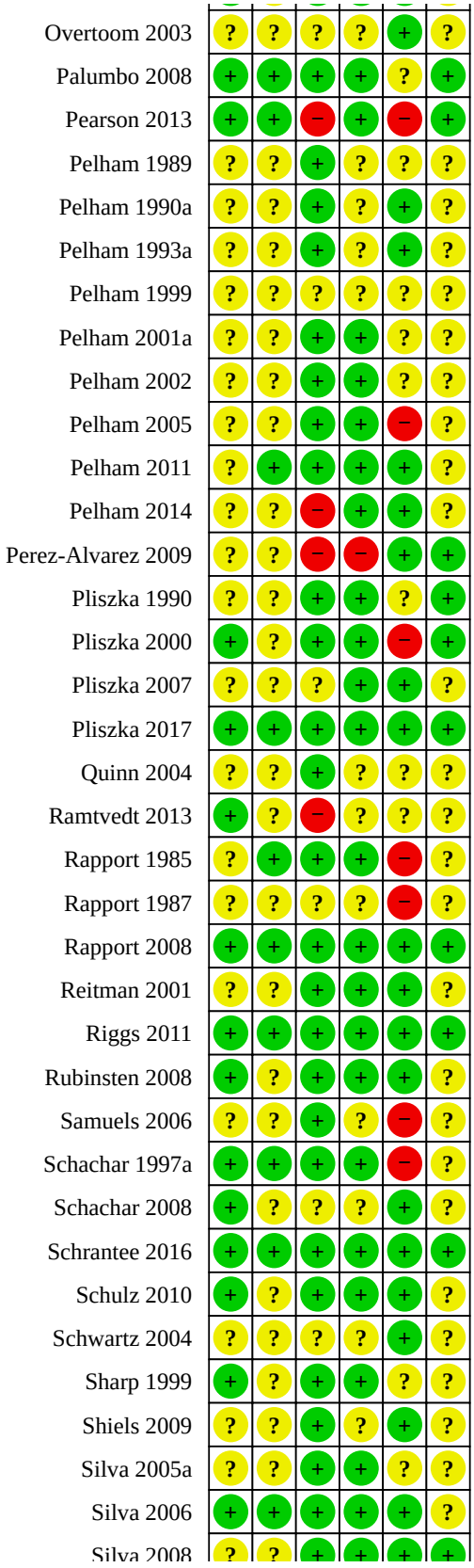


Figure 3. (Continued)

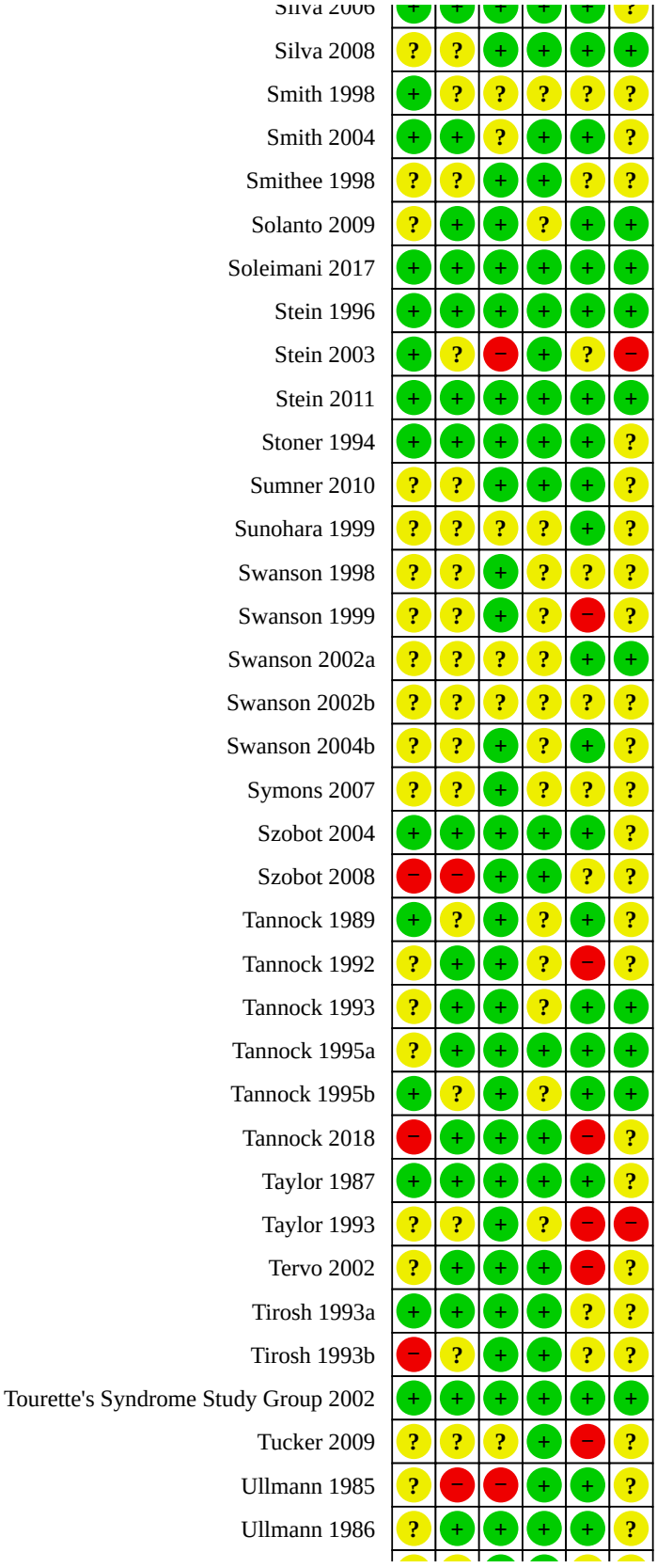
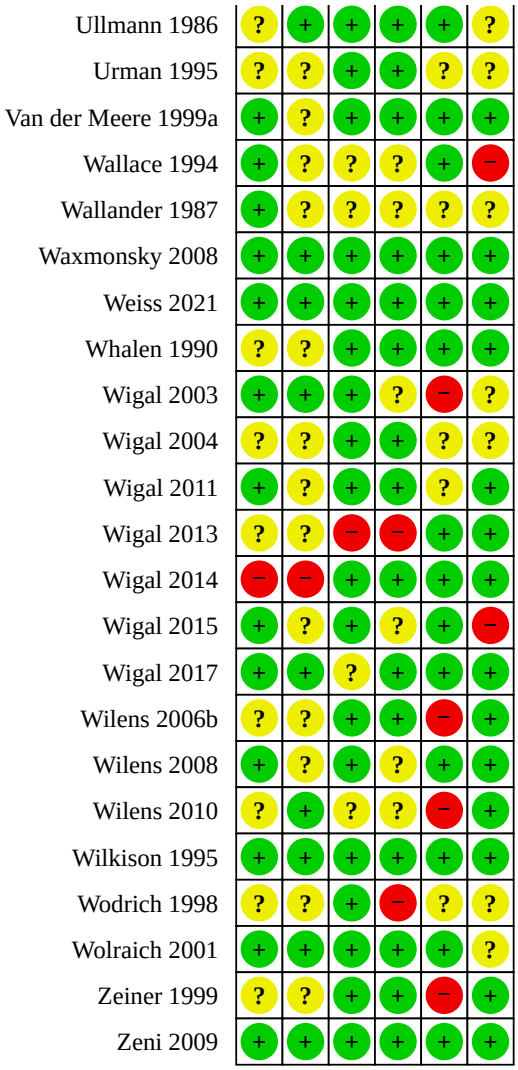


Figure 3. (Continued)



We assessed nine of the 56 included parallel trials at low risk of bias in all bias domains (Childress 2020a; Jacobi-Polishook 2009; Kollins 2006 (PATS); Lehmkuhl 2002; Pliszka 2017; Riggs 2011; Schrantee 2016; Tourette's Syndrome Study Group 2002; Weiss 2021). However, we still considered these trials at risk of deblinding due to prevalent adverse events (see below).

Thirteen of the 157 included cross-over trials were at low risk of bias in all bias domains (Cook 1993; DuPaul 1996; Flapper 2008; Kollins 2006 (PATS); McGough 2006; Moshe 2012; Rapport 2008; Soleimani 2017; Stein 1996; Stein 2011; Waxmonsky 2008; Wilkison 1995; Zeni 2009). However, even these were considered at risk of deblinding due to prevalent adverse events (see below).

Allocation

Parallel trials

Random sequence generation

We considered 34 trials to be at low risk of bias for random sequence generation, four trials to be at high risk of bias (Connor 2000; Green 2011; Heriot 2008; Tannock 2018), and 18 at unclear risk of bias.

Allocation concealment

We considered 26 trials to be at low risk of bias for allocation concealment (often because medications and packaging were identical in appearance for blinding purposes) and two trials to be at high risk of bias (Barragán 2017; Green 2011). Twenty-eight trials did not report allocation concealment in sufficient detail to allow us to make a judgement, so were at unclear risk.

Cross-over trials

Random sequence generation

We considered 64 trials to be at low risk for random sequence generation, nine trials at high risk of bias (Carlson 1995; Fitzpatrick 1992a; Kaplan 1990; Kelly 1989; Manos 1999; McBride 1988a; Szobot 2008; Tirosh 1993b; Wigal 2014), and 84 trials at unclear risk of bias.

Allocation concealment

We considered 57 trials to be at low risk of bias for allocation concealment (often because medications and packaging were identical in appearance for blinding purposes), five trials at high risk of bias (Carlson 1995; Fitzpatrick 1992a; Szobot 2008; Ullmann 1985; Wigal 2014), and 95 trials did not sufficiently report allocation concealment so we judged them at unclear risk of bias.

Blinding

Parallel trials

We considered that 40 trials adequately described their method of blinding of participants and personnel so we judged them to be at low risk of bias. Ten trials gave insufficient information about their methods so we judged them to be at unclear risk of bias (Biederman 2003b; Childress 2009; Childress 2017; Childress 2020b; Childress 2020c; Findling 2010; Greenhill 2006; Lin 2014; Tucker 2009; Wigal 2017). Six trials were not blinded (Barragán 2017; Brown 1985; Duric 2012; Jensen 1999 (MTA); NCT00409708; Perez-Alvarez 2009), so we judged them to be at high risk of bias.

We considered that 34 trials adequately described their method of blinding of outcome assessment so we judged them to be at low risk of bias. Seventeen trials gave insufficient information about their methods and were considered to be at unclear risk of bias. Six trials did not include blinded outcome assessors (Barragán 2017; Brown 1985; Duric 2012; Jensen 1999 (MTA); NCT00409708; Perez-Alvarez 2009), so we judged them to be at high risk of bias.

Cross-over trials

We judged that 118 trials adequately described their method of blinding of participants and personnel so we therefore judged them at low risk of bias. Thirty-one trials were considered at unclear risk of bias. Eight trials were not blinded (Lopez 2003; Manos 1999; Pearson 2013; Pelham 2014; Ramtvedt 2013; Stein 2003; Ullmann 1985; Wigal 2013), so we judged them to be at high risk of bias.

We judged that 86 trials adequately described their method of blinding of outcome assessment and were therefore considered at low risk of bias, and 66 trials were considered at unclear risk of bias. Five trials did not include blinded outcome assessors (Cox 2006; Douglas 1986; Manos 1999; Wigal 2013; Wodrich 1998), so we judged them to be at high risk of bias.

Incomplete outcome data

Parallel trials

Thirty trials adequately addressed incomplete data and were considered at low risk of bias. Twenty trials did not so we judged them to be at high risk of bias. Six trials gave insufficient information for us to assess whether the method they used to handle missing data was likely to bias the estimate of effect (Childress 2020b; Coghill 2013; Firestone 1981; NCT02293655; Palumbo 2008; Wigal 2004), and we therefore considered them at unclear risk of bias.

Cross-over trials

Eighty-five trials adequately addressed incomplete data so we judged them to be at low risk of bias. Forty-eight trials gave insufficient information to assess whether the method they used to handle missing data was likely to bias the estimate of effect so we judged them to be at unclear risk of bias. Twenty-four trials had incomplete outcome data and were therefore considered at high risk of bias.

Selective reporting

Parallel trials

Thirty-four trials reported all pre-defined or otherwise expected outcomes so we judged them at low risk of bias. Five trials did not (Childress 2020b; Greenhill 2006; Lin 2014; NCT02293655; Wigal 2015), and these were considered at high risk of bias. In 17 trials it was unclear whether trial authors reported all pre-defined or otherwise expected outcomes (Arnold 2004; Barragán 2017; Biederman 2003b; Brown 1985; Butter 1983; Findling 2006; Firestone 1981; Greenhill 2002; Heriot 2008; Horn 1991; Ialongo 1994; Schachar 1997a; Szobot 2004; Tannock 2018; Tucker 2009; Wigal 2004; Wolraich 2001), so we judged them at unclear risk of bias.

Cross-over trials

Forty-seven trials reported all pre-defined or otherwise expected outcomes so we judged them at to be at low risk of bias. Thirteen trials did not so these were considered at high risk of bias (Castellanos 1997; Chacko 2005; CRIT124US02; Froehlich 2018; Gonzalez-Heydrich 2010; Gorman 2006; Hawk 2018; Huang 2021; McInnes 2007; NCT02536105; Stein 2003; Taylor 1993; Wallace 1994). In 97 trials it was unclear whether trial authors reported all pre-defined or otherwise expected outcomes so we judged them at unclear risk of bias.

Other potential sources of bias

We identified no other potential sources of bias for either parallel or cross-over trials.

Effects of interventions

See: **Summary of findings 1** Methylphenidate compared with placebo or no intervention for children and adolescents with ADHD

Below, we present the results of meta-analyses performed for the comparison methylphenidate versus placebo or no intervention for two primary outcomes (ADHD symptoms and serious adverse events) and three secondary outcomes (non-serious adverse events, general behaviour, and quality of life). Twenty-nine parallel-group trials (50%) and 60 cross-over trials (38.2%) excluded methylphenidate non-responders, placebo responders or patients with methylphenidate adverse events before randomisation. The subgroup analyses on enrichment designs compared to no enrichment designs are described in each outcome section below. For a summary of key results, please see Summary of findings 1.

Primary outcomes

ADHD symptoms

We were able to combine data on ADHD symptoms from 47 parallel-group trials and 82 cross-over trials, of which five also provided first-period data.

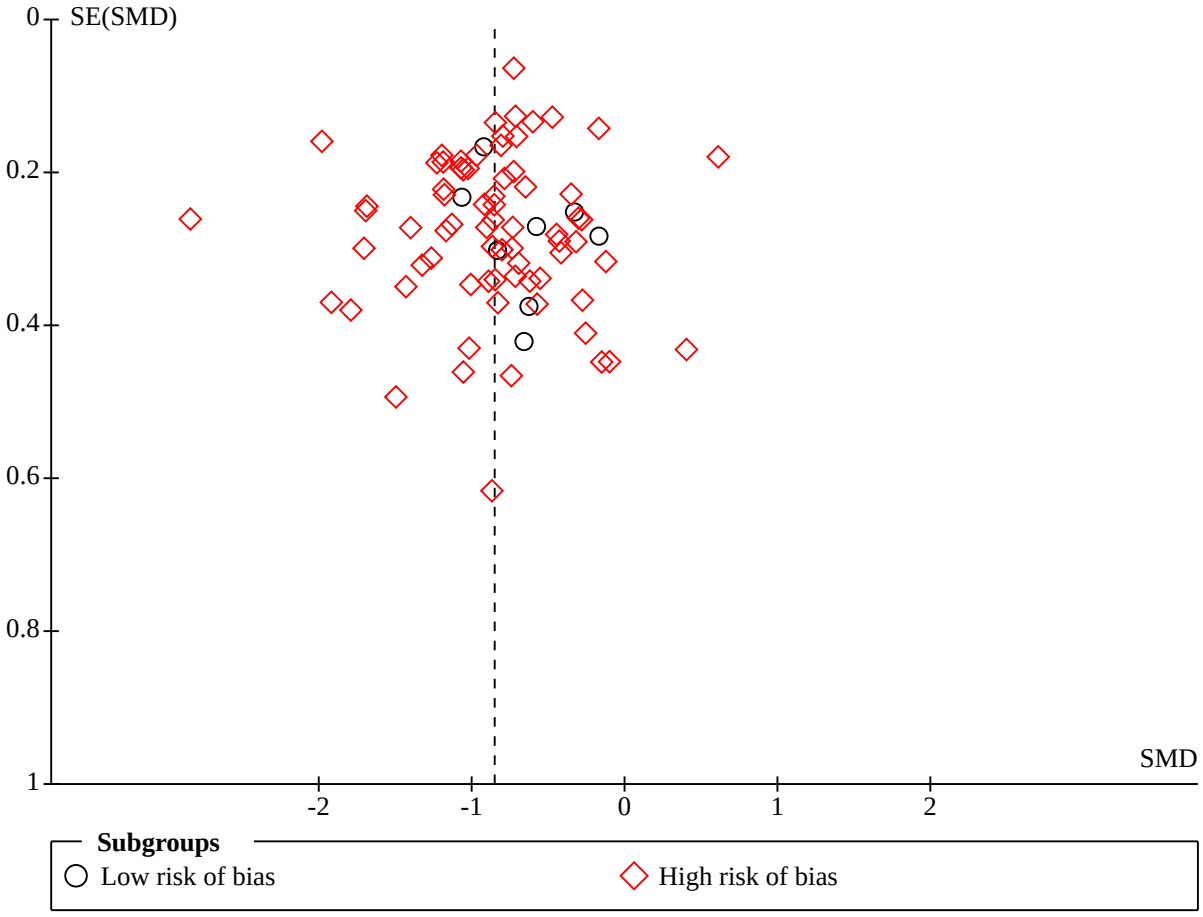
Teacher-rated ADHD symptoms

Parallel-group trials and cross-over trials (end of first-period data only)

A meta-analysis showed a difference in effects between methylphenidate and placebo on teacher-rated ADHD symptoms favouring methylphenidate (SMD −0.74, 95% CI −0.88 to −0.61; I^2 = 38%; 21 trials, 1728 participants; Analysis 1.1). The SMD of −0.74 for ADHD symptoms corresponds to a mean difference (MD) of −10.58 points (95% CI −12.58 to −8.72) on the ADHD Rating Scale (DuPaul 1991a). This is an effect above the minimal relevant difference (MIREDIF; Zhang 2005).

- Subgroup analyses
  - We found that types of scales used influenced the intervention effect of methylphenidate (test for subgroup differences: Chi^2 = 24.94, df = 10 (P = 0.005), I^2 = 59.9%; Analysis 1.2). The differences between the scale that influenced the effect most and least was more than SMD −0.5.
  - We found lower effect of methylphenidate in long-term trials (SMD −0.47, 95% CI −0.72 to −0.22; 1 trial, 253 participants) compared to that of short-term trials (SMD −0.77, 95% CI −0.91 to −0.64; I^2 = 30%; 20 trials, 1475 participants). Test for subgroup differences showed Chi^2 = 4.26, df = 1 (P = 0.04), I^2 = 76.5%; Analysis 1.3. The SMD effect of −0.47 for ADHD long-term trials corresponds to an MD of −6.72 points (95% CI −10.3 to −3.15) on the ADHD-RS (DuPaul 1991a). This is an effect just above the MIREDIF (Zhang 2005).
  - No evidence suggested that any of the following influenced the estimated intervention effect:
    - the risk of bias (test for subgroup differences: Chi^2 = 0.13, df = 1 (P = 0.71), I^2 = 0%; Analysis 1.1)
    - dose (test for subgroup differences: Chi^2 = 3.15, df = 2 (P = 0.21), I^2 = 36.5%; Analysis 1.4)
    - medication status before randomisation (test for subgroup differences: Chi^2 = 0.59, df = 1 (P = 0.44), I^2 = 0%; Analysis 1.5)
    - enrichment design (test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.79), I^2 = 0%; Analysis 1.6)
    - trial design (parallel-group trials compared to first-period cross-over trials, test for subgroup differences: Chi^2 = 0.71, df = 1 (P = 0.40), I^2 = 0%; Analysis 1.7)
    - vested interest (test for subgroup differences: Chi^2 = 2.64, df = 1 (P = 0.10), I^2 = 62.1%; Analysis 1.8) or
    - type of control group (test for subgroup differences: Chi^2 = 0.59, df = 1 (P = 0.44), I^2 = 0%; Analysis 1.9)
  - Inspection of the funnel plot in Figure 4 suggested potential bias (asymmetry), although we found no evidence of significant publication bias: Egger's regression intercept (bias) was −0.2260 (two-tailed, P = 0.81).
  - One of the trials in this meta-analysis used change-from-baseline scores (Palumbo 2008), but removing this trial did not significantly change the estimate.

Figure 4. Funnel plot of comparison 1. Teacher-rated ADHD symptoms, outcome: 1.8 All data at low and high risk of bias (parallel-group and cross-over trials)



We assessed the evidence to be of very low certainty (see GRADE assessment below). Therefore we are uncertain that the estimated effect accurately reflects the true effect, and the addition of more data could change the findings.

Cross-over trials (end of last period)

Meta-analysis suggested a difference in effect between methylphenidate and placebo on teacher-rated ADHD symptoms favouring methylphenidate (SMD −0.88, 95% CI −1.01 to −0.75; I^2 = 82%; 64 trials, 6341 participants; Analysis 1.10).

- Subgroup analyses
  - The estimated intervention effect varied according to risk of bias (test for subgroup differences: Chi^2 = 4.76, df = 1 (P = 0.03), I^2 = 79.0%; Analysis 1.10), and dose of methylphenidate (test for subgroup differences: Chi^2 = 4.12, df = 1 (P = 0.04), I^2 = 75.7%; Analysis 1.11). Three of the trials included some participants with an IQ less than 70 (Pearson 2013; Smith 1998; Taylor 1987). Removing these trials from the analyses did not significantly change the results.

Parallel-group trials and cross-over trials (end of first period) and cross-over trials (end of last period)

Meta-analysis suggested a difference in effects between methylphenidate and placebo on reduced teacher-rated ADHD symptoms favouring methylphenidate (SMD −0.82, 95% CI −0.87 to −0.77; I^2 = 78%; 81 trials, 7564 participants; Analysis 1.12).

- Subgroup analyses
  - No evidence suggested that the intervention effect varied according to trial design (parallel and first period cross-over compared to cross-over trials end of last period; test for subgroup differences: Chi^2 = 3.41, df = 1 (P = 0.06), I^2 = 70.6%; Analysis 1.12).
  - No evidence suggested that the intervention effect varied according to the risk of bias assessment in subgroups (low risk of bias compared to high risk of bias; test for subgroup differences: Chi^2 = 2.13, df = 1 (P = 0.14), I^2 = 53.0%; Analysis 1.13).
  - Nor did it vary according to high or low risk of vested interest (test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.89), I^2 = 0%, Analysis 1.14).

Independent assessor-rated ADHD symptoms

Most independent assessors were clinicians.

Parallel-group trials and cross-over trials (end first-period data only)

A meta-analysis suggested there was a difference in effect between methylphenidate and placebo on independent assessor-rated ADHD symptoms favouring methylphenidate (SMD −1.10, 95% CI −1.44 to −0.77; I^2 = 95%; 22 trials, 3724 participants; Analysis 2.1). The SMD effect of −1.10 for ADHD symptoms corresponds to an MD of −15.7 points (95% CI −14.7 to −7.9) on the ADHD-RS (DuPaul 1991a). This is a clinical effect above the MIREDIF (Zhang 2005). Five trials reported change from baseline scores (Findling 2008; McCracken 2016; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose)), but removing these trials did not significantly change the estimate. Two trials were outliers as they reported unrealistically high effect sizes. These were: Kollins 2021 and Wigal 2017. Removing these trials showed a SMD effect of −0.62 (95% CI −0.79 to −0.46). The SMD effect of −0.62 for ADHD symptoms corresponds to an MD of −8.86 points (95% CI −11.3 to −6.6) on the ADHD-RS (DuPaul 1991a), which is a clinical effect above the MIREDIF (Zhang 2005).

- Subgroup analyses
  - We found lower effect of methylphenidate in trials at low risk of bias (SMD −0.40, 95% CI −0.78 to −0.03; I^2 = 86%; 4 trials, 942 participants), compared to trials at high risk of bias (SMD −1.30, 95% CI −1.70 to −0.89; I^2 = 96%; 18 trials, 2782 participants; test for subgroup differences: Chi^2 = 9.97, df = 1 (P = 0.002), I^2 = 90.0%; Analysis 2.1). The SMD effect of −0.40 in trials at low risk of bias corresponds to a MD of only −5.7 points (95% CI −10.4 to −0.4) on the ADHD-RS (DuPaul 1991a). This is an effect below the MIREDIF (Zhang 2005).
  - Types of scales used (test for subgroup differences: Chi^2 = 16.05, df = 3 (P = 0.001), I^2 = 81.3%; Analysis 2.2).The differences between the scales that influenced the effect most and least was more than SMD −2.0.
  - We found lower effect of methylphenidate in long-term trials (SMD −0.35, 95% CI −0.61 to −0.08; 1 trial, 221 participants) compared to short-term trials (SMD −1.15, 95% CI −1.50 to −0.80; I^2 = 95%; 21 trials, 3503 participants; test for subgroup differences: Chi^2 = 12.82, df = 1 (P = 0.0003), I^2 = 92.2%; Analysis 2.3). The SMD effect of −0.35 for ADHD long-term trials corresponds to an MD of only −5 points (95% CI −8.7 to −1.1) on the ADHD-RS (DuPaul 1991a), which is a clinical effect below the MIREDIF (Zhang 2005).
  - We found larger effect of methylphenidate at high doses (SMD −0.84, 95% CI −1.13 to −0.55; I^2 = 95%; 17 trials, 3005 participants) compared to lower doses (SMD −0.19, 95% CI −0.52 to 0.15; 1 trial, 138 participants; test for subgroup differences: Chi^2 = 12.95, df = 2 (P = 0.002), I^2 = 84.6%; Analysis 2.4. Four trials comprised a subgroup of unknown dose (Findling 2008; Findling 2010; Kollins 2021; Taylor 1987). Including this subgroup in the analysis did not significantly change the subgroup differences between doses.
  - We found larger effects of methylphenidate in trials with enrichment design (SMD −1.24, 95% CI −1.61 to −0.87; I^2 = 95%; 19 trials, 3245 participants) compared to trials without enrichment designs (SMD −0.22, 95% CI −0.62 to 0.17; I^2 = 70%; 3 trials, 479 participants; test for subgroup differences: Chi^2 = 13.65, df = 1 (P = 0.0002), I^2 = 92.7%; Analysis 2.5).
  - We found larger effects of methylphenidate in trials with placebo control group (SMD −1.22, 95% CI −1.58 to −0.85; I^2 = 95%; 20 trials, 3200 participants) compared to trials with no-intervention control groups (SMD −0.14, 95% CI −0.52 to 0.23; I^2 = 79%; 2 trials, 524 participants; test for subgroup differences: Chi^2 = 16.00, df = 1 (P < 0.0001); I^2 = 93.8%; Analysis 2.6).
  - No evidence suggested that trial design (parallel-group trials compared to first-period cross-over trials) influenced the estimated intervention effect (test for subgroup differences: Chi^2 = 3.38, df = 1 (P = 0.07), I^2 = 70.4%; Analysis 2.7). There were not enough data to conduct a test of vested interest.

Cross-over trials (end of last period)

A meta-analysis suggested a difference in effect between methylphenidate and placebo on independent assessor-rated ADHD symptoms favouring methylphenidate (SMD −0.97, 95% CI −1.11 to −0.83; I^2 = 71%; 22 trials, 3854 participants; Analysis 2.8).

- Subgroup analyses
  - We assessed all 22 trials to be at high risk of bias, therefore we could not conduct a subgroup analysis.
  - The estimated intervention effect varied according to dose of methylphenidate, with a seemingly increased effect of a high dose (SMD −1.07, 95% CI −1.27 to −0.86; 13 trials, 2051 participants; I^2 = 77%) compared to a low dose (SMD −0.72, 95% CI −0.86 to −0.58; I^2= 61%; 17 trials, 3067 participants; test for subgroup differences: Chi^2 = 8.86, df = 2 (P = 0.01); I^2 = 77.4%; Analysis 2.9). One trial comprised a subgroup of unknown dose (NCT02536105). Including this subgroup in the analysis did not significantly change the subgroup differences between doses.

Parallel-group trials and cross-over trials (end of first period) and cross-over trials (end of last period)

A meta-analysis suggested there was a difference in effect between methylphenidate and placebo on independent assessor-rated ADHD symptoms favouring methylphenidate (SMD −0.99, 95% CI −1.18 to −0.80; I^2 = 92%; 42 trials, 7277 participants; Analysis 2.10).

- Subgroup analyses
  - The risk of bias assessment influenced the estimated intervention effect when combining parallel and first-period cross-over data with end-of-last-period cross-over data, with a seemingly lower effect in the subgroup of trials assessed to be at low risk of bias (SMD −0.40, 95% CI −0.78 to −0.03; I^2 = 86%; 4 trials, 942 participants), compared to those assessed to be at high risk of bias (SMD −1.06, 95% CI −1.25 to −0.86; I^2 = 92%; 38 trials, 6335 participants; test for subgroup differences: Chi^2 = 9.02, df = 1 (P = 0.003), I^2 = 88.9%; Analysis 2.11).
  - We did not find any subgroup difference on intervention effect between trials at high or unclear risk of vested interest compared to trials at low risk of vested interest (test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.89), I^2 = 0%; Analysis 2.12).
  - No evidence suggested that the intervention effect varied according to trial design (parallel and first-period cross-over compared to cross-over trials end of last period; test for subgroup differences: Chi^2 = 1.42, df = 1 (P = 0.23), I^2 = 29.5%; Analysis 2.10).

Parent-rated ADHD symptoms

Parallel-group trials and cross-over trials (end of first-period data only)

A meta-analysis suggested there is a difference in effects between methylphenidate and placebo in parent-rated ADHD symptoms favouring methylphenidate (SMD −0.63, 95% CI −0.76 to −0.50; I^2 = 58%; 27 trials, 2927 participants; Analysis 3.1). The SMD effect of −0.63 for ADHD symptoms corresponds to an MD of −9.0 points (95% CI −10.9 to −7.0) on the ADHD-RS (DuPaul 1991a). This is a clinical effect above the MIREDIF (Zhang 2005). Three trials in the meta-analysis reported change from baseline scores (Carlson 2007; Newcorn 2008; Tucker 2009), but removing these trials did not significantly change the estimate.

- Subgroup analyses
  - Types of scales (test for subgroup differences: Chi^2 = 27.14, df = 11 (P = 0.004), I^2 = 59.5%; Analysis 3.2). The difference between the scales that influenced the effect most and least was more than SMD −0.5.
  - No evidence suggested that the following influenced the intervention effect:
    - risk of bias assessment (test for subgroup differences: Chi^2 = 1.56, df = 1 (P = 0.21), I^2 = 36.0%; Analysis 3.1)
    - duration of treatment (test for subgroup differences: Chi^2 = 0.27, df = 1 (P = 0.60), I^2 = 0%; Analysis 3.3)
    - dose of methylphenidate (test for subgroup differences: Chi^2 = 0.54, df = 2 (P = 0.76), I^2 = 0%, Analysis 3.4)
    - medication status before randomisation (test for subgroup differences: Chi^2 = 0.51, df = 1 (P = 0.48), I^2 = 0%; Analysis 3.5)
    - enrichment design (test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 = 0%; Analysis 3.6)
    - trial design (parallel group trials compared to first period cross-over trials) (test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.86), I^2 = 0%; Analysis 3.7)
    - type of control group (test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 = 0%; Analysis 3.8)
  - There were not enough data to test the influence of vested interest on the effect estimate.

Cross-over trials (end of last period data)

A meta-analysis suggested a difference in effect between methylphenidate and placebo in parent-rated ADHD symptoms favouring methylphenidate (SMD −0.70, 95% CI −0.86 to −0.55; I^2 = 84%; 45 trials, 4971 participants; Analysis 3.9).

- Subgroup analyses
  - This effect did not vary between:
    - assessed risk of bias ratings (test for subgroup differences: Chi^2 = 2.41, df = 1 (P = 0.12), I^2 = 58.5%; Analysis 3.9);
    - dose of methylphenidate (test for subgroup differences: Chi^2 = 3.81, df = 2 (P = 0.15), I^2 = 47.5%; Analysis 3.10); or
    - trial design (parallel and first-period cross-over compared to cross-over trials, test for subgroup differences: Chi^2 = 0.58, df = 1 (P = 0.45), I^2 = 0%; Analysis 3.11).
  - Two trials included some participants with an IQ less than 70 (Pearson 2013; Taylor 1987), but removing these trials did not significantly change the estimate.

Parallel-group trials and cross-over trials (end of first period) and cross-over trials (end last of last period)

When combining data from parallel-group trials with endpoint data from cross-over trials our meta-analysis suggested a difference in effects between methylphenidate and placebo on reduced parent-rated ADHD symptoms favouring methylphenidate (SMD −0.67, 95% CI −0.78 to −0.56; I^2 = 79%; 69 trials, 7838 participants; Analysis 3.11).

- Subgroup analyses
  - No evidence suggested that the intervention effect varied according to:
    - the risk of bias assessment (test for subgroup differences: Chi^2 = 3.24, df = 1 (P = 0.07), I^2 = 69.1%; Analysis 3.12);
    - high or unclear and low risk of vested interest (test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 = 0%; Analysis 3.13).

Additional subgroup analyses

- We tested for differences between raters (teachers, independent assessors and parents) and found no significant differences (test for subgroup differences: Chi^2 = 2.73, df = 2 (P = 0.26), I^2 = 26.7%; Analysis 4.1).
- We found no evidence suggesting that age (test for subgroup differences: Chi^2 = 2.84, df = 2 (P = 0.24), I^2 = 29.6%; Analysis 4.2) or comorbidity influenced the intervention effect (test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 = 0%; Analysis 4.3). However, the intervention effect was influenced by ADHD subtype, with a greater intervention effect noted for the inattentive subtype (SMD −1.31, 95% CI −1.61 to −1.01; 1 trial, 204 participants) compared to the combined subtype (SMD 0.65, 95% CI −1.30 to 2.60; I^2 = 99%; 2 trials, 559 participants; test for subgroup differences: Chi^2 = 3.79, df = 1 (P value = 0.05); I^2 = 73.6%; Analysis 4.4). This difference rested upon one single trial.
- We found no evidence of a 'carry-over effect' in the cross-over trials. We conducted a subgroup analysis to investigate the difference between first-period data and endpoint data from four cross-over trials (372 participants), and we found no subgroup differences (test for subgroup differences: Chi^2 = 1.91, df = 1 (P = 0.17), I^2 = 47.6%; Analysis 4.5).

Serious adverse events

We were only able to combine data on serious adverse events from 26 parallel-group trials and 17 cross-over trials.

Parallel-group trials and cross-over trials (first-period data only)

Overall serious adverse events

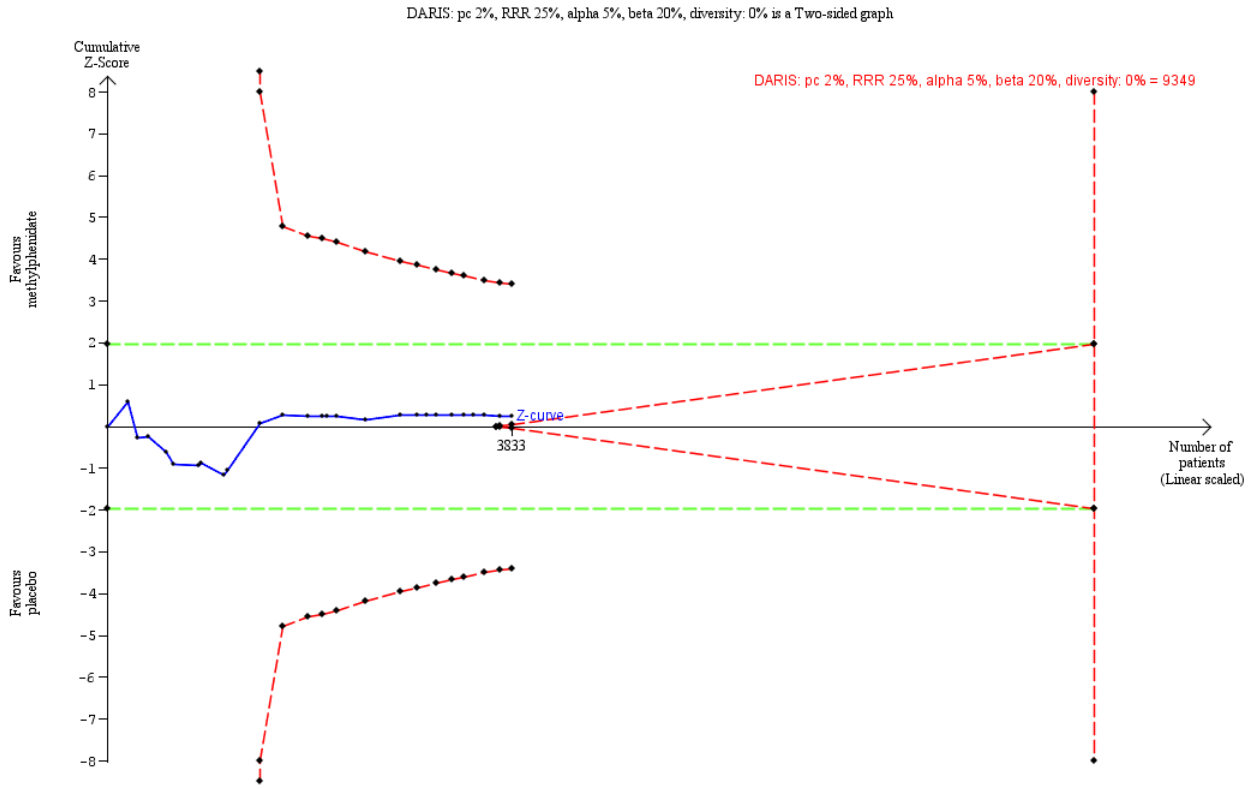
There was no clear evidence of a difference between participants in the methylphenidate group versus those in the control group with regards to the proportion of participants with serious adverse events (RR 0.80, 95% CI 0.39 to 1.67; I^2 = 0%; 26 trials, 3673 participants; Analysis 5.1).

We assessed the evidence to be of very low certainty (see GRADE assessment below). Therefore we are uncertain that the estimated effect accurately reflects the true effect, and the addition of more data could change the findings.

- Trial Sequential Analysis

- We conducted a Trial Sequential Analysis on the 'proportion of participants with serious adverse events' outcome, involving 26 parallel-group and first-period cross-over trials. We had planned to use a relative risk reduction of 20%, but the distance between the accrued information and the required information was too large, and the program failed to calculate and draw an interpretable figure. Therefore, we increased the relative risk reduction to 25%. We included trials with zero serious adverse events by substituting zero with a constant of 0.25 (Carlson 2007; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Green 2011; Huang 2021; Jacobi-Polishook 2009; Kollins 2021; Matthijssen 2019; McCracken 2016; NCT00409708; Pliszka 2017; Schrantee 2016; Wigal 2017; Wolraich 2001). We calculated the DARIS on the basis of serious adverse events in the control group of 2%; a relative risk reduction or increase in the experimental group of 25%; type I error of 5%; type II error of 20% (80% power); and diversity (D^2) of 0%. The DARIS was 9349 participants. The cumulative Z-curve did not cross the conventional or trial sequential monitoring boundaries for benefit, harm, or futility (see Figure 5). As only less than 36% of the DARIS was accrued, risks of random type II error cannot be excluded. The Trial Sequential Analysis-adjusted intervention effect was RR 0.91 (CI 0.31 to 2.68).
- Specific serious adverse events:
  - nervous system: aggression (RR 0.50, 95% CI 0.05 to 5.49; 1 trial, 303 participants; Analysis 5.2)
  - nervous system: concussion (RR 0.34, 95% CI 0.01 to 8.17; 1 trial, 303 participants; Analysis 5.2)
  - nervous system: loss of consciousness (RR 0.33, 95% CI 0.01 to 8.02; 1 trial, 221 participants; Analysis 5.2)
  - nervous system: psychosis (RR 0.81, 95% CI 0.13 to 5.12; I^2 = 0%; 4 trials, 919 participants; Analysis 5.2)
  - nervous system: syncope (RR 1.39, 95% CI 0.23 to 8.47; I^2= 0%; 3 trials, 741 participants; Analysis 5.2)
  - nervous system: suicidal ideation (RR 1.63, 95% CI 0.07 to 38.55; 6 trials, 1032 participants; Analysis 5.2)
  - nervous system: suicidal behaviour: no events; 2 trials, 233 participants; Analysis 5.2)
  - nervous system: oppositional behaviour/negativism (RR 0.17, 95% CI 0.01 to 4.04, 1 trial, 217 participants; Analysis 5.2)
  - nervous system: adjustment disorder (RR 0.78, 95% CI 0.03 to 18.91; 1 trial, 230 participants; Analysis 5.2)
  - digestive system: appendicitis (RR 2.11, 95% CI 0.22 to 20.04; I^2 = 0%; 2 trials, 414 participants; Analysis 5.3)
  - cardiovascular systems: haematoma (RR 0.33, 95% CI 0.01 to 8.02; 1 trial, 221 participants; Analysis 5.4)
  - cardiovascular systems: tachycardia (RR 3.10, 95% CI 0.13 to 73.14; 1 trial, 59 participants; Analysis 5.4)
  - respiratory system: bronchitis (RR 0.34, 95% CI 0.01 to 8.17; 1 trial, 303 participants; Analysis 5.5)
  - respiratory system: asthma (RR 3.02, 95% CI 0.12 to 73.54; 1 trial, 303 participants; Analysis 5.5)
  - urinary system: renal cyst (RR 1.49, 95% CI 0.06 to 36.27; 1 trial, 275 participants; Analysis 5.6)
  - urinary system: kidney infection (RR 3.02, 95% CI 0.12 to 73.54; 1 trial, 303 participants; Analysis 5.6)
  - skeletal and muscular system: clavicle fracture (RR 0.33, 95% CI 0.01 to 8.02; 1 trial, 221 participants; Analysis 5.7)
  - immune system: cyst rupture (RR 3.02, 95% CI 0.12 to 73.54; 1 trial, 303 participants; Analysis 5.8)
  - other: drug toxicity (RR 0.34, 95% CI 0.01 to 8.17; 1 trial, 303 participants; Analysis 5.9
  - other: overdose (RR 2.97, 95% CI 0.12 to 72.20; 1 trial, 221 participants; Analysis 5.9

Figure 5. Trial Sequential Analysis: proportion of participants with one or more serious adverse events



Cross-over trials (end of last period data)

There were no clear differences between participants in the methylphenidate group and individuals in the control group regarding the proportion of participants with serious adverse events (RR 2.46, 95% CI 0.50 to 12.03; I^2 = 0%; 16 trials, 3323 participants; Analysis 6.1).

- Specific serious adverse events:
  - nervous system: hallucinations (RR 1.33, 95% CI 0.06 to 30.42; 1 trial, 37 participants; Analysis 6.2)
  - nervous system: psychiatric disorders (RR 3.21, 95% CI 0.13 to 78.04; 1 trial, 267 participants; Analysis 6.2)
  - urinary system: proteinuria (RR 3.00, 95% CI 0.12 to 72.37; 1 trial, 136 participants; Analysis 6.3)
  - immune system: peritonsillar abscess (RR 2.93, 95% CI 0.12 to 71.32; 1 trial, 322 participants; Analysis 6.4)
  - immune system: oral bullae (RR 2.93, 95% CI 0.12 to 71.32; 1 trial, 322 participants; Analysis 6.4)

Secondary outcomes

Adverse events considered non-serious

We were able to combine data on non-serious adverse events from 26 parallel-group trials and 67 cross-over trials in meta-analyses. We assessed the evidence to be of very low certainty (see GRADE assessment below). Therefore we are uncertain that the estimated effect accurately reflects the true effect and the addition of more data could change the findings.

Parallel-group trials and cross-over trials (end of first-period data only)

Overall adverse events considered non-serious

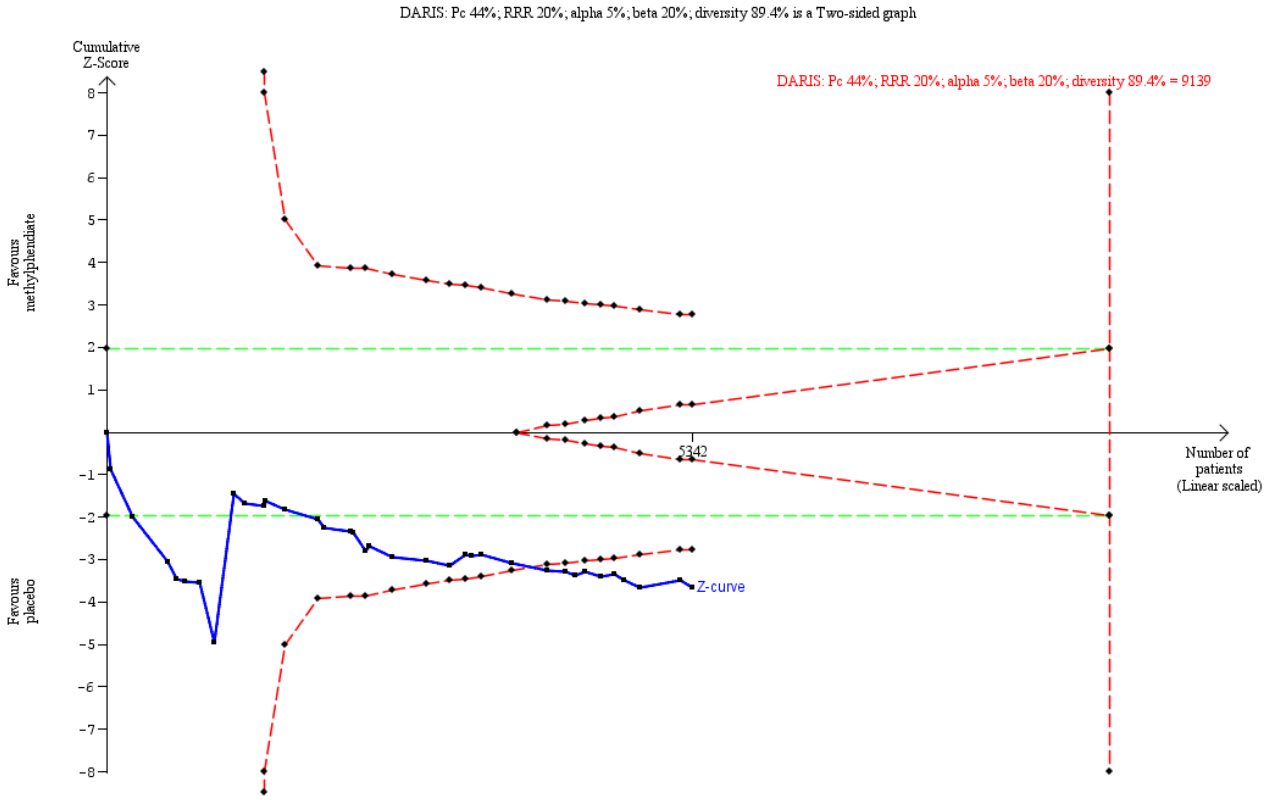
Participants receiving methylphenidate were more likely to experience non-serious adverse events overall (RR 1.23, 95% CI 1.11 to 1.37; I^2 = 72%; 35 trials, 5342 participants; Analysis 7.1). We observed substantial heterogeneity between trials: $Tau^2 = 0.05$; $Chi^2 = 118.99$, df = 33, (P < 0.00001); I^2 = 72%. This heterogeneity could be related to dose, as we observed differences between low-dose and high-dose methylphenidate trials (test for subgroup differences: Chi^2 = 18.52, df = 2 (P < 0.0001), I^2 = 89.2%; Analysis 7.2). Eight trials did not specify the dose they used. Including these trials in the dose subgroup analysis did not significantly alter the subgroup difference between methylphenidate doses.

- Trial Sequential Analysis
  - We conducted a Trial Sequential Analysis on the 'proportion of participants with non-serious adverse events' outcome involving 35 parallel-group and first-period cross-over trials. We included one trial with zero non-serious adverse events by substituting zero with a constant of 0.25 (Jacobi-Polishook 2009). We calculated the DARIS on the basis of adverse events in the control group of 44%; relative risk reduction in the intervention group of 20%; type I error of 5%; type II error of 20% (80% power); and diversity (D-square) of 89.6%. The DARIS was 9139 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundaries for harm (red inward sloping line) after the 25th trial (Figure 6). Accordingly, risk of random error in the finding can be excluded according to the Lan-DeMetz-O'Brien-Fleming

monitoring boundary. The Trial Sequential Analysis-adjusted intervention effect was RR 1.22 (CI 1.08 to 1.43).

- Non-serious adverse events included those affecting the nervous system (Analysis 7.3), the digestive system (Analysis 7.4), the cardiovascular system (Analysis 7.5), respiratory system (Analysis 7.6), the urinary system (Analysis 7.7), the skeletal and muscular system (Analysis 7.8), the immune system (Analysis 7.9), and the integumentary system (Analysis 7.10). Other reported adverse events included sleep variability (Analysis 7.11; Analysis 7.12), vital signs (Analysis 7.13), physical parameters (Analysis 7.14) and others including drug toxicity (Analysis 7.15).
- Compared with those in the control group, participants in the methylphenidate may be more likely to report the following:
  - nervous system: headache (RR 1.33, 95% CI 1.04 to 1.70; I^2 = 32%; 32 trials, 5041 participants; Analysis 7.3)
  - nervous system: tension (RR 23.00, 95% CI 1.42 to 373.44; 1 trial, 60 participants; Analysis 7.3)
  - digestive system: a decrease in appetite (RR 3.35, 95% CI 2.49 to 4.50; I^2 = 48%; 30 trials, 5127 participants; Analysis 7.4)
  - digestive system: a decrease in weight (RR 5.44, 95% CI 2.47 to 11.98; I^2 = 0%; 11 trials, 2001 participants; Analysis 7.4)
  - physical parameters: having a lower body mass index (BMI) (SMD −1.00, 95% CI −1.26 to −0.73; I^2 = 65%; 3 trials, 810 participants; Analysis 7.14)
  - digestive system: having dry mouth (RR 3.79, 95% CI 1.26 to 11.39; I^2 = 0%; 4 trials, 1057 participants; Analysis 7.4)
  - cardiovascular system: pallor (RR 23.00, 95% CI 1.42 to 373.44; 1 trial, 60 participants; Analysis 7.5)
  - sleep variability: trouble sleeping or sleep problems (RR 1.62, 95% CI 1.18 to 2.21; I^2 = 0%; 15 trials, 2620 participants; Analysis 7.11)
  - sleep variability: insomnia (RR 1.90, 95% CI 1.12 to 3.22; I^2 = 49%; 15 trials, 2315 participants; Analysis 7.11)
  - sleep variability: having a lower sleep efficiency percentage (time spent asleep while in bed) after treatment discontinuation (MD 5.42, 95% CI 0.21 to 10.63; 1 trial, 48 participants; Analysis 7.12)
  - vital signs: having a higher diastolic blood pressure (MD 1.90, 95% CI 0.68 to 3.11; I^2 = 54%; 13 trials, 2032 participants; Analysis 7.13
  - vital signs: having a higher pulse (MD 3.86, 95% CI 2.09 to 5.63; I^2 = 65%; 13 trials, 2205 participants; Analysis 7.13).
  - other: excoriation (chronic skin-picking) (RR 3.22, 95% CI 1.20 to 8.64; I^2 = 0%; 2 trials, 389 participants; Analysis 7.15)

Figure 6. Trial Sequential Analysis: proportion of participants with one or more non-serious adverse events



Cross-over trials (end-of-last-period data)

Overall adverse events considered non-serious

Participants receiving methylphenidate were significantly more likely to experience adverse events considered non-serious compared with the control group (RR 1.39, 95% CI 1.13 to 1.70; I^2 = 60%; 24 trials, 2696 participants; Analysis 8.1). In addition, we noted differences in the numbers of events reported in trials of low doses of methylphenidate compared to trials of high doses of methylphenidate as there were more events in the high-dose group (test for subgroup differences: Chi^2 = 5.72, df = 2 (P = 0.026, I^2 = 65.0%; Analysis 8.2). Five trials did not specify the dose they used. Including these in the dose subgroup analysis did not alter the subgroup difference between methylphenidate doses.

Categories of non-serious adverse events included those affecting the nervous system (Analysis 8.3; Analysis 8.4), the digestive system (Analysis 8.5), the cardiovascular system (Analysis 8.6), the respiratory system (Analysis 8.7), the urinary system (Analysis 8.8), the skeletal and muscular system (Analysis 8.9; Analysis 8.10), the immune system (Analysis 8.11), and the integumentary system (Analysis 8.12). Other reported adverse events included effects on sleep variability (Analysis 8.13; Analysis 8.14), vital signs (Analysis 8.15), physical parameters (Analysis 8.16), and others including drug toxicity (Analysis 8.17).

Compared with the control group, participants in the methylphenidate group were less likely to report experiencing the following:

- nervous system: anger (RR 0.45, 95% CI 0.26 to 0.77; I^2 = 0%; 3 trials, 264 participants; Analysis 8.3)
- nervous system: behavioural complaints (RR 0.55, 95% CI 0.35 to 0.86; 1 trial, 82 participants; Analysis 8.3)
- nervous system: daydreaming (RR 0.66, 95% CI 0.44 to 0.98; I^2 = 0%; 3 trials, 222 participants; Analysis 8.3)
- digestive system: an increase in appetite (RR 0.20, 95% CI 0.08 to 0.50; 1 trial, 136 participants; Analysis 8.5)
- sleep variability: a reduction in actigraphic sleep onset latency (time to transition from full wakefulness to sleep; MD 21.10, 95% CI 1.33 to 40.87; 1 trial, 52 participants; Analysis 8.13)

However, they were more likely to report the following:

- nervous system: compulsive acts (RR 2.57, 95% CI 1.45 to 4.56; 1 trial, 90 participants; Analysis 8.3)
- nervous system: headache (RR 1.25, 95% CI 1.06 to 1.48; I^2 = 0%; 43 trials, 5981 participants; Analysis 8.3)
- nervous system: being overly meticulous (RR 40.77, 95% CI 2.35 to 706.72; 1 trial, 96 participants; Analysis 8.3)
- nervous system: obsessive thinking (RR 2.35, 95% CI 1.53 to 3.62; 1 trial, 90 participants; Analysis 8.3)
- nervous system: tics or nervous movements ((RR 1.23, 95% CI 1.02 to 1.50; I^2 = 3%; 24 trials, 3429 participants; Analysis 8.3)
- nervous system: emotional lability (RR 9.25, 95% CI 2.24 to 38.22; 1 trial, 154 participants; Analysis 8.3)
- nervous system: being prone to crying (RR 1.72, 95% CI 1.04 to 2.86; 1 trial, 1052 participants; Analysis 8.3)
- digestive system: a decrease in appetite (RR 3.89, 95% CI 2.76 to 5.48; I^2 = 78%; 41 trials, 6091 participants; Analysis 8.5)
- digestive system: nausea (RR 1.67, 95% CI 1.13 to 2.46; I^2 = 0%; 11 trials, 1182 participants; Analysis 8.5)
- digestive system: stomach ache (RR 1.70, 95% CI 1.35 to 2.15; I^2 = 34%; 38 trials, 5803 participants; Analysis 8.5)
- sleep variability: insomnia or sleep problems (RR 1.88, 95% CI 1.39 to 2.56; I^2 = 69%; 37 trials, 5499 participants; Analysis 8.14)
- vital signs: increased pulse/heart rate (SMD 0.43, 95% CI 0.23 to 0.64; I^2 = 53%; 14 trials, 939 participants; Analysis 8.15).
- skeletal and muscular system: somatic complaints (MD 0.85, 95% CI 0.79 to 0.91; 1 trial, 82 participants; Analysis 8.10)

General behaviour

We were able to include in our analyses data on general behaviour from 13 parallel-group trials and from 21 cross-over trials.

Teacher-rated general behaviour

Parallel-group trials and cross-over trials (end-of-first-period data only)

A meta-analysis suggested a difference in effect between methylphenidate and placebo in teacher-rated general behaviour favouring methylphenidate (SMD −0.62, 95% CI −0.91 to −0.33; I^2 = 68%; 7 trials, 792 participants; Analysis 9.1). The SMD effect of −0.62 for general behaviour corresponds to an MD of −3.58 points (95% CI −5.26 to −1.91) on the CGI (Conners 1998a). Due to a lack of MIREDIF, we do not know whether this is a clinical relevant difference.

We assessed the evidence to be of very low certainty (see GRADE assessment below). Therefore we are uncertain that the estimated effect accurately reflects the true effect and the addition of more data could change the findings.

- Subgroup analyses
  - We were not able to test for subgroup differences based on the risk of bias as all seven trials were at high risk of bias (Analysis 9.1).
  - The intervention effect varied according to type of scale (test for subgroup differences: Chi^2 = 18.75, df = 5 (P = 0.002), I^2 = 73.3%; Analysis 9.2).
  - We found no evidence to suggest a difference in effects between doses (test for subgroup differences: Chi^2 = 0.29, df = 2 (P = 0.87), I^2 = 0%; Analysis 9.3).
  - We were not able to test for subgroup differences according to duration, as all trials were of short duration, that is, less than six months (Analysis 9.4), or according to trial design, as all trials in the analysis were parallel-group trials (Analysis 9.5).

Cross-over trials (endpoint data)

Meta-analysis suggested a difference in effects between methylphenidate and placebo in reduced teacher-rated general behaviour favouring methylphenidate (SMD −0.75, 95% CI −0.87 to −0.63; I^2 = 5%; 16 trials, 1302 participants; Analysis 9.6).

- Subgroup analyses
  - The intervention effect varied according to dose of methylphenidate favouring the high-dose group (test for subgroup differences: Chi^2 = 5.64, df = 1 (P = 0.02), I^2 = 82.3%; Analysis 9.7).

Parallel-group trials and cross-over trials (endpoint data)

When combining data from parallel-group trials with endpoint data from cross-over trials our meta-analysis similarly suggested a difference in effects between methylphenidate and placebo in reduced teacher-rated general behaviour favouring methylphenidate (SMD −0.72, 95% CI −0.84 to −0.60; I^2= 37%; 23 trials, 2094 participants; Analysis 9.8). The intervention effect did not vary according to high or low risk of vested interest (Analysis 9.9)

Independent assessor-rated general behaviour

Parallel-group trials and cross-over trials (first-period data only)

Meta-analysis suggested a difference in effects between methylphenidate and placebo in reduced independent assessor-rated general behaviour favouring methylphenidate (MD 1.10, 95% CI −1.01 to 3.21; 1 trial, 94 participants; Analysis 10.1).

- Subgroup analyses
  - We found only one parallel-group trial that provided data on independent assessor-rated general behaviour, so we were unable to perform any subgroup analyses.

Cross-over trials (endpoint data)

Meta-analysis suggested a difference in effects between methylphenidate and placebo in reduced independent assessor-rated general behaviour favouring methylphenidate (SMD −0.98, 95% CI −1.39 to −0.57; I^2 = 87%; 9 trials, 987 participants; Analysis 10.2).

- Subgroup analyses
  - We were not able to test for subgroup differences based on the risk of bias as all trials were at high risk of bias.
  - The intervention effect did not vary according to dose of methylphenidate (test for subgroup differences: Chi^2 = 1.83, df = 1 (P = 0.18), I^2 = 45.3%; Analysis 10.3)
  - The intervention effect varied according to trial design (test for subgroup differences: Chi^2 = 16.36, df = 1 (P < 0.0001), I^2 = 93.9%; Analysis 10.4).

Parallel-group trials and cross-over trials (endpoint data)

When combining data from parallel-group trials with endpoint data from cross-over trials our meta-analysis similarly suggested a difference in effects between methylphenidate and placebo in reduced independent assessor-rated general behaviour favouring methylphenidate (SMD −0.86, 95% CI −1.27 to −0.46; I^2 = 89; 10 trials, 1081 participants; Analysis 10.4).

- Subgroup analyses
  - The intervention effect did not vary according to high or low risk of vested interest (test for subgroup differences: Chi^2 = 0.26, df = 1 (P = 0.61), I^2 = 0%; Analysis 10.5). One trial had unclear risk of vested interest (Merrill 2021) and including this trial in the subgroup analysis significantly changed the results (test for subgroup differences: Chi^2 = 51.05, df = 2 (P < 0.00001), I^2 = 96.1%; Analysis 10.5).

Parent-rated general behaviour

Parallel-group trials and cross-over trials (first-period data only)

Meta-analysis suggested a difference in effects between methylphenidate and placebo in reduced parent-rated general behaviour favouring methylphenidate (SMD −0.42, 95% CI −0.62 to −0.23; I^2 = 57%; 10 trials, 1376 participants; Analysis 11.1).

- Subgroup analyses
  - The intervention effect was significantly influenced by the type of scale (test for subgroup differences: Chi^2 = 15.13, df = 6 (P = 0.02), I^2 = 60.3%; Analysis 11.2).
  - We found no evidence to suggest that trial design influenced the intervention effect (test for subgroup differences: Chi^2 = 0.63, df = 1 (P = 0.43), I^2 = 0%; Analysis 11.3).
  - We found no evidence to suggest that risk of bias assessment influenced the intervention effect (test for subgroup differences: Chi^2 = 1.90, df = 1 (P = 0.17), I^2 = 47.5%; Analysis 10.1).
  - We were not able to test for subgroup differences according to duration, as all trials were of short duration, that is, less than six months (Analysis 11.4), or according to dose, as no trials reporting parent-rated general behaviour used low-dose methylphenidate (Analysis 11.5).

Cross-over trials (endpoint data)

Meta-analysis suggested a difference in effects between methylphenidate and placebo in reduced parent-rated general behaviour favouring methylphenidate (SMD −0.84, 95% CI −1.05 to −0.63; I^2 = 0%; 6 trials, 384 participants; Analysis 11.6)

- Subgroup analyses
  - The intervention effect was not influenced by the dose of methylphenidate (test for subgroup differences: Chi^2 = 0.91, df = 1 (P = 0.34), I^2 = 0%; Analysis 11.7).
  - All trials were at high risk of bias therefore we could not conduct a subgroup analysis.

Parallel-group trials and cross-over trials (endpoint data)

When combining data from parallel-group trials with endpoint data from cross-over trials our meta-analysis similarly suggested a difference in effects between methylphenidate and placebo in reduced parent-rated general behaviour favouring methylphenidate (SMD −0.56, 95% CI −0.74 to −0.39; I^2 = 59%; 16 trials, 1760 participants; Analysis 11.8).

- Subgroup analyses
  - The intervention effect varied according to trial design (test for subgroup differences: Chi^2 = 8.26, df = 1 (P = 0.004), I^2 = 87.9%; Analysis 11.8).
  - No evidence suggested a difference between subgroups of trials assessed with high, or low risk of bias (test for subgroup differences: Chi^2 = 3.33, df = 1 (P = 0.07), I^2 = 69.9%; Analysis 11.9).
  - No evidence suggested a difference between subgroups of trials with low and high risk of vested interest (test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.83), I^2 = 0%; Analysis 11.10).

Additional subgroup analyses

- Additional subgroup analysis suggested that the intervention effect varied according to raters (teacher, independent assessor and parents), with a higher intervention effect for teacher-rated trials (SMD −0.62, 95% CI −0.91 to −0.33; I^2 = 68%; 7 trials, 792 participants) compared with parent-rated trials (SMD −0.42, 95% CI −0.62 to −0.23; I^2 = 57%; 10 trials, 1376 participants), and

independent assessor-rated trials (SMD 0.21, 95% CI −0.20 to 0.61; 1 trial, 94 participants; test for subgroup differences: Chi^2 = 10.89, df = 2 (P = 0.004), I^2 = 81.6%; Analysis 12.1).

- We found no evidence that comorbidity influences the intervention effect (test for subgroup differences: Chi^2 = 0.13, df = 1 (P = 0.72), I^2 = 0%; Analysis 12.2)
- We found no evidence of a 'carry-over effect' in the cross-over trials (test for subgroup differences: Chi^2 = 2.14, df = 1 (P = 0.14), I^2 = 53.3%; Analysis 12.3).
- No data were available for subgroup analyses by age, sex or ADHD subtype.

Quality of life

We could include data on quality of life from only four parallel-group trials in our analyses. We assessed the evidence to be of very low certainty (see GRADE assessment below).

There was no difference in effects between methylphenidate versus placebo in quality of life at end of treatment (SMD 0.40, 95% CI −0.03 to 0.83; I^2= 81%; 4 trials, 608 participants; Analysis 13.1). The SMD of 0.40 for quality of life corresponds to an MD of 4.94 (95% CI −0.37 to 10.25) on the Child Health Questionnaire (CHQ; Landgraf 1998), which ranges from 0 to 100 points. This is below the MIREDIF of 7.0 points on CHQ (Rentz 2005).

- Subgroup analysis
  - All trials were at high risk of bias therefore we could not conduct a subgroup analysis.
  - It was not possible to investigate subgroup differences of vested interest bias as there were no trials reporting quality of life with low risk in all risk of bias domains.
  - There was no evidence indicating that the type of rating scale influenced the effect of the intervention (Analysis 13.1).

Additional sensitivity analysis

We tested whether a change from a random-effects model meta-analysis to a fixed-effect model meta-analysis changed our results. This was only the case in one analysis 'Socially withdrawn – decreased interaction with others (Analysis 8.3.20). The P value using a random-effects model was P = 0.0002, which changed to P = 0.10 with a fixed-effect model.

DISCUSSION

Summary of main results

We included 55 parallel-group trials and 156 cross-over trials in this review and one trial with a parallel-phase (114 participants randomised) and a cross-over phase (165 participants randomised). Altogether, these trials randomised more than 16,000 participants and were reported in 614 publications. The majority compared methylphenidate with placebo in short-term trials of less than six months' duration. The average trial duration in the 56 parallel trials was 67.1 days (range 1 to 425 days). Most were conducted in outpatient clinics in high-income countries, particularly the USA. Participants' ages ranged from 3 to 18 years across most studies; in two studies ages ranged from 3 to 21 years (Green 2011; Szobot 2008). Both boys and girls were recruited, in a ratio of 3:1.

We considered 22 trials (9 parallel-group trials and 13 cross-over trials, including the two phases in Kollins 2006 (PATS)) to have an overall assessment at low risk of bias. We considered 191 trials to have an overall assessment at high risk of bias. We considered all trials to be of high risk of bias due to the risk of deblinding described elsewhere. This raises important concerns, which are discussed after a summary of the results.

Primary outcomes

ADHD symptoms

A meta-analysis of data from parallel-group trials combined with data from the first period of cross-over trials suggests that methylphenidate may improve ADHD symptoms as reported by teachers. The SMD calculated modest improvement in ADHD symptoms on the ADHD-RS scale (DuPaul 1991a), however, we judged the certainty of the evidence to be 'very low' (see Quality of the evidence).

We found that the types of scales used influenced the intervention effect of methylphenidate. The differences between scales ranged from 0.5 SMD to 2.0 SMD. We found lower effects of methylphenidate in long-term trials compared to short-term trials. There was no difference between the subgroups of trials using placebo compared to the trials using no intervention in the control group.

Serious adverse events

Methylphenidate does not appear to be associated with an increased occurrence of serious adverse events. However, data for this outcome were only available in 42 of the 212 included trials (20%) and we judged the certainty of the evidence to be 'very low' (see Quality of the evidence).

Secondary outcomes

Adverse events considered non-serious

Amongst those in the methylphenidate-exposed groups, 538 per 1000 experienced non-serious adverse events, compared with 437 per 1000 in the control group. The most common non-serious adverse events were sleep problems and decreased appetite.

We also judged the overall certainty of the evidence for this outcome to be 'very low', and as a result, we are uncertain of the magnitude of the harmful effects. Furthermore, for methodological reasons, we used only dichotomous outcomes reflecting the number of participants affected by the event per the total number of participants. As most participants reported more than one adverse event, the actual increase in risk of non-serious adverse events may very well be higher than the 23% calculated.

General behaviour

Meta-analyses of data from only seven parallel-group trials indicated that methylphenidate was associated with an improvement in children's general behaviour, as reported by teachers. We cannot state anything for sure about the clinical importance of this SMD value. Comparable findings emerged from meta-analyses of cross-over trials (endpoint data) as reported by teachers, and from meta-analyses of nine cross-over trials (endpoint data) as rated by independent assessors. We also judged this evidence to be of 'very low' certainty (see Quality of the evidence).

Quality of life

Meta-analyses of data from only four parallel-group trials indicated that methylphenidate was associated with no improvement in children's quality of life as reported by parents and clinicians. We judged the certainty of the evidence to be 'very low' (see Quality of the evidence).

The very low certainty of the evidence, as assessed using the GRADE approach, undermines the confidence that can be placed in the magnitude of any effect. In particular, the prevalence of non-serious adverse events raises questions about the effectiveness of blinding in these trials. If blinding was broken in just 20% or 30% of participants given methylphenidate, the resulting bias might well account for the small but statistically significant findings concerning the possible benefits of methylphenidate (Coghill 2021; Storebø 2015a).

Overall completeness and applicability of evidence

This review highlights two major issues concerning the overall completeness and applicability of the evidence of the benefits and harms of methylphenidate for children with ADHD: the dearth of trials conducted in children and adolescents in low- and middle-income countries, and the lack of follow-up beyond six months. Here, we focus on the impact on the applicability of findings of decisions taken as part of this review (choice of rater for assessing change in ADHD symptoms and quality of life, choice of dose and diagnosis), together with issues relating to rating scales, diagnostic criteria, choice of comparators and adverse events.

ADHD symptoms - choice of teacher report

We chose to use teacher-rated outcomes as the primary measure for both ADHD symptoms and general behaviour, although a number of trials used or relied on parent reports. Some researchers have argued that parent evaluations of ADHD symptoms may not be as reliable as those of other raters such as teachers of pre-school children (Murray 2007), or college students (Lavigne 2012). For example, Caye 2017 suggests inconsistency in ratings between parents, and in the MTA trial (MTA 1999b), information provided by parents was not always thought to be strong (Efstratopoulou 2013). We tested the robustness of our decision by conducting subgroup analyses and found no significant differences between this score and those of other raters.

Importantly, we do not really know what a lower score on an ADHD symptom scale (like that reported in this review) means for a child's quality of life and ability to live, learn and function with other people.

Short-term versus long-term effects

Based on a subgroup analysis comparing 20 short-term trials of six months or less to a single long-term trial of more than six months, we found that the treatment effect for teacher-rated ADHD symptoms decreased over time (test for subgroup differences: P = 0.04). This was also the case for independent assessor ADHD symptoms (test for subgroup differences: P = 0.0003). However, this was not the case for parent-rated ADHD symptoms, for which we found no significant differences between short-term and long-term duration (test for subgroup differences: P = 0.60). The power was limited in all three subgroup analyses.

We did not identify any trials that examined the effects of more extended exposure on children's general behaviour. Overall, evidence on the long-term effects of methylphenidate for children and young people with ADHD is lacking, and it is possible that when used for longer periods, any beneficial effects may be diminished or offset by an increase in the risk of harm (Light 2015). Decisions to initiate and persist with treatment will need to weigh potential improvement in ADHD symptoms against adverse events, such as lack of sleep, since this may impact effects on quality of life and learning abilities. This review indicates that these important issues have not been studied sufficiently.

Quality of life

ADHD can exert a significant, negative impact on children's quality of life, broadly defined. Yet only eight of the 212 included trials measured quality of life in relation both to ADHD and life in general, and it was only possible to synthesise data from four of these trials. In each case the assessments were made by parents, teachers or independent assessors, rather than by children themselves. These external assessors observed no beneficial effects of methylphenidate on quality of life. Children might well have had different views on their own quality of life, and the failure to include child-reported ratings of quality of life is a significant limitation on the completeness of the evidence. Furthermore, observations of quality of life reported by parents, teachers and independent assessors may be subject to both systematic and random errors.

Dose – choice of moderate or high dose

For children weighing 25 kg or less, the maximum recommended dose of methylphenidate is 30 mg/day compared to 60 mg/day for children weighing more than 25 kg. After careful consideration, we renamed the high-dose group as 'moderate/high' dose because doses are not always 'high' in heavier children.

Guidelines from the National Institute for Health and Care Excellence (NICE) recommend that methylphenidate can be increased to 0.7 mg/kg per dose up to three times a day, or a total daily dose of 2.1 mg/kg/day (NICE 2018). European guidelines recommend that dosage should begin at a low level of 0.2 mg/kg per dose up to three times a day and should increase according to response, to a ceiling of 0.7 mg/kg per dose (up to three times a day), or a total daily dose of 60 mg/day. (Taylor 2004).

In the parallel-group trials included in this review, the overall daily dose ranged from 5 mg to 68 mg with a mean reported total daily dose of 34.4 mg/day or 0.78 mg/kg/day. The average dose of any type of modified- or extended-release methylphenidate was 44.2 mg, and the average dose of immediate-release methylphenidate was 23.0 mg.

However, many of the included trials were short-term trials, involving medication-naive children who consequently received lower doses. Furthermore, many of the cross-over trials used only morning and midday doses to achieve a cross-over for trial purposes, with no afternoon dose given. However, extended-release methylphenidate is designed to reduce symptoms in the late afternoon too, so the average expected daily dose would be higher.

We performed subgroup analyses to test differences in the estimate of effect based on differences in dosage. These analyses revealed

no differences between low doses (≤ 20 mg/day) compared to moderate/high doses (> 20 mg/day) of methylphenidate. Given the many adverse events that can result when this medication is used, evidence suggests that higher doses may not be needed.

Rating scales

This review included trials from several countries conducted between 1981 and 2022. Pioneers in ADHD research conduct trials in different countries, and psychometric instruments change with trends over time; this is reflected in the variety of rating scales used by investigators in the included trials. Scales based on the diagnostic criteria of the DSM and the ICD measure slightly different constructs. We found significant differences between scales measuring ADHD symptoms, but not between scales measuring general behaviour; we found fewer differences when we performed sensitivity analyses where we pooled subgroups of scales measuring the same ADHD subtype (e.g. scales measuring the inattentive subtype). All trials using subjective rating scales as proxy measures of outcomes are affected by these problems.

Diagnostic criteria

The concept of ADHD has evolved over many years from Sir George Still's "defect of moral control" in 1902, to Tredgold's 1908 "ostencephalitic behaviour disorder", and Kramer's "hyperkinetic disease of infancy" in 1932 (Lange 2010). Bradley 1937 first reported the positive effects of dextroamphetamine on hyperactive children in 1937 and methylphenidate came onto the market in 1954 (Lange 2010). "Minimal Brain Damage" and "Minimal Brain Dysfunction" were terms used to describe suspected but unproved damage or dysfunction (Lange 2010).

In 1968 the DSM-II included the term "Hyperkinetic Reaction of Childhood" (APA 1968). In this the DSM-II referred to a condition "characterized by overactivity, restlessness, distractibility, and short attention span, especially in young children; the behaviour usually diminishes by adolescence" (APA 1968, p. 50).

In the 1970s the emphasis shifted to inattention in the DSM-III, while the International Classification of Diseases (ICD-9) continued to focus on hyperactivity (WHO 1988). The DSM-III introduced the term "Attention Deficit Disorder: with and without hyperactivity (APA 1980).

The DSM-III-R then introduced the term "Attention deficit hyperactivity disorder", removing the subtypes, and focused on a single list of symptoms of inattention, hyperactivity and impulsivity, with a single cut-off score (Lange 2010).

The DSM-IV reintroduced subtypes: a predominantly inattentive type and a predominantly hyperactive-impulsive type, and they added a combined type, with both inattentive and hyperactive-impulsive symptoms (APA 1994). The DSM-IV-TR modified some descriptive text.

In 2013 the DSM-5 was introduced with several changes, including being placed in the neurodevelopmental section and taking a view across the lifespan (APA 2013). The same 18 symptoms were continued; nine inattentive and nine hyperactive-impulsive symptoms. At least six symptoms of one domain were required for a diagnosis. Subtypes were replaced with presentation specifiers; "predominantly inattentive presentation", "predominantly hyperactive-impulsive presentation" and "combined presentation". Several symptoms are required in each setting, the age of onset has been changed to require that several inattentive or hyperactive-impulsive symptoms should have been present before the age of 12 and examples are provided to the criteria to facilitate diagnosis across the lifespan (APA 2013). Comorbid diagnosis with autism is now permitted as well.

The ICD-11 (WHO 2019), has become more closely aligned with the DSM-5 (APA 2013), with the diagnosis now being called Attention Deficit Hyperactivity Disorder, based on several inattentive and hyperactive-impulsive symptoms being present before the age of 12 and causing impairment of functioning in several settings. There are also "predominantly inattentive", "predominantly hyperactive/impulsive" and "combined" presentations (WHO 2019).

The criteria of both the ICD-11 (WHO 2019), and the DSM-5 (APA 2013), encompass a broader spectrum of children with ADHD compared to the earlier criteria for hyperkinetic disorder in the ICD-10 (WHO 1992) and the DSM-IV-TR (APA 2000).

Comparators

The majority of trials in this review compared methylphenidate with placebo, and we previously highlighted the problems surrounding blinding in these trials, due to the prevalence of non-serious adverse events caused by methylphenidate. Trials that assess methylphenidate using an 'active placebo' (or 'nocebo tablets' - tablets with a placebo-like substance that causes similar adverse events as in the experimental drug arm), can strengthen double-blinding and are thus recommended (Jakobsen 2013; Jakobsen 2014; Moncrieff 2004). We identified no such trials, and so far, no substance has yet been identified that has the necessary properties to act as a nocebo in trials of stimulants. The use of nocebo tablets for all conditions is ethically uncertain, and any decision to conduct nocebo tablet-controlled trials in children would normally be deferred by the Food and Drug Administration (FDA) in the USA or the European Medicines Agency (EMA) regulators, until trials have been done safely in adults. If these show methylphenidate to be superior compared with nocebo in treating ADHD symptoms, a rationale would exist for conducting such trials in children. Laursen and colleagues have conducted a systematic review with the aim of investigating the difference between an active versus a standard placebo when these are compared with an experimental (drug) intervention (Laursen 2022). This difference in effects of the pharmaceutical intervention can be estimated by directly comparing the effect difference between the active and standard placebo intervention. Laursen 2022 included 21 trials with both an active placebo and a standard placebo control arm. The primary analysis showed no difference on patient-reported outcomes between standard and active placebo in preclinical and clinical trials. However, an analysis including only trials at low risk of bias showed a difference of SMD −0.24 (95% CI −0.34 to −0.13). This means that a drug intervention compared with an active placebo (nocebo) control group will show a SMD between −0.34 to −0.13 lower effect than when the drug is compared with standard placebo (Laursen 2020; Laursen 2022).

Adverse events

Twenty-four parallel-group trials and 61 cross-over trials excluded methylphenidate non-responders, placebo responders or participants with methylphenidate adverse events before randomisation. Such designs are often named enrichment

designs (Burnett 2021). We compared the intervention effect of methylphenidate in these trials with that in the remaining trials in subgroup analyses (Analysis 1.6; Analysis 2.5; Analysis 3.6), which found no differences in terms of the intervention effect of methylphenidate in teacher-rated and parent-rated ADHD symptoms. However, there were differences in the intervention effects of methylphenidate when we compared the independent-rated 'enrichment trials' with the remaining trials.

Some of our included trials involved participants who were not medication-naive before randomisation, which may have exaggerated the benefits of methylphenidate. They might have detected the physiological effects (for example, improved concentration or adverse events such as appetite suppression) through prior exposure to the effects of methylphenidate. To investigate this, we performed post hoc subgroup analyses and found that effects of methylphenidate were not different in trials involving medication-naive participants (> 80% of included participants were medication-naive) than in trials involving participants already familiar with methylphenidate before randomisation (< 20% of included participants were medication-naive) for teacher-rated ADHD symptoms (P = 0.44), and parent-rated ADHD symptoms (P = 0.48). One might expect the issue of prior exposure to be of greatest concern in cross-over trials. However, we found no differences between parallel-group trials and cross-over trials in teacher-rated, independent-rated or parent-rated ADHD outcomes. Consequently, we believe that prior exposure is not a major concern when the effects of methylphenidate are assessed.

Our Cochrane systematic review from 2018, which focused on the harms from methylphenidate for children and adolescents with ADHD included 260 non-randomised studies, with around 2.2 million participants (Storebø 2018b). We found that methylphenidate compared to no intervention significantly increased the risk of serious adverse events in comparative studies (RR 1.36, 95% CI, 1.17 to 1.58; 2 trials, 72,005 participants). Serious adverse events included psychotic disorders, arrhythmia, seizures, and hypertension. More than half of participants (51.2%) experienced one or more non-serious adverse event (95% CI 41.2% to 61.1%; 49 trials, 13,978 participants). These included sleep difficulties (17.9%), decreased appetite (31.1%), and abdominal pain (10.7%). Furthermore, 16.2% (95% CI 13.0 to 19.9%; 57 trials, 8340 participants) discontinued methylphenidate because of "unknown" reasons and 6.20% (95% CI 4.90 to 8.00%; 37 trials, 7142 participants) because of non-serious adverse events (Storebø 2018b).

Many claims have been made about significant increases in global rates of methylphenidate prescribing; this drug is usually prescribed for long-term use and seldom with medication-free periods. However, a recent paper reports that many children in primary care in the UK do not continue methylphenidate treatment for longer than six months (Raman 2015). Furthermore, the prevalence of ADHD diagnoses in the UK has decreased between 1998 and 2010 (Holden 2013). In the USA, however, almost 70% of children with ADHD, estimated at 6.4 million children, take medication (Visser 2014). This might mean that clinicians in the UK are more cautious about prescribing methylphenidate, while clinicians in the USA assume that evidence for the safe use of methylphenidate is sound.

Our assessment of the evidence does not deny that some patients may benefit from methylphenidate. However, despite more than 70 years of research in this field, we do not yet know how to identify those in whom the benefits outweigh the harms. Further research, possibly through individual patient data meta-analyses or other new methodologies, is needed to identify such patient characteristics. This personalised medicine approach can be used for discovering predictors and moderators for treatment response (Buitelaar 2022).

Quality of the evidence

We assessed the certainty of the evidence that contributed to all outcomes using the GRADE approach. We downgraded all primary and secondary outcomes by two levels due to the high risk of bias. This was due to risk of bias in several domains, including loss of blinding (explained below) and selective outcome reporting. We rated the risk of outcome reporting bias for adverse events to be high, as we only managed to obtain data on the proportion of participants with total serious adverse events from 43 of the 212 included trials, and on proportions of participants with total non-serious adverse events from 60 of the 212 included trials.

Except for results on serious adverse events, we additionally downgraded all other primary outcomes by one level due to inconsistency as a result of moderate statistical heterogeneity. We additionally downgraded the results on serious adverse events by two levels due to imprecision as a result of wide confidence intervals and because the acquired number of participants was below 50% of the DARIS in Trial Sequential Analysis. Finally, we additionally downgraded general behaviour and quality of life by one level each due to indirectness, considering the discrepancy in the use of rating scales and because the assessment was performed by the parents, respectively. As a result, we assessed the certainty of the evidence for each outcome to be very low, thus reflecting the uncertainty in the robustness of our estimates.

We initially rated 22 of the included trials at low risk of bias, but it is likely that these trials may, in fact, be trials at high risk of bias. This is because methylphenidate gives rise to common, easily recognisable adverse events. This can lead to loss of blinding and overestimation of benefits whilst underestimating the harms (Kjaergard 2001; Savović 2012b; Storebø 2015a; Wood 2008).

To ensure adequate blinding, it is therefore important for researchers to try to reduce the bias that may arise from this. This could include using separate assessors to measure adverse effects and efficacy, which could help maintain blinding of those assessing efficacy whilst allowing both adverse effects and efficacy to be measured. As we found no trials in which separate assessors evaluated adverse effects and efficacy and no trials that used active placebos, we cannot assess the extent of this bias. There is also increasing interest in finding a safe active placebo (a nocebo) that could mimic the adverse effects in the control group without acting as a stimulant. This too could improve blinding significantly. But the practicalities of identifying such a substance, testing the safety, and obtaining regulatory approval for its use, are likely to take many years to achieve. There are researchers working on this already, and increasing interest to find solutions to the important area of protecting blinding. The fact that the intervention effect of methylphenidate on ADHD symptoms did not differ significantly between trials at low risk of bias compared to trials at high risk of bias may be taken as an indication that deblinding has occurred

among former trials. Also, the average duration of treatment was no longer than about two months. Therefore, we can conclude little about the benefits and harms of methylphenidate used for longer than six months. (Coghill 2021; Laursen 2020; Laursen 2022).

Potential biases in the review process

The present systematic review has many strengths. We developed a protocol for this review according to instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a), and this protocol was published before we embarked on the review itself. We conducted extensive searches of relevant databases, and we requested published and unpublished data from pharmaceutical companies manufacturing methylphenidate, including Takeda Pharmaceuticals, Medice (represented in Denmark by HB Pharma), Janssen-Cilag, Novartis, Rhodes Pharmaceuticals, Ironshore Pharmaceuticals and Pfiizer. Two review authors, working independently, selected trials for inclusion and extracted data. We resolved disagreements by discussion with team members. We assessed risk of bias in all trials according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We conducted Trial Sequential Analyses to control the risk of type I errors and type II errors and to estimate how far we were from obtaining the DARIS to detect or reject a certain plausible intervention effect (CTU 2022). In the meta-analyses on non-serious adverse events, the Trial Sequential Analysis showed that observed intervention effects were not likely to be due to type I error and confirmed that sufficient data had been obtained.

Although we added new search terms to the strategy, we limited the search to the period since the previous search (2015 onwards), so it is possible that we did not capture pre-2015 records containing the new search terms. However, we believe that we are unlikely to have missed any important trials because of our supplementary searches, which included identifying studies through reference checks of relevant reviews, and contacting pharmaceutical companies.

We excluded 126 trials described in 144 reports, which assessed the effects of methylphenidate on specialised outcomes (e.g. experimental, neurocognitive or functional outcomes) in children or adolescents with ADHD (see Characteristics of excluded studies). This raises the issue of bias in our review process as we did not write to these authors asking whether they collected data on other outcomes. This potential bias, however, is not likely to change our conclusions.

Agreements and disagreements with other studies or reviews

Over the past 20 years, several published systematic reviews and narrative reviews have examined the efficacy of methylphenidate for ADHD (with or without meta-analysis). All of them described methylphenidate as being very helpful to children and adolescents with ADHD. However, they each had methodological shortcomings.

The 2015 version of this review contradicted earlier published reviews as we reported that methylphenidate may improve teacher-reported ADHD symptoms, teacher-reported general behaviour, and parent-reported quality of life among children and adolescents diagnosed with ADHD, but the low quality of the evidence meant that we could not be certain of the true magnitude of these effects (Storebø 2015a). The 2015 version of this review provoked many critical responses, published in articles, letters to editors and blogs. We responded to all of the comments; for more details please see the section "Why it is important to do this review". An overview article found 24 eligible systematic reviews and meta-analyses published after our 2015 review (Ribeiro 2021). The results from the overview also showed that the evidence was uncertain due to its low quality. Additionally, this overview highlighted the underreporting of adverse events in RCTs, and concluded that evidence supporting methylphenidate being beneficial in the treatment of children and adolescents with ADHD remains uncertain (Ribeiro 2021).

Our current updated review confirms our 2015 findings with 29 additional RCTs included (Storebø 2015a). These results differ from the large network meta-analysis by Cortese and colleagues (Cortese 2018), in which the use of methylphenidate in children and adolescents was strongly supported by the evidence where they compared the efficacy and tolerability of methylphenidate for ADHD to placebo alongside other medications (Cortese 2018). We published a letter to the editor of the Lancet in which we highlighted several problems with their review, namely, the exclusion of many relevant trials in order to fulfil statistical and methodological assumptions that they made. While the pooled comparison for clinician-rated effects of methylphenidate versus placebo for children was rated as "moderate quality of evidence", they also assessed all of the indirect comparisons as being of "low to very low quality of evidence". Indirect evidence differentiates network meta-analyses from conventional meta-analyses. Given the decreased interpretability of the indirect comparisons, there are no novel findings in this network meta-analysis (Faltinsen 2018a; Storebø 2018a). In sum, the part of the network meta-analysis that is different from our review published in 2015 (Storebø 2015a), consists of evidence of low to very low certainty.

In a response to our letter, the authors confirmed that they had excluded 65% of the trials that we had included in our 2015 review. They excluded 51 trials that had under seven days of treatment, 38 cross-over trials without pre-crossover data or a washout, 18 trials with responders to previous treatment, and 14 trials where treatment was not monotherapy (Cipriani 2018). They did this because including these trials would have been a clear violation of their published protocol and would have compromised the transitivity of the network meta-analyses (Cipriani 2018).

Catalá-López and colleagues published a large systematic review with network meta-analyses in 2017 (Catala-Lopez 2017). They included 190 RCTs with a total of 26,114 children and adolescents with ADHD, and found that stimulant monotherapy was significantly more efficacious than placebo; however, all analyses were assessed in GRADE at "low or very low certainty". The authors of the review concluded that stimulants may improve the symptoms of ADHD, but the strength of the underlying evidence remains uncertain (Catala-Lopez 2017).

Padilha and colleagues published a network meta-analysis investigating the benefits and harms of different types of ADHD medication (including methylphenidate) for children and adolescents with ADHD, including 48 trials with 4169 participants (Padilha 2018). The review found that there were beneficial effects of methylphenidate on the Clinical Global Impressions Improvement scale (CGI-I) and that methylphenidate was more effective than the non-stimulants atomoxetine and guanfacine

(Padilha 2018). There are several methodological problems with this review which we commented on in a letter to the editor (Faltinsen 2019). The issues we raised were focused on selection bias (as the authors had excluded placebo-controlled trials), the fact that authors judged the methodological quality of the included trials to be good, asserting that they were well designed, reported, and conducted, even when this clearly was not the case and that they did not include an overall assessment of certainty such as the GRADE system. They also included cross-over trials without reporting the method as to how they pooled this data with that from parallel-group trials and they failed to discuss other possible issues, such as carry-over and period effects (Faltinsen 2019). Furthermore, they did not assess the transitivity assumption in their network meta-analyses (Faltinsen 2018b; Faltinsen 2019).

A review by Cerrillo-Urbina and colleagues investigating the benefits and harms of stimulants and non-stimulants included 15 RCTs, with 4648 children or adolescents, or both, from 6 to 17 years of age diagnosed with ADHD (Cerrillo-Urbina 2018). Only four trials assessed methylphenidate, all of which were conducted before 2013. The GRADE assessment of the evidence concerning the total score of ADHD symptoms was assessed to be “moderately high quality of evidence” for both stimulant and non-stimulant medications. They downgraded the quality of evidence by one level due to a high degree of heterogeneity in the pooled results ($I^2 > 75\%$) but did not downgrade it further for risk of bias or publication bias, even though they found that there was significant publication bias for all outcomes. It is striking that this review only included four trials on methylphenidate, whereas we found 184 trials in our 2015 review covering the same period (Storebø 2015a).

A network meta-analysis by Li and colleagues found that methylphenidate was beneficial in the treatment of ADHD in children and adolescents (Li 2017). Methylphenidate was considered the second safest treatment compared to the other ADHD medications. The review included 62 trials in a meta-analysis, which included 12,930 participants. They did not make any attempt to evaluate the risk of bias or the certainty of evidence, which significantly lowers the robustness and validity of this review.

The NICE guideline recommends methylphenidate as the first-line pharmacological treatment for children over five and adolescents, "1.7.7: Offer methylphenidate (either short or long acting) as the first-line pharmacological treatment for children aged 5 years and over and young people with ADHD" (NICE 2018). The NICE guideline committee concluded that methylphenidate and lisdexamphetamine provide clinically important benefits to patients with ADHD as compared to placebo and other drugs (NICE 2018). We found several methodological problems in the NICE ADHD guidelines as we believe they conducted an erroneous assessment of the certainty of the included studies. They assessed the quality of meta-analysis to be “ high quality”, when it could be strongly argued that it was, in fact, “low quality”. In their assessment of the effect of methylphenidate, they included only 16 trials that focused solely on immediate and osmotic-release methylphenidate in children and adolescents. We included 185 trials (175 of which were placebo-controlled) in our 2015 review (Storebø 2015a). NICE did not adjust for multiple comparisons and did not discuss the concern that all the data arose from short-term follow-up (NICE 2018).

The American Academy of Pediatrics guideline was updated in 2019 based on patients’ age (Wolraich 2019). With regard to preschool children, the guideline recommends evidence-based behavioural interventions (behavioural parent training or behavioural classroom interventions, or both) as the first-choice treatment. Methylphenidate may be considered when a child has moderate to severe problems with functioning and if the behavioural treatment does not provide the necessary improvements. With regard to school children, the guideline strongly recommends pharmaceutical treatments (FDA-approved medications for ADHD) together with behavioural interventions. Regarding adolescents, the guideline strongly recommends pharmaceutical treatment and if possible, evidence-based behavioural interventions. The guideline states that there is a strong effect observed in the trials investigating the effects of stimulant medications (Wolraich 2019). For the comparison of pharmacological treatments versus placebo or usual care, the review only identified eight articles representing seven studies. The review concluded that there was limited additional evidence concerning FDA-approved ADHD medications compared with placebo or usual care across all outcomes in this updated systematic evidence review. The conclusions regarding methylphenidate, therefore, seem overly positive. The risk of harm is considered as low and the benefits, in general, are described as outweighing the risks.

Our current updated review is in line with two recent Cochrane systematic reviews of methylphenidate in adults. These two reviews found low- or very low-certainty evidence that methylphenidate, compared with placebo, improved ADHD symptoms (Boesen 2022; Candido 2021).

AUTHORS' CONCLUSIONS

Implications for practice

Methylphenidate may improve attention deficit hyperactivity disorder (ADHD) symptoms and general behaviour in children and adolescents with ADHD aged 18 years and younger. We rated the evidence to be of very low certainty and, as a result, we cannot be certain about the magnitude of the effects from the meta-analyses. The evidence is limited by the serious risk of bias in the included trials, underreporting of relevant outcome data, and a high level of statistical variation between the results of the trials. There is also very low-certainty evidence that methylphenidate causes numerous adverse events. The risk of serious adverse events seems low, but data were only available from 43 of the 212 included trials. It is also problematic that only 93 of the 212 included trials reported on specific and overall non-serious adverse events. Accordingly, we cannot rule out the possibility that non-serious harms are more prevalent than reported in our review.

If methylphenidate treatment is considered, clinicians might need to use it for short periods, with careful monitoring of both benefits and harms, and cease its use if no evidence of clear improvement of symptoms is noted, or if harmful effects appear. A problem is that clinicians very often rely on their assessment of methylphenidate in their clinical evaluation. Arguments like "I know that this medication helps" can be problematic when they are based on anecdotal evidence and case reports. A new review found that clinicians had difficulties in assessing benefits or harms following treatment, with inaccuracies in both directions (Hoffmann 2017). Clinicians mostly underestimated instead of overestimated harms and overestimated rather than underestimated benefits. Inaccurate perceptions of the benefits

and harms of treatments are likely to result in uncertain clinical management choices (Hoffmann 2017).

Implications for research

This review highlights the urgent need for long-term, high-quality, and large randomised clinical trials (RCTs), at low risk of bias, to investigate the benefits and harms of methylphenidate treatment versus placebo in children and adolescents with ADHD. Such trials ought to be designed according to the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Chan 2013), and reported in keeping with the CONSORT (Consolidated Standards of Reporting Trials) standards Moher 2010). Pre-published protocols could help reduce the inconsistent measurement of benefits and harms caused by the use of many different rating scales and by lack of assessment of adverse events.

The important issue of protecting blinding of these trials needs to be addressed urgently. Immediate measures could be implemented to improve blinding. Having independent, blinded assessors monitor adverse effects, whilst separate, independent blinded assessors measure efficacy, is likely to reduce the risk of unblinding due to adverse effects. Active placebos need to be sought and are likely to be important in the future, but their development is still at the very early stages. Research in this field should be strongly supported, but it is likely to take many years before such substances can be used safely and ethically in research with children and adolescents. The prevalent use of cross-over trials needs to be reconsidered as they usually only provide short-term interventions, which can limit the assessment of benefits and harms. However, we were not able to identify major differences when comparing parallel-group trials with cross-over trials.

Future trials ought to publish depersonalised individual participant data and should report all outcomes, including adverse events, to ensure that future systematic reviews and meta-analyses can access and use individual participant data. Only through meta-analyses will we be able to assess differences between intervention effects according to age, sex, comorbidity, ADHD subtype, and dose. Reviews show that many different rating scales are used for children with ADHD. Consistent use of well-validated scales is needed, as is a country-wide adverse events reporting system, such as the Food and Drug Administration, to increase awareness of adverse events. In addition, the findings in this review clearly show the urgent need for large RCTs to investigate the efficacy of non-pharmacological treatments. As with RCTs, systematic reviews of such trials assess average effects in groups of individuals. Such average effects may comprise strong benefits for a single participant or a few participants and no effect or negative effects for others. Despite more than 50 years of research in this field, we have no knowledge on how to identify patients who may obtain more benefits than harms. Individual patient data meta-analyses are needed to identify such patient characteristics. Therefore, it would be extremely helpful for review authors to gain full access to anonymised individual participant data for inclusion in meta-analyses examining these data (Gluud 2015). Patient subgroups may benefit from intervention if those with reduced rates of adverse events can be identified. This personalised medicine approach can be used for discovering predictors and moderators for treatment response. The use of biomarkers for both more precise diagnoses and for more precise assessment of treatment response is necessary in future RCTs. The use of enrichment designs will improve statistical power for biomarker analyses (Buitelaar 2022).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abikoff 2009

Study characteristics	
Methods	8-week double-blind, randomised, placebo-controlled, cross-over trial with 2 interventions • OROS-MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 19 (15 boys, 4 girls) Number of participants followed up: 19 Number of withdrawals: none Diagnosis of ADHD: DSM-IV (combined (42%), hyperactive-impulsive (0%), inattentive (58%)) Age: mean 10.05 years (SD 1.62, range 8-13) IQ: mean 107.1 (SD 14.3) Methylphenidate-naive: 100% Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: ODD (26.3%), anxiety disorder (10.5%), dysthymic disorder (5.3%), CD (5.3%) Comedication: not stated Additional sociodemographics: none **Inclusion criteria** • DSM-IV criteria for ADHD (combined or inattentive type) • Meeting dimensional criteria for ADHD symptom severity on CTRS-R, long form, defined as a score ≥ 1.5 SD above age and sex norms

Abikoff 2009 *(Continued)*

- Impaired OTMP, defined by a mean total score ≥ 1 SD below the norm on the Children's Organizational Skills Scale - Parent, and the Children's Organizational Skills Scale - Teacher
- Score ≥ 80 on the WASI-II

Exclusion criteria

- Diagnosis of autism, major depression, substance abuse, OCD, PTSD, panic disorder, tic disorders, significant suicidality
- Lifetime history of psychosis or mania
- Learning disability according to a school individualised educational plan
- Taking other CNS medications

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of OROS-MPH and placebo Mean MPH dosage: 48.3 mg (range 18 ± 54 mg); weight-based final OROS-MPH dose was 1.3 mg/kg Administration schedule: not stated Duration of each medication condition: 4 weeks: 2 weeks titration and 2 weeks optimal dose Washout before trial initiation: all were medication-naive Medication-free period between interventions: 2 days Titration period: 2 weeks after randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SNAP, 4th Edition, parent-rated at baseline, after weeks 1 and 2 (during titration) and at end of treatment (4 weeks) • SNAP, 4th Edition, teacher-rated at baseline, after weeks 1 and 2 (during titration) and at end of treatment (4 weeks)
Notes	Sample calculation: no Ethics approval: trial protocol was reviewed and approved by the University's institutional review board **Comment from trial authors** • The 4 weeks of OROS-MPH treatment was relatively brief, and post-treatment measures were obtained after children had been taking their optimal titration dose for 2 weeks **Key conclusion of trial authors** • OROS-MPH reduced children's OTMP deficits, and these improvements were associated with improvement in ADHD symptoms. Some children remained impaired in OTMP even after effective stimulant treatment for ADHD symptoms. These youngsters may require other treatments that target OTMP deficits Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced adverse events while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: a grant from Ortho-McNeil Janssen Scientific Affairs to Dr. Abikoff Email correspondence with trial authors: December 2013. No supplemental information provided

Risk of bias

Abikoff 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-treatment scores for all 19 trial children were obtained from parents. Because 1 child's treatment was delayed and ran beyond the end of the school year, teacher data on 18 youngsters were analysed Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol published

Ahmann 1993

Study characteristics	
Methods	4-week double-blind, placebo-controlled, cross-over trial, in which participants were randomly assigned to • MPH (low and high doses; Ritalin) • placebo
Participants	Number of participants screened: not stated Number of participants included: 234 Number of participants followed up: 206 Number of withdrawals: not stated, but it is described in the text that 4 children experienced severe AEs while taking MPH (Ritalin) and could not complete the protocol **Regarding the 206 participants** Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: 5-15 years IQ: > 70 Sex: 161 boys, 45 girls MPH-naive: not stated Ethnicity: not stated

Ahmann 1993 *(Continued)*

Country: USA

Setting: outpatient clinic

Comorbidity: not stated

Comedication: not stated

Additional sociodemographics: none

Inclusion criteria

- Informed consent from parent
- DSM-III-R diagnosis of ADHD

In addition, ≥ 3 of the following criteria had to be met.

- Attention score on the ADD-H Comprehensive Teacher Rating Scale: ≤ 25th percentile
- Hyperactivity score on the ADD-H Comprehensive Teacher Rating Scale: ≤ 25th percentile
- Inattention/passivity score on CTRS (28 items): ≥ 2 SD above the mean
- Hyperactivity Index on CTRS (28 items): ≥ 2 SD above the mean
- Hyperactivity Index on CPRS (48 items): ≥ 2 SD above the mean

Children were divided into responders and non-responders based on the following criteria.

- Parent reported 1 SD improvement on the Hyperactivity Index of the CPRS (48 items) or gave a positive narrative comment, and
- teacher reported ≥ 2 of the following
  - 10 percentile improvement in Attention Score on the ADD-H Comprehensive Teacher Rating Scale
  - 10 percentile improvement in Hyperactivity Score on the ADD-H Comprehensive Teacher Rating Scale
  - 1 SD improvement on the Inattention/Passivity Scale of CTRS (28 items)
  - 1 SD improvement on the Hyperactivity Index of CPRS (48 items)
  - Positive narrative comment

Exclusion criteria

- Children with a history of seizures, mental disability, Tourette's syndrome or other significant neurological history were not eligible for the trial

Interventions	Participants were randomly assigned to different orders of LD-MPH (0.3 mg/kg), HD-MPH (0.5 mg/kg) or placebo Administration schedule: 3 times a day Duration of each medication condition: 7 consecutive days for both doses Washout before trial initiation: not stated Titration period: no Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADD-H Comprehensive Teacher Rating Scale (24 items): rated each week • CTRS (28 items): rated each week • CPRS (48 items): rated each week **Non-serious AEs** • Barkley's Side Effect Rating Scale: parent-rated, weekly

Ahmann 1993 *(Continued)*

Notes	Sample calculation: no Ethics approval: yes; protocol was approved by the Institutional Review Board at the Marshfield Medical Center **Key conclusion of trial authors** • The Barkley Side Effect Rating Scale proved to be clinically effective in tracking MPH side effects and should be incorporated into the routine evaluation and monitoring of ADHD patients for whom stimulants are prescribed **Comment from review authors** • Trial divided participants into 2 groups: responders and non-responders. 147 children were determined to be MPH responders. Both responders and non-responders (n = 206) were included in the analysis of AEs Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes, (n = 4) Funding source: Marshfield Clinic grants Email correspondence with trial authors: not able to find trial authors' contact information; therefore not able to obtain supplemental information regarding trial design and data on ADD-H Comprehensive Teacher Rating Scale, CTRS, CPRS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, but not described how and/or by whom
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial, identical appearing pills
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial, identical appearing pills
Incomplete outcome data (attrition bias) All outcomes	Low risk	206 had sufficient data for analyses Selection bias: participants were divided into responders and non-responders. However, data from this article pertain to AEs only and include both groups
Selective reporting (reporting bias)	Unclear risk	Not able to obtain protocol or other information

Arnold 2004

Study characteristics

Arnold 2004 *(Continued)*

Methods	7-centre USA trial consisting of a 6-week, open-label, dose-titration phase (Part A) and a 2-week, double-blind, randomised, parallel-group, placebo-controlled withdrawal trial (Part B) with 2 arms • d-MPH • placebo
Participants	Number of patients screened: 116 **Part A** Number of participants included: 89 (72 boys, 17 girls) Number of participants followed up: 76 Number of withdrawals: 13 DSM-IV diagnosis of ADHD (combined 80%) Age range: 6-16 years IQ: not stated MPH-naive: 71.9% Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Additional sociodemographics: none **Part B** Number of participants included: 75 (61 boys, 14 girls) Number followed up in each arm: MPH 34, placebo 39 Number of withdrawals in each arm: MPH 1, placebo 1 DSM-IV diagnosis of ADHD (combined (80%), hyperactive-impulsive (0%), inattentive (20%)) Age range: 6-16 years IQ: > 70 (mean not stated) MPH-naive (MPH 82.9%, placebo 62.5%) Ethnicity: white (MPH 80%, placebo 75%), African American (MPH 14.3%, placebo 12.5%), Hispanic (MPH 5.7%, placebo 12.5%) Country: USA Setting: outpatient clinic and hospital Comorbidity: not stated Comedication: antihistamines, non-steroidal anti-inflammatory agents, multi-vitamins, nasal decongestants or other analgesics or antipyretics (MPH 34.3%, placebo 40.0%) Additional sociodemographics: none No significant differences in baseline demographics were noted between the 2 groups. Thus, slightly more treatment-naive participants were receiving d-MPH than placebo

Arnold 2004 *(Continued)*

Inclusion criteria

- 6-17 years of age
- Enrolled in school
- DSM-IV diagnosis of ADHD, any subtype
- Within 30% of normal body weight
- Able to participate for the full 8 weeks

Exclusion criteria

- History or evidence of cardiovascular, renal, respiratory (other than asthma/allergy), endocrine or immune system disease
- History of substance abuse
- Hypersensitivity to d,l-MPH or other stimulants
- Treatment with any investigational drug within 30 days of screening
- Other significant CNS disorders
- Treatment with antidepressants, neuroleptics/antipsychotics, mood stabilisers, anticonvulsants, beta-blockers, alpha-2-agonists, other stimulants, thyroid medications, long-term oral steroids or sedatives/hypnotics
- Concurrent treatment with other psychoactive drug

Interventions	**Part B** Participants were randomly assigned to d-MPH at optimised dose or placebo Number randomised to each group: MPH 35, placebo 40 Mean MPH dosage: 68.6% of d-MPH continuers and 79.5% of placebo participants were receiving 20 mg at end of Part B, mean (SD) not stated Administration schedule: 10 mg twice daily. Time points 7 am to 8 am and 11:30 am to 12 pm Duration of intervention: 2 weeks Titration period: 6 weeks, initiated before randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms (Part B)** • SNAP, teacher-rated at baseline and at end of treatment • SNAP, parent-rated at baseline and at end of treatment, 3 and 6 h post-dose **Non-serious AEs (Parts A and B)** • Monitoring of AEs and changes from baseline in vital signs (pulse and BP), physical examination and clinical laboratory parameters throughout the trial

Notes	**Comments from trial authors**
	
	• Limitations
	  ○ Study design: treatment effects in such trials may be larger than those seen in unselected populations because, in the randomised withdrawal phase, responders were pre-selected from the open-label titration phase to the drug phase.
	  ○ Another possible limitation is the duration of discontinuation (2 weeks)
	
	Key conclusion of trial authors
	
	• d-MPH is safe, tolerable and effective, with a 6-hour duration of effect suggested by significant differences from placebo at 6 hours on double-blind discontinuation

Arnold 2004 *(Continued)*

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes

Any withdrawals due to AEs: no

Funding source: trial was supported by the Celgene Corporation

Email correspondence with trial authors: October 2013. Supplemental information regarding additional information was received. However, trial authors advised us to contact the sponsoring drug company for additional information. This process has been difficult, and no further communication was attempted to request additional information. (see Storebø 2015a)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was central, irrespective of whether the drug was pre-packaged and pre-randomised, or if it was bottled and labelled by an unblinded dispenser who had no contact with participants and kept the other staff blind
Allocation concealment (selection bias)	Low risk	Randomisation was central. "In all industry studies I have been involved with, either the drug was pre-packaged and pre-randomized or it was bottled and labeled by an unblinded dispenser who had no contact with patients and kept the other staff blind"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. In Part B, participants/guardians and medical personnel were blinded to the drug. Also, d-MPH was available in tablets, each identical in appearance to a matching placebo. trial drug (or placebo) was dispensed in bottles containing a weekly supply, labelled for use at “Home” and “School”, with the strength designated “A,” “B” or “C”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. In Part B, participants/guardians and medical personnel were blinded to the drug
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT sample was used in analysis of efficacy parameters: participants who received d-MPH and had a Part B baseline efficacy evaluation and ≥ 1 post-baseline assessment Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol published

Barkley 1989b

Study characteristics

Methods	Triple-blind, randomised, cross-over trial with 3 interventions • placebo • LD-MPH (0.30 mg/kg) • HD-MPH (0.5 mg/kg)
Participants	Number of participants screened: not stated Number of participants included: 83 (71 boys, 12 girls)

Barkley 1989b *(Continued)*

	Number of participants followed up: 80 Number of withdrawals: 3 Diagnosis of ADHD: DSM-III-R (subtype distribution not stated) Age: mean 8.2 years (range 5-13) IQ: mean 105.1 MPH-naive: 85% Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Additional sociodemographics: mothers, married (n = 48), divorced (n = 13), unmarried or widowed (n = 13) **Inclusion criteria** • 6-13 years of age • ADHD according to DSM-III-R • Complaints from teacher, parents or both, of significant inattention, overactivity and impulsivity • Appearance of symptoms before 7 years of age • Symptoms for 12 months • Above the 93rd percentile of the hyperactivity scale on parent or teacher report forms of the CBC) • Simple language IQ score > 80 on the Peabody Picture Vocabulary Test - Revised **Exclusion criteria** • Gross sensory or motor deficits • Tic disorders, Tourette's syndrome or an immediate family history of such • Seizures • Gross brain damage • Autism • Thought disturbance or schizoid, schizotypal or frank psychotic features • Significant cardiac problems or high BP • Excessive levels of anxiety or fear • Levels of depression that exceed or equal the problems of ADHD • Most participants (n = 74) were subdivided into children placed 2 SD above the normal mean on the Aggressive scale of the parent form of the CBCL (T score > 70) and those who did not have ≥ 2 SD above the normal mean to form aggressive (n = 37) and non-aggressive subgroups (n = 37). Groups did not differ in age, years of education, maternal age or maternal years of education
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of 0.3 mg/kg MPH, 0.5 mg/kg MPH and placebo Mean MPH dosage: not stated Administration schedule: morning and noon Duration of each medication condition: 7-10 days Washout before trial initiation: not stated

Barkley 1989b *(Continued)*

	Medication-free period between interventions: not stated Titration period: none Treatment compliance: unused capsules returned to the clinic each week for adherence check No family was discontinued from the trial because of non-compliance with the drug regimen, defined as more than 1 day of failure to take medication, or 2 missed capsules/week
Outcomes	**ADHD symptoms** • CPRS - Revised: parent-rated at the end of each drug condition • CTRS - Revised: teacher-rated at the end of each drug condition • Child Attention Profile: teacher-rated at the end of each drug condition **General behaviour** • Home Situations Questionnaire: parent-rated at the end of each drug condition (7 to 10 days) • School Situations Questionnaire: teacher-rated at the end of each drug condition (7 to 10 days) **Adverse effects** • Barkley Side Effects Rating Scale: parent- and teacher-rated at the end of each drug condition (7 to 10 days)

Notes	Sample calculation: not stated
	
	Ethics approval: trial was approved by the Human Subjects Committee at the medical centre
	
	Comments from trial authors
	
	• Limitations
	  ◦ Rates of side effects were based on a large sample that was screened before admission to the drug trial
	  ◦ Low doses of medication to detect side effects
	  ◦ Use of rating scale rather than direct behavioural observation
	
	Key conclusions of trial authors
	
	• In their drug responding, aggressive and non-aggressive participants were quite similar. The few exceptions involved measures of conduct, on which aggressive participants were initially rated as more extreme and subsequently showed a greater degree of improvement from medication than non-aggressive participants
	• With this dose range, stimulants result in few/mild side effects; systematic monitoring of side effects suggested before/during clinical trials of stimulants
	
	Comment from review authors
	
	• The Barkley Side Effects Rating Scale was labelled generically as a “behaviour questionnaire” to disguise its intended use as a monitoring tool for potential side effects. The purpose was to prevent prejudice on the part of respondents, who might potentially distort their ratings if they knew these could be side effects of the medication
	
	Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no
	
	Any withdrawals due to AEs: yes; 3. One child discontinued because of nervous facial tics, headache and dizziness; a second as the result of excessive thinking and disjointed thinking (during HD-MPH); and a third because of headache, dizziness and increased hyperactivity
	
	Funding source: trial was internally funded by the medical school

Barkley 1989b *(Continued)*

	Email correspondence with trial authors: July 2013. We obtained additional information regarding funding and ethics approval. Unfortunately, it was not possible to receive from the trial authors supplemental data on ADHD symptoms and general behaviour

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial used a completely counterbalanced design, with participants randomly assigned in relatively equal numbers to 1-6 possible drug conditions
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both medication and placebo were crushed and placed within orange opaque gelatin capsules to disguise distinctive differences in flavour between medication and placebo and dose differences across conditions. Children and their parents and teachers, as well as the research assistant evaluating the children, were blinded to medication conditions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Children and their parents and teachers, as well as the research assistant evaluating the children, were blinded to medication conditions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on incomplete outcome data Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Barkley 1991

Study characteristics

Methods	Triple-blind, placebo-controlled, cross-over design with participants randomly assigned to the following conditions • 3 doses of MPH (5 mg, 10 mg and 15 mg twice/d) • placebo Each intervention period lasted 1 week
Participants	Number of participants screened: not stated Number of participants included: 40 Number of participants followed up: 40 (36 boys, 4 girls) Number of withdrawals: 0 Diagnosis of ADD: DSM-III-R (with hyperactivity: 58%; without hyperactivity: 42%) Age: mean 8.6 years (range 6-12) IQ: 103.5 MPH-naive: not stated

Barkley 1991 *(Continued)*

Ethnicity: not stated

Country: USA

Setting: outpatient clinic

Comorbidity: borderline and low internalising symptoms. No others stated

Comedication: not stated

Other sociodemographics: 54.8 on Hollingheads Two Factor Index

Participants were divided into different categories :

- Based on type of ADD
  - ADD with hyperactivity (n = 2)
  - ADD without hyperactivity (n = 17)
- Based on severity of internalising symptoms by maternal ratings on the Internalising scale of the CBCL
  - High internalising group (> 70) (n = 12)
  - Borderline internalising group (65-70) (n = 17)
  - Low internalising group (< 65) (n = 11)

Inclusion criteria

- Diagnosis of ADD(H) according to DSM-III-R
- IQ estimate of ≥ 80 on a standardised IQ test given within the past year or on the WISC-R, given at trial screening
- Was the biological child of both current parents or had been adopted by them shortly after birth (within the first year)
- No evidence of deafness, blindness, severe language delay, cerebral palsy, epilepsy, autism or psychosis, as established through medical history, parental interview and child play diagnostic interview

Additional criteria for children with combined ADHD

- Teacher complaints of short attention span, impulsivity and overactivity as revealed by parent reports
- Duration of 6 months for these problems
- Age of onset of these problems before 7 years
- Score > 93rd percentile on the Inattention and Overactivity scales of the Child Attention Problems Rating Scale
- No history of treatment with stimulant drugs, or, if such a history, physician consent to stop taking medication for 48 h before evaluation in the trial

Additional criteria for children with ADD-H

- Same criteria as for children with combined ADHD, with the exception of the 4th criterion. Instead, score > 93rd percentile on the Inattention scale of the Child Attention Problems Rating Scale, but a score < 84th percentile on the Overactivity scale of the Child Attention Problems Rating Scale

Differences regarding the 2 ADHD groups

- They differed significantly on child's IQ score, with the ADD without hyperactivity group scoring significantly lower than the ADD with hyperactivity group. Child IQ was correlated with all of the dependent measures (measures that we used in this review were not affected by differences in IQ)

Exclusion criteria

- History of tics or Tourette's syndrome, given the controversy over whether stimulants may create or exacerbate these conditions
- Those with a history of cardiac surgery, high BP or cerebral vascular accident, given the known cardiac pressor effects of stimulants
- Those with a history of adverse reactions to a stimulant

Barkley 1991 *(Continued)*

Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of MPH (5 mg, 10 mg and 15 mg) and placebo Administration schedule: twice/d, morning and noon Duration of each medication condition: 1 week Washout before trial initiation: no Titration period: none, but highest dose was never given unless preceded by moderate dose Compliance: children were permitted to miss 1 day of medication over 7 days and still remain in the trial. No families were removed from this trial because of non-compliance as defined in this way

Outcomes	**ADHD symptoms**
	
	• Parent-rated
	  ○ Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS): rated at the end of each drug condition order
	  ○ Home Situations Questionnaire: number of problem settings and mean severity of problems, rated at the end of each drug condition order
	• Teacher-rated (teachers completed questionnaires at the conclusion of each medication condition)
	  ○ Self Control Rating Scale
	  ○ Child Attention Problems
	  ○ School Situations Questionnaire: number of problem settings and mean severity of problems
	
	Non-serious AEs
	
	• Home Side Effects Rating Scale: parent-rated at the end of each drug condition order
	• School Side Effects Rating Scale: parent-rated at the end of each drug condition order

Notes	Sample calculation: no Ethics approval: trial was approved by the Institutional Review Board at the medical centre **Key conclusion of trial authors** • This trial indicates that ADHD, inattentive type, and ADHD, combined type, do not show dramatic differences in their manner of responding to MPH across 3 dose levels (5 mg, 10 mg and 15 mg), with both groups displaying generally positive drug responses. However, more children with ADHD, inattentive type, had minimal or no response or did best on the low dose of medication, whereas the vast majority of children with ADHD, combined type, showed a positive response, primarily to moderate to high doses of MPH Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; excluded those with history of adverse reactions, but included both naive and prior users of antipsychotics Any withdrawals due to AEs: no Funding source: NIMH Email correspondence with trial author: 18 January 2013. Dr. Barkley informed us that data from the trial on side effects, for example, are no longer available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned to 1 of 6 possible drug conditions

Barkley 1991 *(Continued)*

Allocation concealment (selection bias)	Low risk	Hospital pharmacy prepared placebo (lactose powder) and MPH by crushing and placing them into 6 orange opaque gelatin capsules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	Protocol not available

Barkley 2000

Study characteristics	
Methods	Double-blind, placebo-controlled, within-participant, cross-over trial with 3 interventions • MPH: 5 mg, 10 mg, twice/d • amphetamine and dextroamphetamine mixed salts (Adderall): 5 mg, 10 mg, twice/d • placebo Phases: 5, but high doses of each stimulant always followed lower dose of the same stimulant
Participants	Number of participants screened: 46 Number of participants included: 38 Number of participants followed up: 35 (30 boys, 5 girls) Number of withdrawals: 2. One was a post hoc exclusion Diagnosis of ADHD: DSM-IV (subtype not described) Age: mean 14 years (range 12-17) IQ: mean 103.9 (range 80-141) MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none

Barkley 2000 *(Continued)*

	Inclusion criteria • Adolescents, 12-17 years of age, with a DSM-IV diagnosis of ADHD **Exclusion criteria** • History of motor or vocal tics, Tourette's syndrome, cardiac surgery, high BP, cerebral vascular accident, hyperthyroidism or pregnancy or lactation • Adverse reactions to stimulant medications
Interventions	Participants were randomly assigned to 1 of 4 possible drug condition orders of 5 mg MPH followed by 10 mg MPH and 5 mg MAS (Adderall) followed by 10 mg Adderall and placebo • 5 mg, 10 mg MPH; placebo; 5 mg, 10 mg MAS (Adderall) • 5 mg, 10 mg MAS (Adderall); placebo; 5 mg, 10 mg MPH • Placebo; 5 mg, 10 mg MPH; 5 mg, 10 mg MAS (Adderall) • 5 mg, 10 mg MAS (Adderall); 5 mg, 10 mg MPH; placebo Mean MPH dosage: LD-MPH 10 mg/d; HD-MPH 20 mg/d Administration schedule: morning and midday Duration of each medication condition: 1 week Washout before trial initiation: none Medication-free period between interventions: none Titration period: none, although 5 mg dose was given before 10 mg, initiated after randomisation Treatment compliance: parents were required to return all unused capsules, but nothing further was said about this
Outcomes	**ADHD symptoms** • Parent- and teacher-rated ADHD/ODD Rating Scales: completed over previous treatment week **Non-serious AEs** • Barkley Side Effects Rating Scale: completed by adolescent, parent and teacher at the end of each treatment week
Notes	Sample calculation: not described Ethics approval: yes **Comments from trial authors** • Teens are more independent of their parents than are younger children, spending more time outside parental supervision. This raises serious questions about the sensitivity of parental reports to drug and dose response • Limitations: most noteworthy was the poor co-operation of teachers. As a consequence, the statistical power of the trial to detect drug effects on these measures, often the most sensitive to stimulant drug effects, was greatly reduced **Key conclusion of trial authors** • In conclusion, the present trial suggested that both MAS and MPH may have been clinically effective in the management of teens with ADHD when non-blinded, global clinical judgements of improvement, which were based on multiple sources of information, were used. Even so, these positive drug responses could not be documented at the group level of statistical analysis by using more specific and systematic ratings by parents and teachers. Clinicians undertaking stimulant trials in such con-

Barkley 2000 *(Continued)*

texts need to be aware of the many challenges to the internal validity of these procedures that are likely to occur in drug trials with teens

Comment from review authors

- To exclude participants with low IQ was a post hoc decision

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; excluded patients who had a history of AEs to stimulants

Any withdrawals due to AEs: no

Funding source: University of Massachusetts Medical School

Email correspondence with trial authors: January 2014. We received additional information (see Krogh 2014a [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Email correspondence with trial author: “Randomization was done by me as best as I can recall” (Krogh 2014a [pers comm])
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Opaque gelatin capsules were prepared by the pharmacist
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis reported 11/46 teens LTFU, 15 parents LTFU, 33 English teachers and 31 Maths teachers LTFU Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Email correspondence with trial author: "All planned analyses were done and all measures we collected as treatment endpoints were analyzed" (Krogh 2014a [pers comm])

Barragán 2017

Study characteristics

Methods	A 12-month randomised, unblinded parallel-trial with 3 arms: • omega 3/6 • LA-MPH • omega 3/6 and LA-MPH
Participants	Number of participants screened: 107 Number of participants included: 60 for the 2 relevant groups (90 in all (60 boys, 30 girls))

Barragán 2017 *(Continued)*

	Number of participants followed-up: 49 for relevant groups (69 in all) Number of withdrawals: 11 from omega group and combined group (10 more in MPH group) Diagnosis of ADHD: DSM-IV-TR (51 (57%) combined type, 7 (8%) hyperactive-impulsive type and 32 (36%) inattentive type) Age: mean 8.27 years (SD 1.74; range 6-12) IQ: not stated MPH-naive: 100% Ethnicity: not stated Country: Mexico Setting: outpatient Comorbidity: some were exclusion criteria Comedication: medication for chronic conditions specified as exclusion criteria Additional sociodemographics: none **Inclusion criteria** • 6-12 years • Newly diagnosed with ADHD of any subtype **Exclusion criteria** • Neurologic disorders (epilepsy, brain damage, mental disability) • Autism or pervasive developmental disorders • Known hypersensitivity to components of omega-3/6 • Previous pharmacological treatment for ADHD • Ongoing chronic conditions (e.g. asthma) • Medication for chronic conditions • Children not receiving school assistance
Interventions	30 participants were randomly assigned to: 3 different groups, omega 3/6 twice daily, MPH or a combination Mean medication dosage: combined group: baseline: 0.49 mg/kg, month 1: 0.79 mg/kg, month 3: 0.8 mg/kg Administration schedule: not stated Duration of each medication condition: 12 months Washout before trial initiation: not stated Titration period: during the first 4 weeks Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Spanish version of the ADHD-RS, parent-rated at baseline, 1 month, 3 months, 6 months, and 12 months **Non-serious AEs** • Evaluated at each clinic appointment

Barragán 2017 *(Continued)*

Notes

Sample calculation: no

Ethics approval: "[…] the trial was approved by the local ethical review board."

Comments from trial authors

- Strengths of the present trial:
  - the 3-arm design
  - the 12-month duration
  - the high retention rate
- Limitations of the trial:
  - a possible lack of statistical power as a result of the exploratory nature of the trial
  - no formal sample-size calculation resulting in a small sample size, especially for a non-inferiority trial
  - the non-blinded trial design
  - the lack of a placebo arm
  - the high baseline disease severity

Key conclusion of trial authors

- In conclusion, the tested combination of omega-3/6 fatty acids was slightly less effective than MPH in this unblinded RCT
- While no statistical superiority of the combination of MPH and omega-3/6 fatty acids compared with MPH was found in terms of efficacy, the combination appeared to have some benefits over MPH monotherapy in terms of MPH dosing and tolerability, which may in turn lead to improvements in compliance.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no

Any withdrawals due to AEs: yes, 2 (6 more in the MPH group)

Funding source: Vifor Pharma

Email correspondence with trial authors:contacted through personal email in August and October 2021, for information regarding participant data, but no answer received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised (unblinded) by means of an aleatorised table to receive MPH, omega-3/6, or combination therapy with MPH + omega-3/6.
Allocation concealment (selection bias)	High risk	None
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	The main analyses were ITT analyses with LOCF for patients who dropped out Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, withdrawals due to "no efficacy"

Barragán 2017 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No trial protocol available

Bedard 2008

Study characteristics	
Methods	4-day randomised, double-blind, placebo-controlled, cross-over trial with 2 interventions in 2 groups • MPH • placebo and • ADHD with anxiety • ADHD without anxiety
Participants	Number of participants screened: not stated Number of participants included: 130 Number of participants followed up: 130 (110 boys, 20 girls) Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (63%), hyperactive-impulsive (30%), inattentive (6%)) Age: mean 9 years (SD 1.46, range 6-12) IQ: mean 104.11 MPH-naive: 70% Ethnicity: white (90%) Country: Canada Setting: outpatient clinic Comorbidity: specific learning disorder (34%), CD (24%), ODD (26%), generalised anxiety disorder (17%), separation anxiety disorder (11%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-IV diagnosis via clinical diagnostic assessment: confirmed by PICS and TTI **Exclusion criteria** • IQ < 80 • Evidence of neurological dysfunction, poor physical health or uncorrected sensory impairments • History of psychosis based on physician enquiry • Primary language spoken at home not English
Interventions	Participants were randomly assigned to 1 of 11 possible drug condition orders of MPH and placebo. Children weighing < 25 kg received 5 mg, 10 mg and 15 mg of MPH; children weighing ≥ 25 kg received 10 mg, 15 mg and 20 mg of MPH

Bedard 2008 *(Continued)*

	Mean MPH dosage: 0.28 mg/kg, 0.45 mg/kg, 0.61 mg/kg Administration schedule: not stated Duration of each medication condition: 1 day, 3 days of MPH in all Washout before trial initiation: none Medication-free period between interventions: not stated Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • IOWA-CRS completed by the examiner at the end of each session
Notes	Sample calculation: no Ethics approval: approved by the institutional ethics review board **Comment from trial authors** • We cannot predict that similar results would hold with longer-term treatment or with extended-release preparations **Key conclusions of trial authors** • Findings provide insight into potential mechanisms underlying individual differences in treatment response in ADHD, which may facilitate more targeted treatments • Results from the present trial demonstrate that MPH produces moderate but beneficial effects on selected aspects of working memory that are known to be impaired in ADHD. Furthermore, comorbid anxiety may be a predictor of working memory treatment response Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: Funding and operating grant from the Canadian Institute of Health Research and funding from the Canada Research Chairs Programme Email correspondence with trial authors: December 2013. Not able to get supplemental information from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Master randomisation tables were prepared by the research support pharmacist at the hospital by using simple randomisation with restrictions (high dose not to be given on the first possible drug day nor immediately following placebo; no directly ascending or descending dose order). Therefore, a balanced block 22 design was used
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Examiner, psychiatrist, participant and participant's family were not informed about participant's randomisation order or daily medication status until completion. Placebo and active medication were prepared by the hospital phar-

Bedard 2008 *(Continued)*

		macist and were powdered and packaged in an opaque capsule to prevent identification of contents by colour, taste or volume
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trained clinicians, blinded to other aspects of the participant's assessment, conducted interviews independently
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Bhat 2020

Study characteristics	
Methods	A 2-week cross-over trial with 2 arms: • MPH 0.5 mg/kg/d • placebo Phases: 2 (baseline week and week 2)
Participants	Number of participants screened: 866 Number of participants included: 676 Number of participants followed-up: 670 completed the 3 weeks. Maximum analysed are 575/573 (444 boys, 129 girls) Number of withdrawals: only information on 6 of 676 participants available Diagnosis of ADHD: DSM-IV (percentage for 540 participants: 53.3% combined, 9.6% hyperactive-impulsive and 37.0% inattentive type) Age: mean 9.03 (SD 1.81, 6-12 years) (information for 575 participants) IQ: separated by DRD3 genotype group for 69 participants: 96.94 (13.27), for 236 participants: 97.07 (12.6), for 268 participants: 96.04 (13.42) (information for 573 participants) MPH-naive: 222 (information for 573 participants): 62.9% (information for 540 participants). Ethnicity: 496 whites (information for 573 participants) Country: Canada Setting: outpatient Comorbidity: for 540 participants: CD (18.5%), ODD (41.4%), mood disorders (7.5%), anxiety disorders (42.6%) Comedication: not stated Additional sociodemographics: parental income: percentage low income (defined as ≤ CAD 30,000): 40.1%; marital status: percentage single mothers 43.2%; maternal education: percentage lower education 36.7%; maternal smoking during pregnancy: 38.3% **Inclusion criteria**

Bhat 2020 *(Continued)*

- ADHD
- Age 6-12

Exclusion criteria

- Psychosis
- Tourette's syndrome
- IQ < 70
- PDD

Interventions	Participants were randomly assigned to 1 of 2 possible orders of MPH (Ritalin) 0.5 mg/kg/d and placebo twice/d. 346 allocated to placebo first, 330 allocated to MPH first Mean medication dosage: all participants received a fixed dosage at 0.5 mg/kg/d Administration schedule: twice/d, 0.25 mg/kg, morning and noon Duration of each medication: 1 week of MPH, 1 week of placebo Washout before trial initiation: washout during 1-week baseline assessment week Medication-free period between interventions: none Titration period: none Treatment compliance: at the end of each week of treatment, the blister packs were collected and medication adherence was checked.
Outcomes	**ADHD symptoms** • CGI - Teacher Version rated once a week + 1 week before medication trial • CGI - Parent Version rated once a week (1 week before medication trial and on the Sunday after children were given their medication of the weekend) • The Restricted Academic Situation Scale (RASS) "[...] administered before and 60 minutes after the administration of each treatment" (Bhat 2020 p 316) **Serious AEs** • No important AEs or side effects were noted. Assesed "during each week of treatment" (Bhat 2020 p 315) **Non-serious AEs** • Barkley Side Effects Rating Scale, assessed "during each week of treatment" (Bhat 2020 p 315) The outcome reporting used for this review was taken from Bhat 2020, with data from 526 participants.
Notes	Sample calculation: no Ethics approval: yes. approved by the Research Ethics Board of the Douglas Mental Health University Institute in Montreal, Canada. **Comments from trial authors** • "The within-subject cross-over design increased precision in determining the PR in comparison to the parallel-group design used in previous trials." (Fageera 2017 p 8, secondary reference under Bhat 2020) • "Another advantage is the measurement of an acute PR at one week in comparison with the duration of previous studies, lasting typically one month or more. The PR has been shown to peak in short-duration studies thus a shorter trial design, especially with a medication like MPH, whose benefits are nearly immediate, may succeed in capturing the PR at its time of maximal expression." (Fageera 2017 p 8, secondary reference under Bhat 2020)

Bhat 2020 *(Continued)*

- "The cross-over design carries a risk of bias due to carry-over effects of the interventions across treatment periods. We acknowledge that the absence of a wash-out period between the 2 treatment weeks magnifies this risk." (Fageera 2017 p 9, secondary reference under Bhat 2020)

Key conclusion of trial authors

- "The first main finding in this trial is the higher and highly significant PR [Placebo response] with a larger effect size as assessed by parents compared to teachers. Several factors may account for this observation. First, the desire to improve is a known modulator of the PR (Price, Finniss, & Benedetti, 2008). The parents' desire for their children's behaviour to improve may exceed the desire of the teachers. Second, the capacity to generate expectations of improvement, an integral part of the PR (Price et al., 2008), may be more limited in teachers compared to parents. Alternatively, but not exclusively, it is possible that parents and teachers are attentive to different dimensions of the child behaviours that respond differentially to placebo in different environments (i.e. school and home). These observations imply that general statements regarding 'the PR in ADHD' might lack meaning without specifying who observed the response and in what context. Therefore, our results caution against the common practice in ADHD research of combining ratings from several sources into a single outcome variable (Newcorn et al., 2009)." (Fageera 2017 p 5-6, secondary reference under Bhat 2020)
- "The second main finding from this study is the association between PR and several clinical and demographic characteristics of the child." (Fageera 2017 p 7, secondary reference under Bhat 2020)
- "Previous exposure to medication was also associated with smaller PR as assessed by parents. This observation could be explained by the fact that both parents and teachers have a prior knowledge of how the child responded to active medication, which in case it was poor, will lower their expectations of PR. In contrast, in children without prior exposure to active treatment, the expectations of observers with regard to response might be anchored in more general expectations of treatment response without adjustment to the child prior history of treatment response." (Fageera 2017 p 7, secondary reference under Bhat 2020)

Comments from review authors

- This trial has many articles each reporting different outcomes/outcome analyses. Review authors are having trouble figuring out why only a part of the 676 included participants are included in the separate articles.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no

Any withdrawals due to AEs: yes, unclear how many, but no fewer than 2

Funding source: this work was supported in part by a grant from the Fond de Recherche du Québec and the Canadian Institutes of Health Research. Weam Fageera is a recipient of a PhD scholarship from the Ministry of Education of Saudi Arabia.

Email correspondence with trial authors: October 2013. We received some data from trial authors. We sent another email to ask for additional information but have not received a response. trial authors were contacted again through personal email in August, October and December 2021, for information regarding the flow of participants and first-period data, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Their order of administration was determined by counterbalanced random assignment, using a computer-generated randomisation list prepared by a statistician not otherwise affiliated with the trial.
Allocation concealment (selection bias)	Low risk	Placebo and MPH were prepared individually in opaque gelatin capsules in weekly blister packs by a pharmacist not otherwise involved in the trial to maintain blind allocation of treatments

Bhat 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	MPH and placebo were encapsulated into opaque gelatin capsules in weekly blister packs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both parents and teachers were aware that after 1 week of baseline observation (which served also as a washout period for children who were previously on medication), participants (in a blind order) received either 1 week of active medication (MPH 0.25 mg/kg twice/d) followed by 1 week of placebo or the reverse order to assess their response to medication in an unbiased fashion
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Flowchart in Naumova 2019 (secondary reference under Bhat 2020), claims 676 included and randomised participants, but the articles' outcomes are reported for a maximum of 575 participants with no information on withdrawals. Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All protocol outcomes reported

Biederman 2003b

Study characteristics	
Methods	15-site, multi-centre, double-blind, randomised, 2-week parallel trial with 2 arms: • ER-MPH (Ritalin LA) • placebo Phases: 3. Pre-randomisation (4 weeks' titration plus 1 week washout), randomisation, double-blind treatment and open-label extension
Participants	Number of participants screened: unknown Number of participants included: 164 (122 boys, 39 girls). 137 participants randomised Number of participants followed up: MPH 63, placebo 71 Number of withdrawals: MPH 3, placebo 0 Diagnosis of ADHD: DSM-IV (combined (75.8%), hyperactive-impulsive (1.2%), inattentive (18.6 %)) Age: mean 8.81 years (range 6-14) IQ: not stated MPH-naive: 94 (58.4%) Ethnicity: white (85.7%), African American (3.7%), Asian (1.2%), other (9.3%) Country: USA and Canada Setting: outpatient clinic (naturalistic school setting) Comorbidity: not stated Comedication: not stated Other sociodemographics: none. No significant differences in baseline demographics were noted between the 2 groups

Biederman 2003b *(Continued)*

	Inclusion criteria • Boys and girls 6-14 years of age who met DSM-IV criteria for ADHD and were receiving treatment with MPH, or de novo patients • Meeting ADHD criteria in DISC-4 (NIMH) • Attending school in a classroom setting with the same teacher, who, for the duration of the trial, would perform weekly assessments • Functioning, in the opinion of the investigator, at age-appropriate levels academically • Female patients of childbearing age needed to have a negative pregnancy test and if sexually active had to be using adequate and reliable contraception for the duration of the trial • Ongoing behavioural therapies for ADHD were permitted to continue, but participants were not to initiate behavioural therapy during the trial • Informed consent **Exclusion criteria** • Patients with somatic or psychiatric disorders that could contraindicate treatment or confound efficacy or safety assessments, or those who required treatment with drugs other than MPH • Known hypersensitivity to the trial drug • Likelihood of non-compliance • History of substance abuse • Living with a person with a substance abuse disorder • Pregnancy • Use of other investigational drugs during the trial period
Interventions	Participants were randomly assigned to ER-MPH at optimised dose or placebo Number randomised to each group: MPH 66, placebo 71 Mean MPH dosage: not stated Administration schedule: once daily in the morning Duration of intervention: 2 weeks (mean: MPH 13.91, placebo 13.96) Titration period: 1 week before randomisation Treatment compliance: 130 completed treatment (MPH 61, placebo 69)

Outcomes	**ADHD symptoms**
	• Primary efficacy outcome measure
	  ◦ Conners' ADHD/DSM-IV Scale, Teachers: total subscale, school day weekly assessments
	• Secondary efficacy measure
	  ◦ Conners' ADHD/DSM-IV Scale, Teachers: Inattentive subscale
	  ◦ Conners' ADHD/DSM-IV Scale, Teachers: Hyperactive-Impulsive subscale
	  ◦ Conners' ADHD/DSM-IV Scale, Parents: total subscale, weekends
	  ◦ Conners' ADHD/DSM-IV Scale, Parents: Inattentive subscale
	  ◦ Conners' ADHD/DSM-IV Scale, Parents: Hyperactive-Impulsive subscale
	Non-serious AEs
	• Monitoring of AEs
	• Routine laboratory tests (haematology, blood chemistry, urine)
	• Vital signs (sitting BP and pulse)
	• Height, weight and performance of physical examinations and drug screening

Biederman 2003b *(Continued)*

Notes	Sample calculation: yes. A total of 128 participants (n = 64 per treatment group) were required for analysis of the primary efficacy variable, based on an effect size of 0.5 with a power of 80% and a two-tailed α-level of 0.05 Ethics approval: yes. An institutional review board approved this trial at each participating site **Comment from trial authors** • Limitations: first, participants in this trial were primarily white boys with ADHD. Second, the short trial duration does not predict long-term efficacy or safety. Third, selection of responders during the titration phase may have affected the outcomes of this trial. In clinical practice, response rate may be lower than that observed among the current sample **Key conclusion of trial authors** • Results demonstrate that ER-MPH (Ritalin LA) administered once daily for up to 2 weeks achieved outcomes statistically superior to placebo in children with ADHD **Comments from review authors** • Mean MPH dosage not stated, only range (10 mg/d to 40 mg/d) • IQ not stated Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes Any withdrawals due to AEs: yes (n = 3) Funding source: funding was received from Novartis Email correspondence with trial authors. April 2014. Emailed trial authors for additional information/data but have not received a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by Novartis Drug Supply Management, which used a validated system that automates random assignment of treatment groups to randomisation numbers
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear whether investigator was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear whether investigator was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF analysis of ITT population. ITT population included all participants who received the double-blind trial drug, and from whom ≥ 1 Conners' ADHD/DSM-IV Scale, Teachers, was obtained Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, 2 participants, due to unsatisfactory therapeutic effect

Biederman 2003b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol was published.

Bliznakova 2007

Study characteristics	
Methods	11-day N-of-1 randomised, double-blind, cross-over trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: 1 boy Number included: 1 Number of participants followed up: 1 Number of withdrawals: 1 Diagnosis of ADHD: ICD-10 (predominantly hyperactive type) Age: 15 years IQ: not stated MPH-naive: no Ethnicity: not stated Country: Germany Setting: not stated Comorbidity: not stated Comedication: not stated Other sociodemographics: 2 parents
Interventions	The participant was randomly assigned to MPH and placebo across 11 days Mean MPH dosage: not stated Administration schedule: not stated Duration of each medication condition: the condition was changed daily, but placebo was given for 6 days and MPH for 5 days Washout before trial initiation: not relevant Medication-free period between interventions: none Titration period: none Treatment compliance: 100% according to Table 6
Outcomes	**ADHD symptoms** • CTRS: rated daily • Parent/Teacher Rating Scale: rated daily

Bliznakova 2007 *(Continued)*

	Non-serious AEs • Assessment of stomachaches (yes/no) daily
Notes	Sample calculation: yes Ethics approval: not stated **Key conclusion of trial authors** • Double-blind trial showed significant symptom reduction under the medication condition, which was also noted by the participant himself. Furthermore, towards the end of the trial, the somatic complaints were gone Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not stated Email correspondence with trial authors: December 2013. Emailed trial author to request information about missing data but received no response. Not possible to use data from this trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Blum 2011

Study characteristics

Methods	This double-blind, placebo-controlled, cross-over trial with the child's clinically most effective dose as identified by a systematic open-label titration procedure investigated whether components of attention and executive functioning improve when children with ADHD are treated with OROS-MPH

Blum 2011 *(Continued)*

	2-week, cross-over trial with 2 interventions: • OROS-MPH • placebo
Participants	Number of participants screened: 41 Number of participants included: 34 Number of participants followed up: 30 (24 boys, 6 girls) Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (combined (100%)) Age: mean 8 years 6 months (range 6 years 5 months-12 years 6 months) IQ: mean 97.8 (range 77-132) MPH-naive: number not stated Ethnicity: white (80%), African American (13.3%), other (6.7%) Country: USA Setting: outpatient clinic Comorbidity type: ODD (40%), specific learning difficulty (33.3%), anxiety (6.67%), dysthymia (3.3%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Children 6-12 years of age, in first grade or higher • DSM-IV-TR diagnosis of ADHD combined type • Parent and teacher ratings on the ADHD-RS-IV, of at least the 85th centile for hyperactivity/impulsivity and inattention, or both (if the child was not taking medication at enrolment) • IQ > 75 on the WASI **Exclusion criteria** • Children with a past or current diagnosis of a chronic tic disorder, a pervasive developmental disorder, cerebral palsy, bipolar disorder, major depression, head injury requiring hospitalisation, psychotic disorder, glaucoma, cardiovascular disease, epilepsy, OCD serious enough to warrant separate treatment or suicidal or homicidal behaviour or ideation • History of side effects with MPH requiring discontinuation of the medication • Children were also excluded if they were known to be unable to swallow a tablet • Use within 14 days of MAOI • Long-term treatment with coumarin, clonidine or tricyclic antidepressants
Interventions	Participants were randomly assigned to OROS-MPH and placebo in random order MPH dosage: 9 children treated with 18 mg, 13 with 36 mg and 8 with 54 mg of OROS-MPH Administration schedule: not stated Duration of each medication condition: 1 week Washout before trial initiation: not stated Medication-free period between interventions: not stated

Blum 2011 *(Continued)*

	Titration period: 2- to 3-week open-label, multi-dose-titration protocol to determine the child's optimal dose as recommended by practice guidelines Treatment compliance: 30 children completed the trial; however, compliance regarding trial medication is not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV, both parent- and teacher-rated at the end of each week of the different medication trial **Non-serious AEs** • Stimulant Drug Side Effects Rating Scale, parent-rated at the end of each week of the different medication trial. These data are not reported in the article
Notes	Sample calculation: not stated Ethics approval: yes; approved by the Committee for the Protection of Human Subjects at The Children's Hospital of Philadelphia **Comment from trial authors** • "In conducting analyses for the cross-over trial, our team examined the effects of crossing participants from the first treatment condition to the second treatment condition (i.e. the carry-over effect).(.....) Because no statistically significant sequence effects were noted, data from both periods were combined, and final analyses were reduced to paired comparisons" **Key conclusion of trial authors** • When OROS-MPH was used to treat children with ADHD at the clinically most effective dose, general improvement was noted on tasks requiring response inhibition; response to treatment in other domains was variable or was not demonstrated. Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes Withdrawals due to AEs: 0 Funding source: supported by an investigator-initiated grant from Ortho McNeil Janssen Scientific Affairs Email correspondence with trial authors: January 2014: emailed trial authors twice to request additional information but received no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned and counterbalanced across participants
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Referred to as double-blind but no information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Referred to as double-blind but no information provided

Blum 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis reported Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Clinical trial ID: NCT00530257, no indication of selective reporting

Borcherding 1990

Study characteristics	
Methods	11-week, double-blind, placebo-controlled, cross-over trial with 3 interventions: • MPH • dextroamphetamine • placebo
Participants	Number of participants screened: not stated Number of participants included: 46 (all boys) Number of participants followed up: 45 Number of withdrawals: 1 Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 8.6 years (range 6-12) IQ: mean 106.1 (range > 80) MPH-naive: 13 had not received past stimulant treatment Ethnicity: white (72%), African American (22%), Asian/Hispanic (6%) Country: USA Setting: outpatient clinic Comorbidity: medically healthy Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Medically healthy • Full-scale IQ score > 80 on the WISC • Score 2 SD or above age norms on Factor 4 (Hyperactivity) of CTRS **Exclusion criteria** • Medical or neurological disease, including chronic motor tics or Tourette's syndrome • Other primary Axis I psychiatric disorders
Interventions	Participants were randomly assigned to 1 of the possible drug condition orders of MPH, dextroamphetamine and placebo

Borcherding 1990 *(Continued)*

	Mean MPH dosage: 1.3 mg/kg Administration schedule: twice daily, 9:00 am and 1:00 pm Duration of each medication condition: 3 weeks Washout before trial initiation: 2 weeks Medication-free period between interventions: none Titration period: during the 3 weeks, LD was given week 1, intermediate dose week 2 and high dose week 3 Treatment compliance: not stated
Outcomes	**Non-serious AEs** • Subject Treatment Emergent Symptom Scale completed weekly by the physician and the child's parents; reflected both symptoms and observed effects • Attention given to onset and duration of abnormal movements or obsessive-compulsive behaviours. Collected from several sources
Notes	Sample calculation: no Ethics approval: not stated **Comment from trial authors** • Most movements and compulsive behaviours were seen only by staff sensitive to these possible effects **Key conclusions of trial authors** • Dextroamphetamine tended to produce more compulsive behaviours, which were also more likely to resemble OCD, than did MPH • Abnormal movements and compulsive behaviours tended to co-occur with MPH only; no general Tourette's-OCD diathesis was found for this population • An important clinical point from these data is that abnormal movements and compulsive behaviour due to treatment with 1 stimulant should not necessarily be a cause for discontinuation of stimulant drug treatment; rather, the same stimulant at a different dose or a different stimulant should be tried Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Withdrawals due to AEs: no (the 1 withdrawal due to AE happened while on dextroamphetamine) Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Double-blind random fashion
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Oral medication in identical capsules was administered at 9:00 am and 1:00 pm

Borcherding 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants except 1 (who experienced AEs) completed the trial Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Brams 2008

Study characteristics	
Methods	Randomised, double-blind, cross-over, multi-centre trial evaluating the efficacy of the following over an 8-h laboratory classroom day in children with ADHD • ER-d-MPH (20 mg/d) • placebo Phases: • baseline: day 0 • period 1: days 1-7 (Sunday-Saturday), when Saturday is assessment day (8-h laboratory classroom day) • period 2: days 7-15 • final visit: day 15
Participants	Number of participants screened: 92 Number of participants included: 86 (53 boys, 33 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders Number of participants followed up: 86 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (87.2%), hyperactive-impulsive (0%), inattentive (12.8%)) Age: mean 9.5 years (range 6-12) IQ: > 70 MPH-naive: 0% Ethnicity: white (48.8%), African American (24.4%), Asian (2.3%), Hispanic (23.3%) Country: USA Setting: multi-centre, outpatient clinic (laboratory classroom) Comorbidity: not stated Comedication: no antidepressant or other antipsychotic medication Other sociodemographics: none

Brams 2008 *(Continued)*

Inclusion criteria

- DSM-IV criteria for a diagnosis of ADHD of any type, as established by the K-SADS-PL
- 6-12 years of age
- Only children whose parents or legal guardians, or both, provided written informed consent before any trial-related procedures were performed were enrolled
- Girls of child-bearing potential were required to have a negative urine pregnancy test before enrolment and, if sexually active, to be using adequate and reliable contraception (e.g. double-barrier method), which was documented in the medical record

Exclusion criteria

- Children or their parents/guardians were unable to understand or follow instructions as needed to participate in the trial
- Children deemed by investigators to have below-average cognitive capacity, or to be home-schooled
- Previously diagnosed with Gilles de la Tourette's syndrome or a tic disorder (medication-induced tics were not excluded)
- History of seizure disorder, or history of, or concurrent, significant medical or psychiatric illness or substance abuse disorder
- Taking an antidepressant or other antipsychotic medication; those who initiated psychotherapy within the 3 months preceding screening and those with a positive urine drug screen were deemed ineligible
- Poor response or known sensitivity to all MPH or d-MPH formulations based on past medical history
- Taking other medications for ADHD
- Prospective participants taking or planning to take any other investigational drug within 30 days of the start of the trial
- Previously participated in an analogue classroom trial within 6 months before screening

Interventions

Participants were randomly assigned to 1 of 2 possible drug condition orders of once-daily, ER-d-MPH 20 mg (Focalin XR (Novartis Pharmaceuticals Corporation) and placebo

Mean MPH dosage: fixed dose of 20 mg

Administration schedule: once daily in the morning

Duration of each medication condition: 7 days

Washout before trial initiation: 1 week before the trial

Titration period: before trial participation, all participants were stabilised on a total daily dose or nearest equivalent dose of MPH 40 mg to 60 mg or d-MPH 20 mg to 30 mg for ≥ 2 weeks before screening

Treatment compliance: not stated

Outcomes

ADHD symptoms

- Primary efficacy outcome
  - Change on the SKAMP: combined score from pre-dose to the 0.5-h post-dose time point during the 8-h classroom day. Rated by observer
  - Change in SKAMP: combined scores from pre-dose to 1, 2, 4, 6 and 8 h post-dose. Rated on classroom day by observers
  - Change from pre-dose on SKAMP: Attention and Deportment scores at all time points (0.5, 1, 2, 4, 6 and 8 h post-dose)
  - Conners' ADHD/DSM-IV Scales, Parent: completed by parent/legal guardian on classroom day

Non-serious AEs

- Vital signs: recorded at each visit (days 0, 7, 14)
- Spontaneously reported AEs, including serious AEs, at the end of each treatment period
- Heart rate and BP measured at pre-dose, 4 and 8 h post-dose at days 7 and 14

Brams 2008 *(Continued)*

- Weight at screening and at day 15
- ECG at screening and at day 15

Notes

Sample calculation: yes

Ethics approval: not stated

Comments from trial authors

- Several limitations with regard to the design of this trial should be considered in interpretation of these data
- Participant population was required to have had previous exposure to MPH or d-MPH. It is likely that this patient population already demonstrated a therapeutic response to MPH or d-MPH, as well as tolerance to these drugs
- Only a fixed dosage of 20 mg/d was evaluated, making it difficult to compare results observed in the current trial with those of other doses currently available, or when treatment is optimised

Key conclusions of trial authors

- Compared with placebo, once-daily, ER-d-MPH 20 mg provided rapid and significant improvement at 0.5 h post dose in attention, deportment and academic performance, which was sustained for 8 h post-dose
- Overall, once-daily ER-d-MPH 20 mg was well tolerated
- In an analysis of parental assessment of diary responses, children appeared better organised, and morning preparation for school was smoother and less frustrating, with once-daily ER-d-MPH compared with placebo

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; children with poor response or known sensitivity to MPH or d-MPH were excluded

Withdrawals due to AEs: no

Funding source: Novartis Pharmaceuticals Corporation

Email correspondence with trial authors: September 2013. We received an email from Dr. Brams, in which we were told that Novartis had control and ownership of trial data. Consequently, we had to contact the Public Affairs Department at Novartis to request the information (e.g. protocols) (Krogh 2013a [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated by the trial sponsor, who used an automated random assignment of treatment sequences to randomisation numbers in the specified ratio
Allocation concealment (selection bias)	Low risk	All trial medications and packaging were identical in appearance for blinding purposes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, parents, trial centre personnel and those who assessed outcomes were blinded to trial treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, parents, trial centre personnel and those who assessed outcomes were blinded to trial treatment

Brams 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	The safety population consisted of all participants who took ≥ 1 dose of trial medication. The efficacy population included all randomly assigned participants who provided valid efficacy measurements for both treatment periods Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No published protocol

Brams 2012

Study characteristics	
Methods	Randomised, double-blind, 3-period × 3-treatment cross-over trial in a 12-h laboratory classroom setting with 3 interventions • 20 mg ER-d-MPH • 30 mg ER-d-MPH • Placebo Each period lasted 7 days
Participants	Number of participants screened: not stated Number of participants included: 165 (57% boys, 43% girls) Number of participants followed up: 157 Number of withdrawals: 8 Diagnosis of ADHD: DSM-IV (combined or predominantly hyperactive-impulsive subtype) Age: mean 9.6 years (range 9.3 to 10.0) IQ: above normal MPH-naive: 0% Ethnicity: white (38.2%), African American (31.5%), Hispanic (22.4%), other (7.9%) Country: USA Setting: outpatient clinic (laboratory classroom) Comorbidity: no significant medical illness Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Boys and girls aged 6-12 years • Meeting DSM-IV criteria for primary diagnosis of ADHD combined subtype or predominantly hyperactive-impulsive subtype • Girls of childbearing potential required to have a negative urine pregnancy test before enrolment and, if sexually active, to use adequate and reliable contraception • Stabilised on a total daily dose or nearest equivalent dose of 40 mg-60 mg of MPH or 20 mg-30 mg d-MPH (36 mg and 54 mg of ER-MPH and 10 mg-20 mg of transdermal MPH were allowed) for ≥ 2 weeks before screening

Brams 2012 *(Continued)*

	Exclusion criteria • Children or their parents/guardians were unable to understand or follow instructions necessary to responsibly participate in the trial • Children were deemed by the investigator to have below average cognitive ability • Home-schooled • Previously diagnosed with Gilles de la Tourette's disorder or similar tic disorder (medication-induced tics were not excluded) • History of a seizure disorder • History of or concurrent long QT syndrome or QTc > 450 milliseconds at screening, or any clinically significant ECG abnormality • Significant medical or psychiatric illness or substance abuse disorder • Children were taking an antidepressant or other antipsychotic medications • Children initiated psychotherapy within the 3 months before screening • Positive urine drug screen • Children with a poor prior response, or known sensitivity, to all MPH or d-MPH products, based on medical history • Children currently taking non-MPH-based medications for ADHD • Those taking or planning to take any other investigational drug within 30 days of trial start • Children who had previously participated in an analogue classroom trial within 6 months before screening • ALT/AST, gamma glutamyl transferase or serum creatinine > 2 x the upper limit of normal at screening
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of 20 mg ER-d-MPH, 30 mg ER-d-MPH and placebo Administration schedule: once daily, morning Duration of each medication condition: 7 days Washout before trial initiation: 1 week Medication-free period between interventions: no Titration period: none (fixed doses) Treatment compliance: no information
Outcomes	**ADHD symptoms** • SKAMP (-combined, -attention and -deportment), performed by independent blinded raters throughout the 12-h testing period **Serious AEs** • Spontaneously reported serious AEs were recorded weekly 1 participant experienced 2 serious AEs (peritonsillar abscess and oral bullae) while receiving 20 mg ER-d-MPH and was hospitalised for 6 days for the peritonsillar abscess. Serious AEs were considered not related to trial drug. Participant discontinued the trial for missed trial drug during hospitalisation **Non-serious AEs** • Vital signs were assessed, and spontaneously reported AEs were recorded weekly • Heart rate and BP were measured after weeks 1 and 2 • Weight was measured and ECG tests were conducted at screening and at the final visit
Notes	Sample calculation: no Ethics approval: yes

Brams 2012 *(Continued)*

Comments from trial authors

- Limited exposure to both doses of ER-d-MPH for each participant to 1 week
- Potential for carry-over effects between trial periods due to cross-over design
- Children with the inattentive subtype of ADHD were excluded from this analysis
- Efficacy data presented as change from pre-dose scores, rather than as effect sizes or response rates
- Pharmacokinetic and pharmacodynamic data were not collected and analysed
- Results reported for school-aged children may not be relevant to other ADHD patient populations
- Higher percentage of girls recruited

Key conclusions of trial authors

- Significantly greater improvement in ADHD symptoms was noted with 30 mg ER-d-MPH compared with 20 mg ER-d-MPH at hours 10 through 12
- Tolerability was comparable between doses. 30-mg dose of ER-d-MPH may provide further benefit to patients who do not maintain optimal symptom control later in the day with 20-mg ER-d-MPH
- ADHD symptoms significantly improved with 30 mg ER-d-MPH compared with 20 mg ER-d-MPH at hours 10 to 12 in all ethnic parameters, with a statistically significant difference in the white subgroup
- 30 mg ER-d-MPH may provide further benefit to patients of all ethnic backgrounds who do not obtain optimal late-day symptom control with 20 mg ER-d-MPH

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; children with a poor prior response, or known sensitivity, to all MPH or d-MPH products based on medical history were excluded

Withdrawals due to AEs: no

Funding source: Novartis Pharmaceuticals Corporation

Email correspondence with trial authors: September 2013. Not possible to contact trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to 1 of 6 treatment sequences. All participants were given the lowest available number from the randomisation numbers provided at each site. A randomisation list was produced by using a validated system that automated the random assignment of treatment sequences to randomisation numbers in the specified ratio
Allocation concealment (selection bias)	Low risk	Randomisation data were kept strictly confidential until the time of unblinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All trial medications and packaging were identical in appearance for blinding purposes. Participants, parents, trial centre personnel and those who assessed outcomes were blinded to trial treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All trial medications and packaging were identical in appearance for blinding purposes. Participants, parents, trial centre personnel and those who assessed outcomes were blinded to trial treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 dropouts from the MPH group. The ITT population included all randomly assigned participants who took ≥ 1 dose of trial medication and had ≥ 1 post-dose efficacy measurement. The safety population consisted of all participants who took ≥ 1 dose of trial medication Selection bias (e.g. titration after randomisation → exclusion): no

Brams 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No published protocol

Brown 1984a

Study characteristics	
Methods	4-week cross-over trial with 2 interventions: • MPH • placebo Phases: 2 weeks of placebo and 2 weeks of MPH treatment with sequence according to randomisation
Participants	Number of participants screened: not stated Number of participants included: 11 (all boys) Number of participants followed up: 11 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III Age: mean 10 years, 5 months (range 9 years 1 month-12 years 1 month) IQ: > 80 MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-III diagnosis of ADD **Exclusion criteria** • Known neurological or sensory impairment • IQ > 80
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg MPH and placebo Mean MPH dosage: not stated Administration schedule: twice/d Duration of each medication condition: 2 weeks Washout before trial initiation: not stated

Brown 1984a *(Continued)*

	Medication-free period between interventions: time of day the pills were taken not stated Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS: rated at the end of each school week • CTRS: rated at the end of each school week **Non-serious AEs** 1. Cardiovascular measures: heart rate, SBO and DBP. Heart rate was recorded after the child had rested for 5 min by placing a stethoscope over the precordium and measuring the rate for 1 minute. BP was obtained with a sphygmomanometer with the child seated after he had rested 5 minutes. Tested at the end of each 2-week drug period 2. "No deleterious side effects"
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • Of additional importance in the present trial was the finding that MPH had no deleterious side effects and was well tolerated by all children participating in the research project • Table 2 shows that individual variations in heart rate and BP associated with MPH trials are quite large **Key conclusions of trial authors** • Results demonstrated significant improvement in sustained attention and impulse control, as well as in ratings of social behaviour, by both teachers and parents • Cardiovascular functioning did not significantly increase as a function of MPH Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: funded by NIMH and NIH. Placebo and MPH were supplied by CIBA-GEIGY Corporation, Summit, New Jersey Email correspondence with trial authors: November 2013. We received additional information regarding ethics approval, sample calculation, etc., from trial authors. However, it was not possible to receive all requested data, as the trial author no longer possessed raw data from the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The sequence of the 2 medication conditions was randomly assigned, but no information was provided on methods
Allocation concealment (selection bias)	Low risk	Triple blinding; dosage was administered twice daily in the form of opaque capsules packaged by hospital pharmacists to conceal the contents
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Child and parent, teacher and the physician were blinded to the child's medication condition

Brown 1984a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physician was blinded to the child's medication concealment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided on all 11 participants Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Brown 1985

Study characteristics	
Methods	12-week, randomised, parallel trial • Cognitive training • MPH combined with cognitive training • No treatment (not randomly assigned) Cognitive training programme: individual, twice-weekly, 1-h sessions for a total of 24 sessions spanning a 3-month period
Participants	Number of participants included: MPH + cognitive training 10, cognitive training 10 Number of participants followed up: MPH + cognitive training 10, cognitive training 10 Number of withdrawals: MPH + cognitive training 0, cognitive training 0 Diagnosis of ADHD: DSM-III (types not stated) Age: mean 11.36 years (range 6.4-11.9) IQ: 101.92 (range 91-136) MPH-naive: not stated Ethnicity: not stated Country: USA Setting: not stated Comorbidity: not stated Comedication: no. No child was receiving any psychopharmacological treatment Other sociodemographics: none. No significant differences in baseline demographics between the 2 groups **Inclusion criteria** • Demonstrating ADHD symptoms in serious and persistent form, agreed by parents and teachers • Symptoms present for ≥ 12 months (parents to verify) • Meeting criteria for ADD including hyperactivity • According to DSM-III • Reading deficit of ≥ 2 grade levels **Exclusion criteria**

Brown 1985 *(Continued)*

- Symptoms seem to stem from stress at home or from inconsistent child management
- No major diseases or obvious physical defects (gross neurological, sensory, motor impairment or psychosis)

Interventions	Participants were randomly assigned to MPH + cognitive training or to cognitive training only Mean MPH dosage: 0.3 mg/kg (range 5 mg/d-15 mg/d) Administration schedule: twice daily (morning and lunch) Duration of intervention: 12 weeks + 3 months (only with medication) Titration period: none Treatment compliance: not stated Cognitive training programme: individual, twice-weekly, 1-h sessions for a total of 24 sessions spanning a 3-month period
Outcomes	**ADHD symptoms** • CPRS and CTRS-Abbreviated: baseline, 12 weeks, 3 months • Teacher Rating of Attention: baseline, 12 weeks, 3 months • Teacher Rating of Impulsivity: baseline, 12 weeks, 3 months
Notes	Sample calculation: no Ethics approval: no information **Key conclusion of trial authors** • Children in the 2 medication treatment conditions demonstrated improvement in attentional deployment and in behavioural ratings Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: research supported by US Public Health Services Grant from the NIMH, and by the Biomedical Research Award from the NIH. MPH provided by CIBA-GEIGY Corporation, Summit, New Jersey

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label MPH
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

Brown 1985 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol/design published

Brown 1988

Study characteristics	
Methods	8-week, double-blind, randomised, cross-over trial with 4 interventions: • Placebo • 0.15 mg/kg MPH • 0.30 mg/kg MPH • 0.5 mg/kg MPH
Participants	Number of participants screened: not stated Number of participants included: 11 (all boys) Number of participants followed up: 11 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 13 years, 7 months (range 12 years and 10 months-14 years and 10 months) IQ: full-scale mean 92.91 (range 86-104) MPH-naive: not stated, but none of the participants had been treated with stimulants during the year preceding the trial Ethnicity: African American (100%) Country: USA Setting: outpatient clinic Comorbidity: CD, socialised aggressive (45%) Comedication: no Other sociodemographics: none **Inclusion criteria** • Sexual rating of ≥ 3 according to Tanner's classification of stages of development, to ensure post-pubertal status • ADD according to DSM-III • Score of ≥ 15 on the Abbreviated CTRS **Exclusion criteria** • Mental disability or gross neurological disorders
Interventions	Participants were randomly assigned to possible drug condition orders:

Brown 1988 *(Continued)*

	Interventions (mean dosage) • Placebo • MPH low (0.15 mg/kg) • MPH medium (0.30 mg/kg) • MPH high (0.5 mg/kg) Mean MPH dosage: MPH low (4.38 mg), medium (12.55 mg), high (21.28 mg) Administration schedule: twice daily; morning and noon Duration of each medication condition: 2 weeks Washout before trial initiation: none (but no stimulant treatment for the past year) Titration period: none Treatment compliance: compliance was determined to be satisfactory
Outcomes	**ADHD symptoms** At the end of each 2-week trial, parents and teachers completed the following rating scales • CPRS - Revised • Abbreviated Conners' Parent Hyperactivity Index • Abbreviated Conners' Teacher Hyperactivity Index • ADD/H Comprehensive Teacher Rating Scale **Non-serious AEs** • Side Effects Rating Scale (includes questions about sleep disturbances, dysphoria, decreased appetite, physiological complaints such as headaches and generalised anxiety), parent-rated (assessing the preceding week) • Cardiovascular measures (heart rate, resting SBP and DBP measures for BP) assessed ≥ 1 h after administration of MPH or placebo. Apical pulse rates taken for 1 full minute • Weight (during every clinic visit)
Notes	Sample calculation: no Ethics approval: yes; Institutional Review Board (IRB) at Emory University **Key conclusion of trial authors** • Significant drug effects were found for most measures. In general, higher doses resulted in the most beneficial response in behavioural, academic and laboratory measures of attention and impulsivity. However, a significant linear increase occurred in DBP. Results suggest that MPH is an effective adjunct to the treatment of ADD in adolescents **Comment from trial authors** • We do not know whether our findings can be generalised in non-black populations Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Withdrawals due to AEs: no Funding source: Biomedical Research Support Grant Program, Division of Research Resources, NIH and Emory University Research Email correspondence with trial authors: October 2013. We received from trial authors additional information about ethics approval, planned outcomes and participants followed up. Unfortunately, it

Brown 1988 *(Continued)*

	was not possible for trial authors to provide other data that we needed because the trial was conducted many years ago, and trial authors no longer had the data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Drug order was randomly assigned across participants; no further description
Allocation concealment (selection bias)	Low risk	All medication was prepared in identical capsules by hospital pharmacists. Medication was dispensed in dated envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All medication was prepared in identical capsules by hospital pharmacists. Medication was dispensed in dated envelopes. Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Researchers administered all measures that were proposed and reported these data in the published report

Brown 1991

Study characteristics

Methods	Double-blind, randomised, cross-over trial with 2 interventions: • MPH • placebo Phases: • MPH 10 mg • MPH 15 mg • MPH 20 mg • placebo
Participants	Trial consisted of 22 participants, but only 7 had ADD. As outcomes were reported separately for these 7 participants, we were able to include the trial Number of participants screened: 25 Number of participants included: 7/22 (all boys) Number of participants followed up: 22 Number of withdrawals: 0 Diagnosis: DSM-III (CD, with 7 of 22 also diagnosed with ADD)

Brown 1991 *(Continued)*

	Age: mean:15.8 years (range 12.9-18.9) IQ: 96.22 (SD 15.12, range 80-123) MPH-naive: not stated Ethnicity: white (100%) Country: USA Setting: hospital Comorbidity: CD (100%) Comedication: occasional allergy medication was allowed Other sociodemographics: middle and upper-middle class **Inclusion criteria** • Hospitalised adolescents diagnosed with CD **Exclusion criteria** • Mental disability, psychosis and organic brain disorder
Interventions	Participants were randomly assigned to 1 of 24 possible drug condition orders of MPH (10 mg, 15 mg, 20 mg) and placebo (in counterbalanced order) Mean MPH dosage: 0.15 mg/kg, 0.22 mg/kg and 0.31 mg/kg Administration schedule: twice daily, 8:00 am and 12:00 pm Duration of each medication condition: 1 day each, 3 days of MPH in all Washout before trial initiation: not stated Titration period: 1 day before first phase to test tolerability Treatment compliance: 100%
Outcomes	**General behaviour** • CTRS (conduct factor): teacher-rated daily **Non-serious AEs** • Side Effects Rating Scale (including 17 known AEs for MPH): observer-rated daily • Cardiovascular measures were recorded 90 min after 12:00 pm administration
Notes	Sample calculation: not stated Ethics approval: not stated **Comments from trial authors** • "... in our trial, mean milligram per kilogram doses were lower than in previously published reports … doses may simply have been too small to induce any real change in behaviour" • "Another limitation that may have influenced the results is timing of the measurements of behaviour. As behavioural ratings were made by teachers at the end of the day, it is possible that medication effects (particularly for lower doses) had dissipated by the time the ratings were made" **Key conclusions of trial authors**

Brown 1991 *(Continued)*

- "In summary, results are of theoretical importance and with additional research may suggest the potential efficacy of stimulants for treating adolescents with CDs in the absence of ADD"
- "The present data may be interpreted to suggest that ADD may be managed with stimulant medication when it presents comorbidly with CD"

Comment from review authors

- Data on the CD + ADD group were reported separately in the trial - that is why we could use the data

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; initially participants received a 1-day open trial of MPH. 3 participants were excluded because of intolerability

Any withdrawals due to AEs: no

Funding source: not stated

Email correspondence with trial authors: unable to locate contact details for trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	All participants received each of the 4 doses in 1 of 24 possible randomly assigned sequences
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	MPH and placebo were packaged in coloured gelatin capsules by the hospital pharmacist to avoid detection of dose, visually or by taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Under double-blinded conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol published

Buitelaar 1995

Study characteristics

Methods	Randomised, cross-over trial with 3 interventions: • pindolol • MPH • placebo Phases: • Phase 1: 4-week treatment block

Buitelaar 1995 *(Continued)*

- Phase 2: 2-week drug-free interval
- Phase 3: 4-week treatment block

First 32 participants were randomly assigned to interventions 1-3 in the first treatment block, and to intervention 1 or 2 in the second treatment block. Next 20 participants were randomly assigned to intervention 2 or 3 in the first treatment block, and to intervention 2 or 3 in the second treatment block

Participants	Number of participants screened: not stated Number of participants included: 52 (46 boys, 6 girls); however, because of an incomplete block design, only 46 were treated with MPH and 31 were treated with placebo in first or second treatment block Number of participants followed up: 52 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 9.3 years (range 6-13) IQ: mean 94.2 MPH-naive: 100% Ethnicity: not stated Country: the Netherlands Setting: outpatient clinic Comorbidity: CD (38%); depressive disorder, dysthymia or major depressive disorder (15%); anxiety disorder, overanxious disorder or avoidant disorder (42%); psychomotor epilepsy (2%) Comedication: antiepileptic medication (carbamazepine) at a fixed dosage (2%) Other sociodemographics: none. 20% were from families of high socioeconomic status, 50% of middle socioeconomic status and 30% of low socioeconomic status (on the Hollingshead Index). No significant difference in baseline characteristics were noted between groups of children treated with MPH, pindolol or placebo **Inclusion criteria** • ADHD according to DSM-III-R criteria • Scores in the clinical range on both the CBCL and CTRS, Hyperactivity factors • Deficits in attention performance on a reaction time task or a continuous performance task in neuropsychological testing • No previous treatment with psychotropic medication • Clinical indication for drug treatment **Exclusion criteria** • Diagnosis of tic disorder or pervasive developmental disorder • Family history of tic disorder • Contraindications to treatment with blockers such as cardiac disease, in particular, conduction abnormalities and bradycardia, hypotension, obstructive pulmonary disease and insulin-dependent diabetes
Interventions	Participants were randomly assigned to possible drug condition orders of 40 mg pindolol, 20 mg MPH and placebo Fixed dosage: 10 mg MPH, twice daily (approximately 0.6 mg/kg/d) Administration schedule: morning and noon

Buitelaar 1995 *(Continued)*

	Duration of each medication condition: 4 weeks Washout before trial initiation: no (medication-naive) Medication-free period between interventions: 2 weeks Titration period: yes. After randomisation, during the first 3 days of a treatment period, participants received 1 morning dose (10 mg MPH, 20 mg pindolol or placebo). After completion of endpoint assessment, medication was tapered off (3 days with 1 morning dose) Treatment compliance: good to very good in 96% of children. 2 children had poor compliance under MPH treatment as the result of side effects
Outcomes	**ADHD symptoms** • 10-Item Abbreviated Conners' Rating Scale: rated by parents, teachers and a psychologist • 93-Item CPRS • 39-Item CTRS Parents and teachers completed ratings at baseline, at week 2 and at endpoint of each treatment period. The psychologist completed ratings at baseline and at endpoint of each treatment period. Furthermore, ACRS was rated 30 min after drug administration **Non-serious AEs** • Adverse effects checklist (encompassing 20 possible side effects, modified from the Stimulant Drug Side Effects Rating Scale, rated by parents after 2 and 4 weeks of treatment • Treatment-emergent adverse effects were further assessed systematically at endpoint by research psychiatrist • Pulse and BPs were recorded at each clinical visit
Notes	Sample calculation: yes; for comparison of pindolol with MPH (50 participants) Ethics approval: yes; approved by the Committee for Research on Human Subjects of Utrecht University Hospital **Comments from trial authors** • Interim analysis of side effects indicated that pindolol was associated with significantly more intense AEs when compared with placebo and MPH. Consequently, pindolol was dropped from the trial design, and the next 20 participants were included in a randomised MPH-placebo cross-over design • Trial was limited by use of fixed dosage, with exclusive focus on behavioural symptoms - not on improvement in neuropsychological measures of information processing, and with an incomplete and unbalanced block design **Key conclusions of trial authors** • Beta-blocker pindolol appeared to be modestly effective in the treatment of behavioural symptoms of children with ADHD. Data suggest some utility for pindolol in treating hyperactivity and conduct problems in children with ADHD, but safety concerns about troubling side effects clearly limit use of pindolol in ADHD • Only strong levels of response could be predicted by baseline characteristics. Severity of disorder based on clinical judgement and improvement after a single dose of MPH are found to be important contributors to response prediction **Comments from review authors** • Trial designed to compare usage of pindolol and MPH • Few participants • Trial design changed during the trial because of AEs. Phase 2 changed intervention from pindolol versus MPH to MPH versus placebo

Buitelaar 1995 *(Continued)*

- Phase 1: given the relatively small sample sizes, effects of single treatments (i.e. MPH vs placebo, and pindolol vs placebo) were not robust enough to reach conventional levels of statistical significance

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no; only medication-naive participants

Any withdrawals due to AEs: no; however, in 4 participants, dosages of MPH had to be adjusted in the first 2 weeks of the trial because of increased agitation, restlessness and insomnia. 2 participants remained on 5 mg of MPH for 4 weeks, whereas dosage for the other 2 participants could be gradually increased to 10 mg MPH in the last 2 weeks

Funding source: not stated

Email correspondence with trial authors: January to March 2014. Requested but did not receive from trial authors supplemental efficacy and safety data and information regarding randomisation, allocation concealment and blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, not further described
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, not further described. MPH and placebo were administered in identical-looking tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants from the MPH group had bad compliance but were included in the analyses, as an ITT analysis was planned Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no, but design of trial changed during the course of the trial because of AEs
Selective reporting (reporting bias)	Unclear risk	Protocol not identified

Bukstein 1998

Study characteristics

Methods	Cross-over trial with 3 interventions: • MPH 0.3 mg MPH/kg • MPH 0.6 mg MPH/kg • placebo

Bukstein 1998 *(Continued)*

	Phases: trial included 2 phases: a baseline phase and the medication trial itself. The baseline phase occurred during the first 2 weeks (9 days) of the programme, when the children were medication-free. Each medication condition was administered for 7 days of the programme during the 21-day trial
Participants	Number of participants screened: not stated Number of participants included: 18 Number of participants followed up: 18 (14 boys, 4 girls) Number of withdrawals: 0 DSM-III-R criteria for ADHD and ODD or CD Age: mean 9.4 years (range 6.1-12.2) IQ: not stated MPH-naive: not stated Ethnicity: white (17%), African American (83%) Country: USA Setting: outpatient clinic (summer school at clinic) Comorbidity: ODD (56%) and CD (44%) Comedication: no Other sociodemographics: participants were predominantly from lower socioeconomic classes, with an average Hollingshead Index of Social Status of 3.83 (SD 1.65, range 1 to 5). 13 (72%) of the participants' families were receiving public assistance. Only 4 of the children lived with both biological parents; 12 (67%) lived with their biological mother only. Inner city environment characterised by higher than average rates of poverty and community violence. No significant differences in baseline demographics between groups **Inclusion criteria** • DSM-III criteria for ADHD and ODD or CD, while attending the Summer Treatment and Enrichment Program (STEP) **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of MPH (0.3 mg/kg or 0.6 mg/kg) and placebo Mean MPH dosage: not stated Administration schedule: 8:30 am, 11:45 AM and 3:00 pm Duration of each medication condition: 7 days Washout before trial initiation: 9 days Medication-free period between interventions: none Titration period: none Treatment compliance: poor compliance with the weekend medication condition; most families missed ≥ 1 dose each weekend of the trial. Poor compliance with the 3-dose regimen was so widespread that trial authors omitted from the trial all data on weekend doses

Bukstein 1998 *(Continued)*

Outcomes	**ADHD symptoms** • IOWA CRS: rated by staff daily • IOWA CPRS: rated by parents daily • CTRS: rated daily **Non-serious AE** • Side Effects Rating Scale: adaptation of the Barkley Side Effects Rating Scale, rated daily by staff and also rated by parents
Notes	**Key conclusions of trial authors** • Staff ratings of behaviour of children in the programme and in an academic classroom showed that children displayed significant improvement in ADHD symptoms and aggressive behaviour with LD-MPH and HD-MPH conditions • At home, parents and guardians reported few significant differences in behaviour ratings between placebo and MPH • In both settings, MPH was well tolerated, with few side effects found during active drug conditions Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Schedule for each condition was randomly assigned across the 5 weekdays to minimise programme effects; the only qualifying condition was that approximately half of the 7 days of each medication condition would occur during each half of the 21-day trial
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Nurse and other Summer Treatment and Enrichment Program (STEP) staff, children and parents were blinded to dosages and schedules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each child's daily data were collected and entered by trained research associates, who were unaware of medication status
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included in the analyses Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no. Number of non-responders and responders was calculated but not used to exclude participants
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Butter 1983

Study characteristics	
Methods	1-week, double-blind, parallel trial with 3 arms: • adrenocorticotropic hormone • MPH (10 mg, 15 mg or 20 mg, weight-adjusted) • placebo
Participants	Number of participants screened: not stated Number of participants included: 30 (all boys) Number of participants followed up: MPH 10, placebo 10 Diagnosis of ADHD: DSM-III Age: mean not stated (range 6-12) IQ: > 85 MPH-naive: not stated Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: no information about significant differences in baseline demographics between groups **Inclusion criteria** • Clinical ADHD diagnosis of ADD with hyperkinesis (DSM-III) • Hyperkinesis rating required a score of ≥ 15 on Short Form CRS, and hyperkinetic behaviour had to be apparent throughout most of the day • Untreated behaviour had to be a cause of severe difficulty both at home and at school **Exclusion criteria** • WISC score < 85 or abnormal perceptual functioning
Interventions	Participants were randomly assigned to adrenocorticotropic hormone, MPH or placebo Number of participants randomly assigned to each group: adrenocorticotropic hormone 10, MPH 10, placebo 10 Mean MPH dosage: 0.5 mg/kg Administration schedule: once daily, 7.30 am Duration of intervention: 1 week. 1 week drug-free followed by 1 week of placebo treatment. After placebo washout, randomly assigned to adrenocorticotropic hormone, MPH or placebo Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms**

Butter 1983 *(Continued)*

- Short Form CRS: completed by parents and clinicians
- CTRS: rated during placebo and active drug phases

Non-serious AE

- EEG, haematology, liver and kidney function test, BP and pulse, blood chemistry, urinalysis before and after treatment

EEG, haematology, blood chemistry and urinalysis were within normal limits before treatment and remained so after treatment

Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusion of trial authors** • Children treated with MPH show significantly greater vasomotor reactivity, behavioural improvement and learning receptivity than children treated with adrenocorticotropic hormone and placebo Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: the Scientific Development Group, Organon International B.V., Oss, the Netherlands

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	After placebo washout, treatment was assigned in a double-blind and random manner
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Neurologist assessing EEG blinded. Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Carlson 1995

Study characteristics

Carlson 1995 *(Continued)*

Methods	Double-blind, placebo-controlled, repeat-measures (across drug and dosage), cross-over trial with 6 interventions: • MPH at 10 mg twice/d • MPH at 15 mg twice/d • MPH at 20 mg twice/d • desipramine alone • desipramine + MPH • placebo Phases: each child received placebo, desipramine, each of the 3 doses of MPH (10 mg, 15 mg, 20 mg) and combined desipramine and MPH (at the same 3 doses)
Participants	Number of participants screened: not stated Number of participants included: 16 (all boys) Number of participants followed up: 16 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (62.5%), inattentive (12.5%), "in partial remission" (25%)) Age: mean: not reported (range 7.9-12.10 years) IQ: mean not stated (range overall 81-121; range verbal 74-113, range performance 73-126) MPH-naive: 4 (25%) Ethnicity: white (87.5%), African American (12.5%) Country: USA Setting: inpatient ward Comorbidity: yes; major depressive disorder (68.75%), dysthymic disorder (31.25%). "All had ODD, CD or both" Comedication: yes Other sociodemographics: none **Inclusion criteria** • Initial team diagnosis of ADHD, non-bipolar major depressive disorder, dysthymic disorder or a combination thereof • ≥ 7 years old • WISC-R, full-scale IQ > 80 **Exclusion criteria** • Medical contraindication to medications being investigated • Family history of bipolar disorder in first- or second-degree relatives • Abnormal baseline laboratory values or ECG
Interventions	Participants were randomly assigned to different possible drug condition orders of MPH (10 mg, 15 mg and 20 mg), twice/d at 7:30 am and 11:30 am × 6 days, then 1-day washout; the titrated therapeutic level (125 ng/mL to 225 ng/mL) of desipramine twice daily at 3:30 pm and 7: 30 pm x 3 weeks minimum before final measures taken; and placebo Mean MPH dosage: not stated Duration of each medication condition: 1 week

Carlson 1995 *(Continued)*

	Washout before trial initiation: 14 days Medication-free period between intervention: 1 day Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ACTeRS: ADD/H **General behaviour** • Humphrey's Teacher Self-Control Rating Scale • Inpatient Global Rating Scale **Non-serious AEs** • Subjective Treatment Emergent Symptom Scale: side effect ratings, collected weekly by nurse • Somatic factor of the Inpatient Global Rating Scale: collected weekly by nurse • CDRS-R: Appetite and Sleep disturbance items collected weekly by research psychologist • Cardiovascular side effects (daily morning BP and pulse rates + weekly ECG)
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusion of trial authors** • "With regard to differential efficacy, the major findings of this study were that a combination of DMI [desipramine] and MPH (at 20 mg) was somewhat more effective than DMI or MPH alone for improving hyperactive, inattentive and oppositional defiant, and 'aggressive' behaviours across both school and unit settings. Efficacy was also demonstrated for MPH and DMI alone in school, but less so on the unit" **Comment from review authors** • Small sample of 16 participants entering the trial seems heterogeneous and opportunistic rather than clearly defined, with a mixture of diagnoses including mood, ADHD and ODD/CD. This makes it difficult to believe that the results are reliable Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not stated Email correspondence with trial authors. Emailed first trial author to ask for outcome data in mean and SD format. Trial authors replied in July 2014 to say that they were unable to help us

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not stated
Allocation concealment (selection bias)	High risk	Not stated

Carlson 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medications were packaged in identical grey capsules (size 00) that were administered 4 times/d
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For this protocol, all raters (including teachers, nurses, psychologist and physicians, except for the attending child psychiatrist, who controlled the desipramine dosage but did not rate the children), children and parents were blinded to all medication conditions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): not stated
Selective reporting (reporting bias)	Unclear risk	Not protocol identified

Carlson 2007

Study characteristics	
Methods	6-week, multi-centre, double-blind, parallel, RCT with 2 arms: • atomoxetine + MPH • atomoxetine + placebo RCT was preceded by a 4-week, open-label, atomoxetine and placebo phase, during which participants who had adequate response were removed
Participants	Number of participants screened: not stated Number of participants included: met inclusion criteria 25; phase 1 (4-week open-label atomoxetine and placebo phase) 24 (20 boys, 4 girls); phase 2 (6-week, double-blind RCT) 17 Number of participants followed up: MPH 8, placebo 7 Number of withdrawals: MPH 1, placebo 1 Diagnosis of ADHD: DSM-IV (combined (79% in phase 1)) Age: phase 1 mean 9.6 years (range 6-12) IQ: > 70 Stimulant-naive: 4% Ethnicity: white (83%), other (17%) Country: USA Setting: outpatient clinic Comorbidity: ODD (50% in phase 1) Comedication: no Other sociodemographics: none **Inclusion criteria**

Carlson 2007 *(Continued)*

- 6-12 years of age
- DSM-IV diagnosis of ADHD, any type
- Rating on ADHD-RS-IV, Parent Version - Investigator Administered and Scored Version of ≥ 1.5 SD above age and sex norms
- Severity rating of at least moderate on the CGI-S
- History (preceding 12 months) of insufficient response to an adequate stimulant trial, which was defined as gradual titration of stimulant medication for ≥ 2 weeks at specified doses for each medication. Inadequate response was determined by the child's prescribing physician, who also documented his or her opinion that a change in treatment was needed
- Participants must be of normal intelligence, as assessed by the investigator (i.e. without a general impairment of intelligence, and likely, in the investigator's judgement, to achieve a score ≥ 70 on an IQ test) (Administration of a formal IQ test is not an entry requirement for this trial. Specific learning disabilities are not considered general impairments of intelligence)
- Participants must be able to swallow capsules

Exclusion criteria

- Weighed < 22 kg or > 60 kg at trial entry
- Had any other Axis I diagnosis, including pervasive developmental disorder, mood or anxiety disorder (presence of comorbid ODD was not an exclusion criterion)
- Bipolar disorder, autism
- Any medical conditions that would contraindicate the use of atomoxetine or ER-MPH
- History of any seizure disorder and/or Rolandic seizures (other than febrile seizures) or prior ECG abnormalities in the absence of seizures, or history of taking (or are currently taking) anticonvulsants for seizure control
- History of severe allergies to > 1 class of medication or multiple adverse drug reactions, including hypersensitivity to MPH
- History of intolerance or non-response to atomoxetine
- Used any concomitant psychotropic or excluded medications
- Ingestion of any excluded medications 5 days before baseline ratings and randomisation

Interventions	Participants were randomly assigned to ER-OROS-MPH or placebo Co-intervention: atomoxetine Number of participants randomly assigned: MPH 9, placebo 8 MPH mean dosage: 1.02 mg/kg Administration schedule: once/d Duration of intervention: 6 weeks Titration period for MPH: after randomisation to target dose of 1.08 mg/kg/d (max 1.2 mg/kg/d) Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV, Parent Version - Investigator-Administered and scores: parent-rated • CPRS Revised, Short Form: parent-rated at baseline and at weeks 4, 5, 6 and 10 **General behaviour** • Weekly parent ratings of evening and morning behaviour: parent-rated at baseline and at weeks 4, 5, 6 and 10 **Non-serious AEs** • Vital signs, at each visit

Carlson 2007 *(Continued)*

- Weight, at each visit
- Spontaneous AE reports, at each visit

Notes

Sample calculation: included sample (25 participants) is too small in relation to the sample calculation (85 participants)

Ethics approval: yes

Comment from trial authors

- The present findings can be applied only to children with an inadequate stimulant response. Given the small trial sample, particularly in the combination treatment groups, the findings must be considered preliminary

Key conclusion of trial authors

- Methylphenidate appears to be safely combined with atomoxetine, but conclusions are limited by small sample

Comment from review authors

- For the review, we used data from trial phase 2, that is, the RCT with 2 arms (intervention: MPH + atomoxetine; control: placebo + atomoxetine)

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no, but exclusion of atomoxetine/placebo responders before trial phase 2

Withdrawals due to adverse events: yes, 2

Funding source: research was funded by Eli Lilly and Company, Indianapolis, Indiana

Email correspondence with trial authors. June-November 2013. We received from trial authors and sponsoring pharmaceutical company, supplemental information regarding IQ and blinding procedures, as well as data on weight, treatment-emergent AEs and ECG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned via an interactive voice response system to receive ER-MPH or placebo
Allocation concealment (selection bias)	Low risk	Investigators and participants were blinded to the precise visit at which randomisation to blinded placebo or MPH occurred, as this visit is not identified in the investigator's copy of the protocol, and as use of blinded trial drug begins at visit 2 and continues up to visit 8
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Efficacy outcome measures were conducted on the ITT sample by using an LOCF method

Carlson 2007 *(Continued)*

		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, 1 participant discontinued due to perceived lack of efficacy
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Castellanos 1997

Study characteristics	
Methods	9-week, double-blind, cross-over trial with 3 interventions for 3 weeks each: • MPH • dextroamphetamine • placebo Trial was followed up by an open clinical follow-up of 22 months
Participants	Number of participants screened: 64 Number of participants included: 22 (all boys) Number of participants followed up: 20 Number of withdrawals: 2 Diagnosis of ADHD: DSM-III-R Age: mean 9.4 years (range 6-13) IQ: mean 98.8 MPH-naive: not stated Ethnicity: white (80%), African American (10%), Asian (5%), Hispanic (5%) Country: USA Setting: outpatient clinic Comorbidity: Tourette's disorder (95%), chronic motor tics (5%), CD (5%), ODD (30%), reading disorder (5%), overanxious disorder (5%), OCD (10%), enuresis (20%) Comedication: 4 received haloperidol Other sociodemographics: none **Inclusion criteria** • DSM-III criteria for Tourette's disorder, with tics confirmed by a knowledgeable clinician ≥ 1 year before referral • Symptoms of ADHD present in ≥ 2 settings • Conners' hyperactivity factor scores from home teacher ≥ 2 SD > age norms **Exclusion criteria** • Full-scale IQ < 75 (WISC-R) • Evidence of medical or neurological disease

Castellanos 1997 *(Continued)*

- Any other Axis I psychiatric disorder except OCD, CD or ODD, overanxious disorder and specific developmental disorders

Interventions	Participants were randomly assigned to 1 of the possible drug condition orders of MPH and placebo. MPH was increased weekly. For body weight > 30 kg, weekly MPH doses were 15 mg/dose, 25 mg/dose and 45 mg/dose twice/d. For weight ≤ 30 kg, 12.5: 25 mg/dose and 45 mg/dose, twice/d Mean MPH dosage: main cohort 1.20 mg/kg, 2nd cohort 0.69 mg/kg, 3rd cohort 1.22 mg/kg Administration schedule: twice/d: breakfast and lunch Duration of each medication condition: 3 weeks. 1st cohort underwent weekly increases in stimulant doses described as low, medium and high. 2nd cohort underwent increase described as low, medium and medium, and the 3rd cohort as low, high and high Washout before trial initiation: minimum 4 weeks Medication-free period between interventions: 20 h Titration period: during the first 3 weeks of intervention Treatment compliance: no information
Outcomes	**ADHD symptoms** • CTRS: completed by day programme teachers, weekly ratings **Non-serious AEs** • AEs • Tic severity: Unified Rating Scale (Tourette Syndrome Association): variety, frequency, intensity, complexity and interference of motor and vocal tics based on observations by programme staff and derived by consensus at weekly meetings

Notes	Sample calculation: no
	
	Ethics approval: approved by NIMH Institutional Review Board
	
	Comments from trial authors
	
	• Limitations
	  ○ Small sample size
	  ○ Drug dosage was not randomly assigned
	  ○ Allowed 4 participants to continue on a constant dose of haloperidol
	  ○ Exploration of different dose schedules
	  ○ As MPH undergoes much more rapid and complete metabolism than dextroamphetamine, we would expect blood level curves of the 2 stimulants to differ markedly
	
	Key conclusion of trial authors
	
	• Substantial minority of comorbid participants had consistent worsening of tics while taking stimulants, although most experienced improvement in ADHD symptoms with acceptable effects on tics
	
	Comment from review authors
	
	• Trial consists of a main trial of 12 boys followed by 2 smaller cohorts of, respectively, 6 and 4 boys
	
	Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no
	
	Withdrawals due to AEs: yes, 1 on placebo
	
	Funding source: not stated

Castellanos 1997 *(Continued)*

	Email correspondence with trial authors: January 2014. Corresponding author was not able to supply us with further information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsule formulation prepared by a pharmacy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	2 dropouts; their data are not included in subsequent analyses. One of these was dropped from the trial because of acute exacerbation of tics, and 1 because of excessively disruptive behaviour Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	Yes; they seem to have reported only hyperactivity scores from CTRS

Chacko 2005

Study characteristics

Methods	6-week within-participant, randomised, placebo-controlled, double-blind, daily cross-over trial with 3 interventions: • MPH at 0.3 mg/kg given at 7:45 am and 11:45 am • MPH at 0.6 mg/kg given at 7:45 am and 11:45 am • Placebo given at 7:45 am and 11:45 am Phases: daily cross-over between medication conditions. 2 weeks of baseline and adjustment period before 6-week medication trial. Data from this paper pertain to 5- and 6-year-old children attending a summer treatment programme between 1987 and 1997 (Pelham 1996)
Participants	Number of participants screened: not stated Number of participants included: 36 (32 boys, 4 girls) Number of participants followed up: 36 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (n = 35, subtype not stated); DSM-IV (n = 1, combined type) Age: mean 6.13 years (range 5-6)

Chacko 2005 *(Continued)*

	IQ: mean 102 (SD 15.50) MPH-naive: not reported Ethnicity: white (86%), other (14%) Country: USA Setting: outpatient clinic (summer treatment programme) Comorbidity: ODD (50%), CD (27.7%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Diagnosis of ADHD according to DSM • Between 5 and 6 years of age • Parental consent **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned, daily, to 1 of 3 possible interventions: 0.3 mg/kg MPH, 0.6 mg/kg MPH and placebo Mean MPH dosage: not stated Administration schedule: twice/d 7:45 am and 11:45 am from Monday through Thursday Duration of each medication condition: daily shifted Washout before trial initiation: not stated Medication-free period between interventions: maximum 18-h gap between doses (11:45 am to 7:45 am the following day) and no medication Thursday to Sunday Titration period: before the 6-week trial began, participants underwent a 2-week baseline and adjustment period Treatment compliance: not stated
Outcomes	**Serious AEs** • None reported **Non-serious AEs** • "Classroom teachers, counselors, and parents completed daily ratings of the presence and severity of common stimulant side effects" Side effects are reported as occurring: "none" (i.e. symptom was assessed and was found absent), "mild" (i.e. symptom was present but was not sufficient to cause concern among child, peers or adults), "moderate" (i.e. symptom caused impairment of functioning or social embarrassment to the degree that benefits of medication must be considerable to justify risks of continuing medication) or "severe" (i.e. symptom caused significant impairment of functioning or social embarrassment to the degree that the child should not continue to receive medication). Rating of "moderate" or "severe" signifies clinically significant side effects. Side effects are based on staff/parent subjective report on severity of the side effect. Children were considered to have significant side effects in a particular area if clinically significant side effects were reported within that area for ≥ 50% of observations in a given condition

Chacko 2005 *(Continued)*

Notes

Sample calculation: no information

Ethics approval: no information

Comments from trial authors

- Trial limitations. Most participants were white males, limiting the generalisability of findings to females and ethnic minorities
- Furthermore, the sample size did not allow statistical analyses of ADHD subtype or comorbidity

Key conclusion of trial authors

- Stimulant medication is an effective treatment for young children diagnosed with ADHD; however, multiple domains of functioning must be assessed for the most effective dose for young children with ADHD to be determined

Comments from review authors

- Participants in this trial were attending a summer treatment programme between 1987 and 1997 (Pelham 1996)

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: unclear; 2 weeks of adjustment period before the medication condition - no information on how many were screened and how many participated during baseline weeks

Withdrawals due to AEs: none

Funding source: during the conduct of this research, Dr. Pelham was supported by grants from the NIMH (MH48157, MH47390, MH45576, MH50467, MH53554, MH62946), NIAAA (AA06267, AA11873), National Institute on Drug Abuse (NIDA) (DA05605, DA12414), National Institute of Neurological Disorders and Stroke (NINDS) (NS39087), National Institute for Environmental Studies (NIES) (ES05015) and National Institute of Child Health and Human Development (NICHHD) (HD42080)

Email correspondence with trial authors: December 2013. We emailed trial authors to request additional information about trial sample and side effects. Trial authors replied to say that the data are no longer available. Data from this trial could not be used in meta-analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Active medication and placebo were disguised in opaque capsules and were dispensed in daily pill reminders. Each condition occurred one or two times per week, with the order of the conditions randomized on a daily basis. Data were averaged across days within conditions for each child"
Allocation concealment (selection bias)	Unclear risk	“Each condition occurred one or two times per week, with the order of the conditions randomized on a daily basis”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Active medication and placebo were disguised in opaque capsules and were dispensed in daily pill reminders” Double-blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Side effects were measured for 30 participants

Chacko 2005 *(Continued)*

		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	Unclear how the population sample was selected from the group of attendees at these programmes over a 10-year period

Childress 2009

Study characteristics	
Methods	5-week, multi-centre, multiple-setting, phase III, double-blind, randomised, placebo-controlled, parallel-trial with 4 arms • Placebo • ER-d-MPH 10 mg • ER-d-MPH 20 mg • ER-d-MPH 30 mg 1-3 weeks titration and 2-4 weeks maintenance period dependent on the allocated active drug group
Participants	Number of participants screened: 332 Number of participants included: 253 (163 boys, 90 girls) Number of participants followed up: ER-d-MPH 161 (10 mg, n = 56; 20 mg, n = 54; 30 mg, n = 51), placebo 57 Number of withdrawals: ER-d-MPH 27 (10 mg, n = 10; 20 mg, n = 8; 30 mg, n = 9), placebo 8 Diagnosis of ADHD: DSM-IV (combined (73.9%), hyperactive-impulsive (2.8%), inattentive (21.7%), missing data (1.6 %)) Age: mean 8.7 years (6-12 years) IQ: not stated MPH-naive: 69.2% Ethnicity: white (57.7%), African American (28.9%), Asian (0.8%), other (12.6%) Country: 34 centres in the USA Setting: outpatient clinic Comorbidity: respiratory, thoracic and mediastinal disorders (MPH 26.9%, placebo 38.1%), immune system disorders (MPH 22.5%, placebo 14.3%), nervous system disorders (MPH 18.7%, placebo 19.0%), surgical and medical procedures (MPH 15.4%, placebo 11.0%), infections and infestations (MPH 14.3%, placebo 17.5%) and skin and subcutaneous tissue disorders (MPH 11.0%, placebo 9.5%) Comedication: ≥ 1 concomitant medication or non-drug therapy after start of trial (MPH 39.0%, placebo 44.4%). The most common concomitant medications were analgesics, antihistamines and allergy medications Other sociodemographics: none reported. Treatment groups were well balanced in relation to participant background characteristics, and baseline demographics were comparable among treatment groups **Inclusion criteria** • 6-12 years of age • DSM-IV-TR diagnosis of ADHD

Childress 2009 *(Continued)*

- Patients attending school had to have the same teacher (English or Math) for the entire duration of the trial, who was willing and able to spend sufficient time with the patient to make valid weekly assessments
- Drug-naive or not treated with any MPH-related medication during the month before the trial
- Patients receiving psychological or behavioural therapies before the screening visit were considered eligible to participate, provided that therapy had been ongoing for ≥ 3 months with the same therapist
- Patients had to have academic competence appropriate to their age and the following subscale total scores on Conners' ADHD/DSM-IV Scales - Teacher Version: for boys, baseline scores on Conners' ADHD/DSM-IV Scales - Teacher Version, Total subscale were required to be 27 for those 6-8 years old, 24 for those 9-11 years old and 19 for those 12 years old. For girls, respective baseline cut-off scores on Conners' ADHD/DSM-IV Scales - Teacher Version, for the same age groups were 16, 13 and 12

Exclusion criteria

- Home-schooled children
- Any medical condition that interfered with trial assessments or that was not stable for ≥ 3 months before screening
- Clinically significant abnormalities detected during screening
- Family history of long-QT syndrome, current diagnosis or history of cardiac abnormalities, seizures, psychiatric disorders such as schizophrenia, schizoaffective disorder, severe OCD, CD, autism, chronic tic disorder, Tourette's disorder or any mood or anxiety disorder
- Antidepressants, antipsychotics, herbal preparations with psychotropic effects, amphetamine-based medications, benzodiazepines, barbiturates, sedatives or hypnotics, MAOI and atomoxetine had to be stopped 1-4 weeks before randomisation according to their half-lives. All concomitant medications that could interfere with absorption, metabolism and distribution of trial drug were excluded from the start of screening until the end of all evaluations. Over-the-counter analgesics, short-term antibiotic treatment for minor infections and any medication needed to treat AEs were allowed
- Additionally, patients who were judged by the investigator as likely to be non-compliant with trial procedures, including those with a suspected history of substance abuse and those living with a person diagnosed with a substance abuse disorder, or whose parent or guardian was unable or unwilling to complete Conners' ADHD/DSM-IV Scales - Parent Version
- Pregnancy or lactation
- Positive drug screen

Interventions	Participants were randomly assigned to ER-d-MPH or placebo Fixed MPH dosage: 10 mg, 20 mg or 30 mg Number of participants randomly assigned: ER-d-MPH 188 (10 mg, n = 66; 20 mg, n = 62; 30 mg, n = 60), placebo 65 Administration schedule: once daily, morning Duration of intervention: 5 weeks Washout before trial initiation: up to 28 days (duration dependent on the half-life of any previous psychotropic medication) Titration period: 1-3 weeks, initiated after randomisation Treatment compliance: 86% completed
Outcomes	**ADHD symptoms** • Conners' ADHD/DSM-IV - Teacher Version: rated by teacher at baseline and each week • Conners' ADHD/DSM-IV - Parent Version (including 12-item ADHD Index and 18-item DSM-IV Subscale total): rated by parent or guardian at baseline and each week **Non-serious AEs**

Childress 2009 *(Continued)*

- Regular monitoring and recording of AEs, serious AEs, vital signs, body weight, ECG, physical examination, haematology parameters, blood chemistry and urinalysis. While vital signs were recorded at every visit, physical, laboratory and ECG evaluations were completed during the screening visit and the final trial visit. Weight was recorded at baseline and at the final visit. Notable value for weight loss was defined as a decrease from baseline weight at trial end of 7%

Notes	Sample calculation: yes; 252 participants (63 per treatment group) Ethics approval: institutional review boards or ethical review committees at each centre approved the trial **Comment from trial authors** • Limitations: short duration of trial, forced-dose titration, not powered to assess differences in treatment effects within ER-d-MPH groups **Key conclusions of trial authors** • All 3 doses of ER-d-MPH (10 mg, 20 mg or 30 mg/d) were significantly more effective than placebo in improving ADHD symptoms, as confirmed by teacher, parent and clinician • Additionally, ER-d-MPH was well tolerated and demonstrated a consistent safety profile. Mean changes from baseline in vital signs in ER-d-MPH groups were small, clinically irrelevant, unrelated to dose and similar to placebo • Despite the forced-titration design of the trial, the cardiovascular safety profile of ER-d-MPH (10 mg/d, 20 mg/d and 30 mg/d) is similar to placebo in children with ADHD **Comment from review authors** • Additionally, participants judged by the investigator as likely to be non-compliant with trial procedures were excluded Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes, 6 all in the MPH groups Funding source: Novartis Pharmaceuticals Corporation. Novartis Pharma has been helping with development of the manuscript Email correspondence with trial authors in December 2013. We have contacted trial authors twice in an attempt to obtain supplemental information regarding blinding, allocation concealment and weight loss. We have not received a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by using a validated system that automated the assignment of treatment arms to randomisation numbers in the specified ratio
Allocation concealment (selection bias)	Low risk	Allocation concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no detailed description
Blinding of outcome assessment (detection bias)	Unclear risk	Double-blind, but no detailed description

Childress 2009 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT population. LOCF Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Childress 2017

Study characteristics	
Methods	A 1-week parallel trial with 2 arms: • ER-MPH orally disintegrating tablet (ODT) • placebo Phases: 5 (screening, washout, open-label stepwise dose optimisation, dose stabilisation, and double-blind parallel group treatment)
Participants	Number of participants screened: 87 entered open-label phase Number of participants included: 83 Number of participants followed-up: 80 (82 included in full analysis) (54 boys (65.9%), 28 girls (34.1%) Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV-TR (65 (74.7%) combined type, 1 (1.1%) hyperactive-impulsive type, 21 (24.1%) inattentive type) Age: mean 9.2 years (SD 1.75, range 6-12) IQ: not stated MPH-naive: 0% Ethnicity: Hispanic/Latino (n = 28, 34.1%), not Hispanic/Latino (n = 54 (65.9%). Race was reported: white (n = 65, 79.3%), black or African American (n = 10, 12.2%), Asian (n = 2, 2.4%), Native Hawaiian or other Pacific Islander (n = 1, 1.2%), and other (n = 4, 4.9%) Country: USA Setting: outpatient clinic, laboratory classroom setting Comorbidity: most were specified as exclusion criteria Comedication: exclusion criterion Additional sociodemographics: none **Inclusion criteria** • Age 6-12 • DSM-IV-TR diagnosis of ADHD, any type • Positive response to a stable dose of MPH (20–60 mg of Metadate CD (UCB, Inc, Smyrna, GA) or comparable dose of another ER-MPH or IR formulation) for at least 1 month before screening • A score of > 3 (mildly ill) on the clinician-administered CGI-S scale

Childress 2017 *(Continued)*

	• > 90th percentile normative value for gender and age on the ADHD-RS-IV total score, inattentive or hyperactive/impulsive subscales on day 1 after MPH washout **Exclusion criteria** • History of poor response, known allergy, serious adverse reactions to any MPH formulation or allergy to any of the components of the ER-MPH ODT • Comorbidity that made ADHD diagnosis difficult • Need for additional medication to control ADHD symptoms • Known medical conditions that would preclude the use of ER-MPH ODT (or history (within the past year) • Presence of clinically significant disease or dysfunction that—in the opinion of the investigator—could put the participant at substantial risk or confound trial results • Current or recent history (within the past year) of drug abuse in the immediate family or by someone living at the participant's home, • Positive urine drug screen for other stimulant medications or drugs of abuse at the screening visit • Significant cognitive impairment • Chronic medical illnesses • Structural cardiac defects • Significant abnormal lab tests
Interventions	After the screening period, all participants went through a washout period of 3-7 days, then an open-label dose optimisation period of 4 weeks, then a 1-week dose stabilisation week at their optimised dose (20-60 mg). Participants were randomly assigned to: ER-MPH ODT (at optimised dose between 20-60 mg) or ODT placebo Number randomised to each group: intervention = 44, placebo = 41 Mean medication dosage: 34.3mg (SD 9.06) Administration schedule: once daily in the morning Duration of each medication: ER-MPH ODT group: 42.6 days; placebo group: 35.5 days; ER-MPH ODT plus 7 days placebo Washout before trial initiation: 3-7 days before open-label period depending on prior medications Titration period: 4 weeks before randomisation Treatment compliance: drug adherence was assessed at each visit from visits 3-8 by recording pill counts of returned medication. Non-adherence was defined as taking < 75% of the trial medication between 2 consecutive visits. No participants were excluded on lack of compliance
Outcomes	**ADHD symptoms** • SKAMP Score, assessed at baseline and at 1, 3, 5, 7, 10, 12, and 13 h post-dose **Serious AEs** • Spontaneous reporting • C-SSRS; Children's Baseline version "The C-SSRS (Children's Baseline version) assessment was performed at visit 1, and the C-SSRS (Children's Since-Last-Visit version) assessment was performed at each visit, starting at visit 2" (Childress 2017 p 69) **Non-serious AEs** • Assessed on classroom day
Notes	Sample calculation: yes, 84

Childress 2017 *(Continued)*

Ethics approval: yes, “The study was approved by a central Institutional Review Board (IRB; Copernicus Group, Research Triangle Park, NC), and each site, if required, submitted the protocol and consent/assent forms to its local IRB”

Comments from trial authors

- "The duration was relatively short and the trial enrolled only children aged 6–12 years without comorbidities that could potentially confound trial results, consistent with other phase 3 trial designs. Therefore, results may not be relevant for some patients who have ADHD"
- "Only participants with a previous history of response to MPH were included after being washed out of their current treatment before receiving ER-MPH ODT"

Key conclusion of trial authors

- "The results of this trial demonstrate the efficacy, safety, and tolerability of ER-MPH ODT in the laboratory classroom trial"
- "Although it is difficult to draw conclusions between formulations without head-to-head comparisons, this ER-MPH ODT appears to have a duration of efficacy similar to that of other ER-MPH products compared with placebo in laboratory classroom studies"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: no

Funding source: supported by funds from Neos Therapeutics, Inc

Email correspondence with trial authors: trial authors were contacted for information regarding risk of bias through personal email in August and October 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial is referred to as randomised, however the method used to generate the allocation sequence is not described in sufficient detail to allow an assessment of whether it produced comparable groups.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Several mentions of “double blind” and the “double blind phase” or “double blind classroom”, but no information on method or if the blinding was successful.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Protocol mentions blinding of outcome assessors, but the method is not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	The 1 participant who was excluded from the full analysis set did not have a baseline SKAMP rating and also had a positive drug screen for amphetamine. 2 other participants were excluded from the per-protocol set because they used prohibited medications. One had been assigned to placebo and the other to ER-MPH ODT Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Outcomes according to protocol/trial registration

Childress 2020a

Study characteristics	
Methods	A 1-week parallel-trial with 2 arms: • multilayer, ER-MPH (PRC-063) • placebo Phases: 4 (washout (3 days), open-label dose-optimisation (6 weeks), placebo-controlled double-blind trial (1 week), and follow-up phone call (after 1 week))
Participants	Number of participants screened: 156 included in open-label phase (102 (65.4%) boys, 54 (34.6%) girls) Number of participants included: 148 randomised Number of participants followed-up: 140; per protocol population: 112 Number of withdrawals: 8 Diagnosis of ADHD: DSM-5 (131 (84.0%) combined, 0 hyperactive-impulsive and 25 (16.0%) inattentive type) Age: mean 9.4 years SD 1.88, range 6-12) IQ: > 80 MPH-naive: not stated Ethnicity: Hispanic/Latino (n = 42), not Hispanic/Latino (n = 105) (of 147). Race: 1 Asian (n - 1), black or African American (n = 58), white (n = 81), more than one race (n = 7) (of 147) Country: USA Setting: outpatient (classroom laboratory) Comorbidity: some comorbidity allowed under exclusion criteria 4. Prevalence not stated Comedication: not stated Additional sociodemographics: none **Inclusion criteria** • Boys or girls ≥ 6 and ≤ 12 years of age • Girls who are non-pregnant and non-nursing • Girls of child-bearing potential who agree to practice a clinically accepted method of contraception during the trial and for at least 1 month prior to trial dosing and 1 month following completion of the trial. Acceptable contraceptive methods include abstinence, oral contraception, surgical sterilisation (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), intrauterine device, or diaphragm in addition to spermicidal foam and condom on male partner, or systemic contraception (e.g. levonorgestrel-releasing implant) • Diagnosis of ADHD (any type: combined, predominately hyperactive impulsive type or predominately inattentive type) by a psychiatrist, psychologist, developmental paediatrician or licensed allied healthcare professional using the DSM-5 and confirmed by administration of a structured diagnostic interview using the K-SADS-PL • Ratings on the ADHD-RS-V based on when the participant is not receiving treatment for ADHD, the participant must have ≥ 90th percentile normative value for gender and age in at least 1 of the categories: total score, inattentive subscale or hyperactive/impulse subscale • Unsatisfied with his or her current pharmacological therapy for treatment of ADHD or not currently receiving pharmacological therapy for ADHD. Inclusion of participants who are naive to pharmacological therapy for ADHD is permitted

Childress 2020a *(Continued)*

- Must be functioning at an age-appropriate level intellectually as determined by an intelligence quotient of ≥ 80 on a documented IQ assessment such as the WASI-II vocabulary and matrix reasoning components, or the KBIT-2
- Must have the ability to complete the Permanent Product Measure of Performance (PERMP) assessments
- Have parental consent (signed informed consent form) and written or verbal assent from the child
- Participant and parent(s)/caregiver are willing and able to comply with all the protocol requirements and parent(s) or caregiver must be able to provide transportation for the participant to and from the analogue classroom sessions

Exclusion criteria

- Has BP and pulse > 95th percentile for age and gender
- Has current or recent history (within the past 6 months) of drug abuse or dependence disorder in the participant or the immediate family or by someone living at the participant's home or positive urine drug screen for stimulant medication (other than currently prescribed stimulant for the treatment of ADHD) or drugs of abuse at the screening visit
- Has untreated thyroid disease, glaucoma, Gilles de la Tourette's disorder, chronic tics or a history of seizures during the last 2 years (except simple febrile seizures), a tic disorder (exclusive of transient tic disorder). Mild medication-induced tics are not exclusionary
- Primary and/or comorbid psychiatric diagnosis other than ADHD with the exception of simple phobias, motor skill disorders, communication disorders, learning disorders and adjustment disorders so long as such disorder is judged not to interfere with trial participation or the safety of the participant or other participants. Children meeting CD or ODD criteria but without history of prominent aggressive outbursts that could interfere with trial participation or the safety of the participant or other participants will be allowed to enrol at the discretion of the investigator
- Participants with a family history (first degree relatives) of sudden cardiac death require review and approval by the medical monitor for participation in the trial
- Has a current or recent history of hypertension, symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug
- Has a concurrent medical condition that, in the opinion of the investigator, could cause participation in this trial to be detrimental to the participant
- Has used any investigational drug within 30 days of the screening visit
- Has a known history of physical, sexual, or emotional abuse in the last year
- Has a medical history of hepatitis A, B, C or HIV, or tests positive for any of these at screening
- Has a positive urine pregnancy test (if applicable) at screening
- Has positive findings on C-SSRS for suicidal ideation or behaviours at screening

Interventions	Participants went through a 6-week, open-label dose-optimisation phase before being randomised. Participants were randomly assigned to: ER-MPH (PRC-063) at optimised dose (either 25 35, 45, 55, 70, or 85 mg/d) or placebo for 1 week Number randomised to each group: 75 to MPH, 73 to placebo Mean medication dosage: for the 148 47.84 (SD: 15.12) mg/d Administration schedule: once/d Duration of each medication: 6 weeks of MPH for all participants, 1 more week for participants allocated to MPH otherwise 1 week placebo Washout before trial initiation: 3 days before open-label Medication-free period between interventions: none Titration period: 6 weeks

Childress 2020a *(Continued)*

	Treatment compliance: 1 participant excluded due to noncompliance in week 1
Outcomes	**ADHD symptoms** • SKAMP Score, assessed at baseline (30 minutes predose) and at 1, 2, 4, 6, 8, 10, 12, and 13 h post-dose **Serious AEs** • CSSR-S, assessed at each clinic visit (once weekly for 6 weeks) • Spontaneous reporting **Non-serious AEs** • Observed AEs measured at each clinic visit (once weekly for 6 weeks) • Vital signs were measured at each clinic visit (once weekly for 6 weeks) • ECGs were measured at each clinic visit (once weekly for 6 weeks) The text reported no meaningful changes in haematology, urinalysis and chemistry, but no exact data were reported that could be used for analyses.
Notes	Sample calculation: no Ethics approval: yes. The trial was approved by an Institutional Review Board (Schulman IRB, Cincinnati, OH). **Comments from trial authors** • Consistent with other phase 3 studies, the trial duration was relatively short and the trial eligibility criteria, which included children aged 6–12 without comorbidities, could potentially confound the trial results. • In addition, multiple participants were provided with the incorrect 8-h test PERMP tests of the incorrect difficulty level leading to a reduction in the number of correct and attempted problems. These participants were excluded from the population for the confirmatory analysis. **Key conclusion of trial authors** • This trial successfully demonstrates significant improvements in attention and ADHD symptoms over a 13-h laboratory classroom in children 6–12 years of age who received optimised oral doses of ER-MPH (PRC-063), ranging from 25-85 mg daily, compared with placebo. • This trial demonstrates that ER-MPH (PRC-063) was a well tolerated, safe, and effective treatment of ADHD with rates of AEs similar to those observed with other ER stimulant treatments. Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes Any withdrawals due to AEs: no Funding source: Purdue Pharma Email correspondence with trial authors: August 2021. Supplemental information regarding risk of bias was received through personal email correspondence with the authors in August 2021.(Storm 2021 [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was applied centrally across all sites via an interactive voice/web response system and was stratified by individual dose level so that approximately half the participants within each dose level received ER-MPH (PRC-063) and half received placebo.

Childress 2020a *(Continued)*

Allocation concealment (selection bias)	Low risk	Through the interactive voice/web response system randomisation, sites were instructed which bottles to provide to each patient through a unique bottle ID code.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial medication was packaged in bottles containing 10 capsules with a unique bottle ID code. The treatment assignment was not identified on the bottles, and the trial medication capsules (ER-MPH (PRC-063) and placebo) were indistinguishable.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the participant nor any trial staff (including investigators, trial co-ordinators and trained observers) were unblinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5.4% withdrawal rate, no imputed data Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Outcome reporting according to protocol

Childress 2020b

Study characteristics	
Methods	A 1-week parallel trial with 2 arms: • DR/ER-MPH (HLD200) • placebo Phases: 4 (screening and wash-out (up to 4 weeks), open-label dose-optimisation (6 weeks), double-blind trial (1 week), and follow-up call (after 2 weeks)
Participants	Number of participants screened: 161 included in open-label phase Number of participants included: 155 randomised (85 (68.0%) boys, 40 (32.0%) girls of 125) Number of participants followed-up: 117 Number of withdrawals: 38. Of these, 36 were due to exclusion (after randomisation) of a full trial site by the FDA due to concerns about data integrity. Diagnosis of ADHD: DSM-5 (108 (86.4%) combined, 0 hyperactive-impulsive and 17 (13.6%) inattentive type) Age: mean 9.4 years (SD 1.65, range 6-12 years) IQ: not stated MPH-naive: no Ethnicity: Hispanic/Latino (n = 49, 39.2%), non-Hispanic/Latino (n = 76, 60.8%). Race: white (n = 99, 79.2%), black/African American (n = 15, 12.0%), Asian (n = 0), native Hawaiian/Pacific Islander (n = 2, 1.6%), other (n = 9, 7.2%) Country: USA Setting: outpatient; assessment on last trial day in laboratory classroom Comorbidity: not stated, but many were defined as exclusion criteria

Childress 2020b *(Continued)*

Comedication: specified list of allowed comedication not available for review authors

Additional sociodemographics: none

Inclusion criteria

- Participants must be male or female children (6-12 years at the time of consent)
- Participants must have a diagnosis of ADHD as defined by DSM-5 criteria and confirmation using the MINI-KID
- Participants must have a baseline ADHD-RS-IV score at or above the 90th percentile normalised for sex and age in at least 1 of the following categories:
  - Hyperactive Impulse
  - Inattentive
  - Total Score.
  - In addition, this ADHD-RS-IV Total Score must be ≥ 26
- Participants must have a CGI-S score ≥ 4 and a CGI-P score >10 at the baseline visit.
- Participants who are not currently on MPH treatment must either
  - have prior experience with MPH treatment and have shown clinical response to therapy during that time; or
  - be treated with the same dose of MPH and show a clinical response with acceptable tolerability to MPH for ≥ 2 weeks prior to screening.
- Parental or legal guardian confirmation of before-school function impairment and difficulties performing morning routine
- Regular weekday morning routine of no less than 30 min
- Participant must be considered clinically appropriate for treatment with DR-MPH and ER-MPH (HLD200), including ability to swallow treatment capsules
- Participant must be in general good health based upon medical history, physical examination, and laboratory results (including urine drug screen)
- Participant and parent or legal guardian must be able to read, write, and/or understand at a level sufficient to provide informed consent (parent/legal guardian) and assent (participant) prior to trial participation and to complete trial-related materials. Participant and a parent/legal guardian must plan to be available for the entire trial period
- Female participants of childbearing potential (i.e. post-menarche) are required to have a negative result on urine pregnancy testing at screening (and will be given specific instructions for avoiding pregnancy during the trial)
- A medically highly effective form of birth control must be used during the trial and for 90 days thereafter for participants of either sex of childbearing potential. Examples of medically highly effective forms of birth control are as follows:
  - no sexual activity
  - use of acceptable methods of birth control including intra-uterine device, oral, implantable, or injectable contraceptives

Exclusion criteria

- History of, or current, medical condition or laboratory result which, in the opinion of the investigator, unfavourably alters the risk-benefit of trial participation, may jeopardise participant safety, or may interfere with the satisfactory completion of the trial and trial-related procedures
- Serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other cardiac problems that may place the participant at increased vulnerability to the sympathomimetic effects of a stimulant drug
- History of seizure disorder (except febrile seizures prior to age 5 and at least 1 year prior to trial participation), Tourette's disorder, or intellectual disability of minor severity or greater (DSM-5 criteria)
- History of psychosis, bipolar disorder, anorexia nervosa, bulimia, or suicide attempt. Current depression, anxiety, conduct/behavior disorder, substance use disorder, or other psychiatric condition which, in the investigator's opinion, may jeopardise participant safety or may interfere with the satisfactory completion of the trial and trial-related procedures
- Active suicidal ideation as evidenced by an ideation score of ≥ 2 on the C-SSRS
- History of severe allergic reaction to MPH

Childress 2020b *(Continued)*

- History of no response or intolerance to the adverse effects of MPH
- ALT/AST, total bilirubin, or creatinine > 1.5 x the upper limit of normal. Elevated bilirubin due only to Gilbert's syndrome is not exclusionary
- History of alcohol abuse or illicit drug use
- Use of prescription medications within 7 days of baseline (visit 2), except for ADHD stimulant medication (5 days) and MAOIs (14 days), and over-the-counter medications (except birth control and allowed medications) within the 3 days preceding baseline (visit 2). Medications not covered in allowed medications or prohibited medications must be cleared by the medical monitor prior to enrolling the participant.
- Participation in a clinical trial with an investigational drug within the 30 days preceding trial enrolment
- Previous treatment experience with ER-MPH (HLD200)
- Positive screening for illicit drug use or nicotine and/or current health conditions or use of medications that might confound the results of the trial or increase risk to the participant
- In the opinion of the investigator, the participant may have problems complying with the protocol or the procedures of the protocol, or could face unnecessary safety risks from the trial. This includes current health conditions or use of medications that might confound the results of the trial or increase risk to the participant.
- Participant's SBP or DBP measurement exceeds the 95th percentile for age, sex, and height at the baseline visit
- Participant is significantly underweight based on CDC BMI-for-age sex-specific values at the screening visit. Significantly underweight is defined as a BMI < 5th percentile.
- Participant is significantly overweight based on CDC BMI-for-age sex specific values at the screening visit. Significantly overweight is defined as a BMI > 95th percentile.

Interventions	Participants went through a 6-week open-label dose-optimisation phase before being randomised. Participants were randomly assigned to: continuation of optimised dose of ER-MPH (HLD200) (20, 40, 60, 80 or 100 mg/d) or placebo for 1 week No. randomised to each group: 65 to ER-MPH (HDL200), 54 to placebo Mean medication dosage: 66.2 mg/d Administration schedule: once/d in the evening (8:00 ± 1.5h) Duration of each medication: mean of 40.4 days of MPH during open-label phase, plus 1 week MPH or placebo Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: 6 weeks, starting at 10 mg, increases/decreases of 10-20 mg Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP Score, assessed at 8:00 am, 9:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, 7:00 pm, and 8:00 pm during the laboratory classroom day **Serious AEs** • Spontaneous reporting **General behaviour** • PREMB-R PM • PREMB-R AM • PERMP

Childress 2020b *(Continued)*

"PREMB-R results were investigator-rated summary scores derived from clinician-administered parent interviews, with the parent PREMB-R ratings based on the last 2 weekdays before the laboratory classroom day." (Childress 2020b p 4). "PREMB-R AM and PREMB-R PM at Visit 9 were assessed by using an analysis of covariance model with treatment as the main effect and trial centre and baseline score at baseline (Visit 2) as the covariates" (Childress 2020b p 5)

Non-serious AEs

- Spontaneously reported TEAEs queried at each visit, from informed consent through the follow-up call 14–3 days after final dose
- Vital signs, no information on timing of outcome assessment
- ECG, no information on timing of outcome assessment
- Clinical laboratory tests, no information on timing of outcome assessment
- Physical examination findings, no information on timing of outcome assessment

Notes

Sample calculation: no

Ethics approval: yes, approved by each site's Institutional Review Board

Comments from trial authors

- First, the exclusion of a trial site (n = 36) may have reduced power to detect significant differences at some secondary endpoints.
- Furthermore, differences in baseline characteristics, with more children diagnosed with predominantly inattentive only and with less clinical severity based on the CGI-S in the placebo group, may have also affected treatment differences.
- Moreover, the trial included only school-age children (6–12 years of age) with a history of at least partial response to MPH and most psychiatric comorbidities were excluded. Therefore, the applicability of these findings to other age groups (i.e. preschool children, adolescents, and adults), MPH-naive, and other presentations of ADHD is unknown.

Key conclusion of trial authors

- Evening-dosed, treatment-optimised DR/ER-MPH significantly improved ADHD-related functional impairment in the before-school early morning period, during the laboratory classroom period, and in the late afternoon/early evening period compared with placebo in children with ADHD.
- Treatment-optimised DR/ER-MPH was well tolerated: during the double-blind phase there were no discontinuations due to TEAEs, TEAEs did not differ between DR/ER-MPH and placebo groups, and all TEAEs were mild/moderate.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: no

Funding source: Ironshore Pharmaceuticals

Email correspondence with trial authors: September and October 2021. No supplemental information was gained through personal email correspondence with trial authors in September 2021 and no answer was received in October 2021.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

Childress 2020b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, method not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A full trial site was excluded: 36 participants. Beside that only 2 withdrawals from double-blind phase (1.7%) Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	CSSR-S is reported as a safety assessment, but no results are reported.

Childress 2020c

Study characteristics	
Methods	A 2-week parallel-trial with 2 arms: 1. MPH-MLR 2. placebo Phases: 6 (screening and wash-out (up to 4 weeks), behaviour-management treatment (2-4 weeks), eligibility confirmation (2 weeks), open-label phase (6 weeks), double-blind trial (2 weeks), and follow-up phone call after 2 weeks)
Participants	Number of participants screened: 194, 128 entered open-label phase Number of participants included: 90 entered double-blind phase (68 (75.6%) boys, 22 (24.4%) girls) Number of participants followed-up: 88 completed the double-blind trial Number of withdrawals: 4 Diagnosis of ADHD: DSM-5 (from safety population: placebo group: 88% combined type, 12% hyperactive/impulsive type; MPH group: 89.9% combined type, 8.4% hyperactive/impulsive type, 1.7% inattentive type) Age: mean 58.9 months, approximately 4.9 years (SD 6.1, range 48-68 months) IQ: estimated IQ ≥ 80 MPH-naive: not stated Ethnicity: white (n = 54, 60.0%), African American (n = 33, 36.7%), Asian (n = 1, 1.1%), other (n = 2, 2.2%), Hispanic or Latino (n = 11, 12.2%) Country: USA Setting: outpatient Comorbidity: not stated, but many comorbidities were specified as exclusion criteria Comedication: non-sedating antihistamines, acetaminophen (paracetamol), ibuprofen, antibiotics for treatment of a minor illness, and vitamins were permitted during the trial.

Childress 2020c *(Continued)*

Additional sociodemographics: none

Inclusion criteria

- Male and female participants aged 48 months to 68 months inclusive at time of consent
- Meet DSM-5 criteria for ADHD, combined, hyperactive/impulsive or inattentive presentation made during a clinical interview by an experienced clinician and confirmed with K-SADS-PL
- ADHD symptoms must have been present for at least 6 months
- Age- and sex-adjusted ratings of ≥ 90th percentile Total Score on the ADHD-RS-IV Preschool Version (rated over past 6 months)
- Score of < 65 on the Child Global Assessment Scale
- Must have a score of ≥ 4 on the CGI-S at visit 2
- Estimated IQ ≥ 80 on the KBIT-2
- The participant has a parent or legal guardian who will give written informed consent for the participant to participate in the trial
- Participant and parent or legal guardian must be able to speak and understand English
- Participant must live with primary carer/rater and have been living with primary carer for at least 6 months
- Participant and parent or legally authorised representative must be willing and able to comply with all requirements of this protocol
- SBP and DBP < 95th percentile for age and gender

Exclusion criteria

- The participant has had a lack of response to a trial of adequate dose and duration of MPH or intolerance to previous MPH treatment
- The participant is using any other current psychotropic medication except clonidine, guanfacine, atomoxetine and/or stimulants or has taken an investigational drug in the 30 days prior to screening
- The participant has used MAOIs within 14 days of the screening visit
- The participant plans to use prohibited drugs or agents at any point between the screening visit and the end of the trial
- Use of anticonvulsants, antidepressants or antipsychotics in the 30 days prior to screening
- The participant should not start any additional psychotherapy outside of the trial during the duration of the trial
- The participant has a history of chronic vocal or motor tics or Tourette's syndrome
- The participant has any clinically significant ECG abnormalities at screening
- The participant has any major medical conditions that would interfere with involvement in a trial or could be affected negatively by MPH
- The participant has chronic medical illnesses including a seizure disorder (excluding a history of febrile seizures), severe hypertension, untreated thyroid disease, known structural cardiac abnormalities, serious arrhythmias, cardiomyopathy, glaucoma, or a family history of sudden death
- History (in the past 12 months) or presence of clinically significant cardiovascular, cerebrovascular, renal, hepatic, gastrointestinal, pulmonary, immunological, haematological, endocrine, or neurological disease that in the opinion of the investigator could put the participant at risk if he/she participates in the trial or could confound trial results
- Family history (parent or sibling) of structural cardiovascular disease
- Current or recent (past 12 months) history of drug abuse in someone living in the participant's home
- Current symptoms or history of major psychiatric illness (for example schizophrenia, psychosis, bipolar disorder, PTSD, depression, severe anxiety disorder, OCD or autistic spectrum disorder) in addition to ADHD that requires treatment with additional medication or, in the opinion of the principal investigator, would contraindicate trial participation
- History or presence of suicidal ideation or significant self-injurious behavior
- The participant shows evidence of current physical, sexual, or emotional abuse
- Both biological parents of the participant have a history of bipolar disorder

Interventions	Participants went through a 6-week, open-label, dose-optimisation phase before being randomised.

Childress 2020c *(Continued)*

	Participants were randomly assigned to: either continue MPH at optimised dose between 10-40 mg or have placebo Number randomised to each group: 40 to MPH-MLR, 50 to placebo Mean medication dosage: 27.5 mg Administration schedule: once/d Duration of each medication: 8 weeks MPH-MLR for MPH group (6 weeks open label and 2 weeks randomised phase), 6 weeks for placebo group (open label phase) + 2 weeks placebo (randomised phase) Washout before trial initiation: a minimum of 3 days before open-label, none before double-blind trial Medication-free period between interventions: no Titration period: 6 weeks Treatment compliance: not stated
Outcomes	**ADHD Symptoms** • ADHD-RS-IV Preschool Version, assessed at baseline and at 2 weeks (end of treatment) **Serious AEs** • C-SSRS assessed at baseline and at 2 weeks (end of treatment) • Spontaneous reporting **General behaviour** • Conners' Early Childhood Behavior—Parent Short Response Scale. While this scale was measured and reported to show no meaningful difference between the MPH and the placebo group, no means were reported. Therefore, this scale is not included in the analysis. **Non-serious AEs** • Profile and frequency of AEs assessed at baseline and at 2 weeks (end of treatment) **Non-serious AEs** • Clinical laboratory evaluations (haematology, serum chemistry, and urinalysis). Timing of outcome assessment not reported • Physical examinations (including height and body weight) Timing of outcome assessment not reported • Vital signs (temperature, BP, and heart rate). Timing of outcome assessment not reported • ECG. Timing of outcome assessment not reported • CSHQ. Insufficient information was reported to include the CSHQ data in the analysis.
Notes	Sample calculation: yes Ethics approval: yes **Comments from trial authors** • No standardised scale for assessment of TEAEs was used; rather, the presence of TEAEs was spontaneously reported • …although the CGI was used to assess global improvement, and found to be different between the drug and placebo groups, the primary focus on assessment of symptoms (ADHD-RS-IV), rather than other aspects of functioning, may have obscured other facets of functional impairment and their relationship to treatment **Key conclusion of trial authors**

Childress 2020c *(Continued)*

- MPH-MLR at doses up to 40 mg was efficacious and well tolerated in preschool children 4 to < 6 years of age with ADHD
- The safety profile of MPH-MLR in preschool children was consistent with the known safety profile of MPH in older children

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes; to participate in the double-blind trial, participants must have completed the open-label with good results

Any withdrawals due to AEs: 1

Funding source: Rhodes Pharmaceuticals LP

Email correspondence with trial authors: August and October 2021. Trial authors were contacted for information regarding risk of bias through personal email in August and October 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were randomised in a 1:1 ratio through a computer-generated randomisation schedule to either continue their optimised dose or receive matching placebo
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, method not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data from 2.2% of participants Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All protocol outcomes reported

Chronis 2003

Study characteristics

Methods

8-week within-participant, placebo-controlled, randomised, cross-over trial (summer treatment camp) with 3 interventions:

- MPH
- MAS (Adderall)
- placebo

Phases: 2-week baseline assessment followed by 6-week medication trial

Chronis 2003 *(Continued)*

Participants	Number of participants screened: 48 Number of participants included: 21 (19 boys, 2 girls) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 10.3 years (±1.9, range 6-12) IQ: mean 109.9 (± 18.8) MPH-naive: 14 children had received MPH before start of the trial Ethnicity: white (100%) Country: USA Setting: outpatient clinic (summer treatment programme) Comorbidity: learning problems (42.9%), ODD (66.7%), CD (23.8%) Comedication: not stated Other sociodemographics: (median family income = USD 35,000/year (< USD 15,000/year to > USD 100,000/year); 66.7% of parents married **Inclusion criteria** • DSM-IV diagnosis of ADHD **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned to 1 of 7 possible drug condition orders of IR-MPH, MAS (Adderall) and placebo • Placebo at 7:30 am, 11: 30 am and 3:30 pm • 0.3 mg/kg MPH at 7:30 am, 11:30 am and 3:30 pm • 0.3 mg/kg MPH at 7:30 am and 11:30 am with 0.15 mg/kg at 3:30 pm • 0.3 mg/kg MPH at 7:30 am only • 0.3 mg/kg MAS at 7:30 am and at 3:30 pm • 0.3 mg/kg MAS at 7:30 am with 0.15 mg/kg received at 3:30 pm • 0.3 mg/kg MAS at 7:30 am only Mean MPH dosage: not stated Administration schedule: MPH once, twice or 3 times daily according to the randomisation procedure Duration of each medication condition: all participants received medication each Monday through Friday throughout a period of 6 weeks for a 24-day clinical assessment period. Assessment period was divided into three, 8-day segments. Within each segment, placebo occurred twice and each other condition occurred once, with the order of conditions randomly assigned on a daily basis Washout before trial initiation: not stated Medication-free period between interventions: none Titration period: none Treatment compliance: not stated

Chronis 2003 *(Continued)*

Outcomes	**ADHD symptoms** • IOWA CRS: rated by counsellors at the end of each day, by teachers after the classroom period each day and by parents in the evening **Non-serious AEs** • Pittsburgh Side Effects Rating Scale: rated by counsellors and teachers daily, rated by parents each evening with the addition of an item assessing difficulty falling asleep
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • Additional (late-afternoon) stimulant dose has beneficial effects on parent-child interactions • At the end of the summer treatment programme for the 21 children, it was determined that 5 children did not show a sufficient positive response **Key conclusions of trial authors** • Single morning dose of MAS (Adderall) had effects for an entire school day • Single dose of MAS (Adderall) was equivalent to IR-MPH twice/d **Comments from review authors** • No mean MPH dose • Behavioural intervention was also implemented during the entire 8-week trial period • As intervention sequences were switched on a daily basis according to randomisation, we did not ask about first-period data from this trial Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: a grant from Shire-Richwood Pharmaceuticals, Incorporated - manufacturer of Adderall - and from the NIMH Email correspondence with trial authors: July 2014. Emailed trial authors twice to request additional information. Trial author was not able to provide us with additional data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized by day", no description of how randomisation took place
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To ensure blinding, placebo capsules were given at 11:30 am in the MAS conditions and for applicable doses in the other conditions. Active medication and placebo were disguised in opaque gelation capsules by a local pharmacy and were dispensed in daily pill reminders by the trial doctor. Furthermore, children were informed that they would be receiving 2 different kinds of medication to see how well they worked, and that some days they would receive inactive pills, but that they, their counsellors or teachers and their parents would not know what kind of pill they would get each day

Chronis 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Children were informed that they would be receiving 2 different kinds of medication to see how well they worked, and that some days they would receive inactive pills, but that they, their counsellors or teachers and their parents would not know what kind of pill they would get each day
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of dropout Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All outcomes reported

Coghill 2007

Study characteristics	
Methods	12-week randomised, placebo-controlled, double-blind cross-over trial with 3 interventions: • MPH 0.3 mg/kg • MPH 0.6 mg/kg • placebo
Participants	Number of participants screened: not stated Number of participants included: 75 (all boys) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (combined type); ICD-10 (hyperkinetic disorder) Age: mean not reported (range 7-15 years) IQ: > 80 MPH-naive: 100% Ethnicity: not stated Country: UK Setting: outpatient clinic Comorbidity: ODD (41.3%), CD (28%), depressive disorder (4%), generalised anxiety disorder (2.7%), separation anxiety disorder (4%), tic disorder (2.7%), social phobia (1.3%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Eligible boys (scoring 1.5 SD from the mean on both CPRS Short Version, and CTRS Short Version) were interviewed by an experienced child and adolescent psychiatrist using the K-SADS-PL • Those meeting criteria for hyperkinetic disorder (HD F 90) (ICD-10) and combined subtype (DSM-IV) were invited to participate **Exclusion criteria**

Coghill 2007 *(Continued)*

- History of neurological impairment/learning disability
- IQ < 80
- Chronic physical illness
- Sensory or motor impairment
- Current or previous exposure to stimulant medication
- Abuse of any illegal drugs

Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders: 0.3 mg/kg/dose MPH or 0.6 mg/kg/dose MPH and placebo Administration schedule: twice daily Duration of each medication condition: 4 weeks Washout before trial initiation: no Titration period: none Treatment compliance: assessed by pill count and clinical enquiry but not further described
Outcomes	**ADHD symptoms** • CGI, Parent Version and Teacher Version (10 item): rated by parents and teachers, each after 4 weeks
Notes	Sample calculation: no Ethics approval: yes **Key conclusions of trial authors** • Chronic MPH (MPH administered two cross-over periods in a row) predominantly enhanced neuropsychological functioning on "recognition memory" component tasks with modest "executive" demands • Neuropsychological measures offer only modest contributions to the prediction of clinical responses to MPH in ADHD **Comment from trial authors** • Doses (0.3 mg/kg and 0.6 mg/kg) were chosen to reflect low- and high-dose regimens, respectively Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: supported by a local trust through a Tenovus Scotland initiative Email correspondence with trial authors in 2013. Emailed trial authors twice with a request for additional information regarding protocol and number of participants on which analyses were based. Have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by an independent clinical trials pharmacist (using a computer-generated random number sequence with block design to ensure equal numbers in each treatment arm)
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned by an independent clinical trials pharmacist

Coghill 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled, double-blind, no further information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical status was assessed by interview conducted by an experienced, blinded child and adolescent psychiatrist. Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	No description about how many participants were included in analyses Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): not stated
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Coghill 2013

Study characteristics	
Methods	7-week, multi-centre, double-blind, parallel, dose-optimised trial with 3 arms: • LDX dimesylate • OROS-MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 221 (181 boys, 40 girls) (To the MPH and placebo group, not the LDX group) Number of participants followed up: MPH 74, placebo 42 Number of withdrawals: MPH 38, placebo 68 Diagnosis of ADHD: DSM-IV-TR (combined (MPH 86.4%, placebo 79.1%), hyperactive-impulsive (MPH 0.9%, placebo 6.4%), inattentive (MPH 12.7%, placebo 14.5%) Age: mean 10.9 years (range 6-17) IQ: normal MPH-naive: MPH 60 (54.1%), placebo 58 (52.7%) Ethnicity: white (MPH 96.4%, placebo 98.2%), African American (0%), Asian (0%), Hispanic/Latino (MPH 1.8%, placebo 0%) Countries: Germany, Sweden, Spain, Hungary, France, UK, Italy, Belgium, Poland, the Netherlands Setting: outpatient clinic Comorbidity: ODD (MPH 9.0%, placebo 7.3%), concomitant psychiatric diagnosis (MPH 26.1%, placebo 18.2%) Comedication: not stated Other sociodemographics: no significant differences in baseline demographics were noted between the 2 groups

Coghill 2013 *(Continued)*

Inclusion criteria

- Boys and girls
- 6-17 years of age
- Meeting criteria for ADHD according to DSM-IV-TR
- Baseline ADHD moderate severity with ADHD-RS-IV score of ≥ 28
- Age-appropriate intellectual functioning
- BP measurements within the 95th percentile for age, sex and height
- Ability to swallow a capsule
- Girls of childbearing potential had to have a negative urine pregnancy test at baseline and to comply with any contraceptive requirements of the protocol

Exclusion criteria

- Failure to respond to previous OROS-MPH therapy
- Presence of a CD (excluding ODD)
- Pregnancy or lactation
- Weight < 22.7 kg; BMI > 97th percentile for age and sex
- Positive urine drug test (with the exception of patient's current ADHD therapy)
- Clinically significant ECG or laboratory abnormalities
- Suspected substance abuse or dependence disorder (excluding nicotine) within the previous 6 months
- History of seizures
- Tics or Tourette's disorder
- Known structural cardiac abnormality
- Any other condition that might increase vulnerability to the sympathomimetic effects of a stimulant drug
- Patients whose current ADHD medication provided effective control of symptoms with acceptable tolerability
- Patient currently considered a suicide risk, with previous suicide attempt or with history of, or currently demonstrating, active suicidal ideation
- Patient with glaucoma
- Patient with documented allergy, hypersensitivity or intolerance to amphetamine or MPH
- Patient with documented allergy, hypersensitivity or intolerance to any excipients in test or reference products
- Patients with known family history of sudden cardiac death or ventricular arrhythmia
- Patients with pre-existing severe gastrointestinal tract narrowing (pathological or iatrogenic)
- Patients unable to tolerate the trial drug were withdrawn from the trial

Interventions	Participants were randomly assigned to OROS-MPH or placebo Number of participants randomly assigned: MPH 112, placebo 111 Mean MPH dosage: 45.4 ± 12.7 mg/d (9.9% 18 mg, 19.8% 36 mg, 53.2% 54 mg) Administration schedule: once/d, 7:00 am Duration of intervention: 7 weeks Titration period: 4-week stepwise dose-optimisation period after randomisation. 3-week dose-maintenance period followed by 1-week washout and safety follow-up Treatment compliance: 2 discontinued in placebo group because of non-compliance, 3 in MPH group
Outcomes	**ADHD symptoms**

Coghill 2013 *(Continued)*

- ADHD-RS-IV: total score at endpoint, investigator-rated at baseline and weekly for 7 weeks. Endpoint was defined as the last on-therapy, post-randomisation treatment visit with a valid ADHD-RS-IV, total score

Quality of life

- Health Utilities Index-2: parent-rated at baseline and at weeks 4 and 7. Scoring ranges from 0.00 (dead) to 1.00 (perfect health). Higher scores represent better health status
- Child Health and Illness Profile, Child Edition: Parent Report Form: parent-rated at baseline and at weeks 4 and 7. Questionnaire comprises 76 items classed into 5 domains and 12 associated subdomains. Most items relate to the past 4 weeks; the remainder are not associated with a specific time period. Parents use a 5-point response format to assess each item. Achievement is considered the primary health-related quality of life outcome

Non-serious AEs

- Safety assessments included TEAEs, clinical laboratory evaluations, physical examinations, vital signs and ECGs, observer-rated weekly for 8 weeks

Notes

Sample calculation: yes

Ethics approval: approved by an independent ethics committee/institutional review board and regulatory agency at each centre (as appropriate) before trial initiation

Comments from trial authors

- Individuals with comorbid conditions, such as PTSD, bipolar affective disorder or severe anxiety disorder, were excluded from this trial
- As a result of European regulations, the maximum dose of OROS-MPH administered in this trial was 54 mg/d. However, it is possible that the smaller than usual placebo response did, at least in part, contribute to this large treatment effect. ADHD is currently less frequently diagnosed in Europe than in North America, with evidence of underrecognition and underdiagnosis (healthcareimprovementscotland.org). Consequently, it is likely that individuals who are diagnosed are at the more severe end of the spectrum and therefore would be less likely to show a response to placebo. Consistent with this suggestion, reassessment of data from the MTA trial revealed that children who had been diagnosed with ADHD on the basis of DSM-IV criteria, but also met the more restrictive ICD-10 criteria for hyperkinetic disorder, showed a more robust response to medication compared with those who met DSM-IV criteria alone

Key conclusions of trial authors

- In this European 7-week phase III trial, LDX dimesylate was more effective than placebo in improving symptoms in children and adolescents with ADHD
- Compared with placebo, significant improvements in both ADHD core symptoms and global functioning were observed
- LDX dimesylate was well tolerated, with TEAEs consistent with those reported in previous studies
- Robust efficacy outcomes were also observed for OROS-MPH, which was included in this trial as a reference arm

Comment from review authors

- Very confused on the number of participants included in the different analyses

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes

Any withdrawals due to AEs: yes, 2 in the MPH group and 2 in the placebo group (as well as 5 in the LDX dimesylate group)

Funding source: Shire Development LLC

Risk of bias

Coghill 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice/web response system was used to allocate a unique randomisation number to each participant. Randomisation was stratified by country and age group (6 to 12 or 13 to 17 years of age)
Allocation concealment (selection bias)	Low risk	Interactive voice/web response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial drugs were over-encapsulated and appeared identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking: double-blinded (participant, caregiver, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF approach was used when efficacy assessments were incomplete for a participant owing to early withdrawal from the trial or for missing data. However, as the review authors cannot understand the relationship between the *n* of the full analysis set and the endpoint data, we assessed risk of bias as unclear Selection bias (e.g. titration before randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Outcomes according to protocol

Connor 2000

Study characteristics	
Methods	3-month, randomised, blind, parallel-group trial with 3 arms: • MPH and clonidine • clonidine monotherapy (clonidine + placebo) • MPH monotherapy (MPH + placebo)
Participants	Number of participants screened: 24 Number of participants included: 24 (MPH + clonidine 8 boys, 0 girls; clonidine + placebo 8 boys, 0 girls; MPH + placebo 8 boys, 0 girls) Number of participants randomly assigned: MPH + clonidine 8, placebo + clonidine 8, placebo + MPH 8 Number of participants followed up: MPH + clonidine 8, placebo + clonidine 6, placebo + MPH 7 Number of withdrawals: MPH + clonidine 0, placebo + clonidine 2, placebo + MPH 1 Diagnosis of ADHD: DSM-III-R (combined (100%)) Mean age: MPH + clonidine 10.1 years, placebo + clonidine 9.3 years, placebo + MPH 8.9 years IQ: > 70 MPH-naive: 54% Ethnicity: white (11%), African American (1%), Asian (0%), Hispanic (0%), other (0%)

Connor 2000 *(Continued)*

	Country: USA Setting: outpatient clinic Comorbidity: ODD or CD (100%) Comedication: not stated Other sociodemographics: no significant differences in baseline demographics were noted between groups **Inclusion criteria** • DSM-III-R for ADHD • DSM-III-R for ODD or CD, score of 1.5 SD above the mean for age and sex on the Parent CBCL, Attention problems scale (T score > 65) and a score on the Teacher Child Attention Problem Rating Scale of ≥ 93rd percentile • Score 1.5 SD above the mean for age and sex on the Parent or Teacher CBCL, Delinquency or Aggression problems scale • Normal findings from general physical examination by family physician within 6 months before trial entry **Exclusion criteria** • Medical history that contraindicated use of stimulants or clonidine
Interventions	Participants were randomly assigned to MPH + clonidine or placebo + clonidine MPH dose: 35.0 (5.67) mg/d Administration schedule: twice/d Duration of intervention: 12 weeks Titration period: 4 weeks after randomisation Treatment compliance: “All subjects were acceptably compliant with the protocol”
Outcomes	**General behaviour** • Disruptive Behavior Disorders Rating Scale: parent- and teacher-rated monthly • Home Situations Questionnaire: parent-rated monthly • School Situations Questionnaire: teacher-rated monthly **Non-serious AEs** • Possible side effects of MPH and clonidine: combined Stimulant/Clonidine Side Effects Rating Scale, parent- and teacher-rated monthly • Pulse and BP obtained monthly. ECG measured after first month. Height and weight obtained monthly
Notes	Intervention groups used: MPH + clonidine; control group: placebo + clonidine Ethics approval: yes Sample calculation: no Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no (1 in the MPH-only group, not included here) Funding source: supported by a UMMS (University of Massachusetts Medical School) Small Grants Project Award

Connor 2000 *(Continued)*

	Email correspondence with trial authors: June 2013. We obtained additional information from trial authors, but it was not possible to receive supplemental data. We could not perform a meta-analysis on any of the outcomes, as we did not have relevant data and transformation was not possible.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	8 participants were randomly assigned to each group. 3 participants were previous MPH treatment failures and refused randomisation to the MPH-alone trial arm. These 3 participants were partially randomly assigned to MPH and clonidine or to clonidine alone. All other children were fully randomly assigned
Allocation concealment (selection bias)	Low risk	After trial completion, the medication blind was broken. All medication capsules and placebo capsules were prepared by the UMMS (University of Massachusetts Medical School) Pharmacy in identical capsules to disguise taste and smell. All participants in all trial groups received an equal number of capsules per day.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All teachers, school nurses, parents, children and research assistants completing dependent measures were blinded to the child's treatment group for the trial duration. Completion of ECGs for only 2 clonidine treatment groups may have broken blinding for parent raters and for the child (but not for teacher raters nor for research assistants administering the Gordon Diagnostic System (GDS), who remained blinded as to whether the child had received an ECG). This is not relevant to us, as we are using data only on the 2 groups completing ECGs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As stated above
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Reply from trial author on our request for the protocol: protocol described in the trial

Cook 1993

Study characteristics

Methods	6-week, double-blind, single cross-over, placebo-controlled trial conducted on a group of 15 participants with ADD and a comparison group of 10 age-matched participants who did not have ADD ADD group was randomly assigned to 1 of 2 experimental groups: • MPH • placebo
Participants	**ADD group** Number of participants screened: not stated Number of participants included: 15 (all boys)

Cook 1993 *(Continued)*

	Number of participants followed up: 15 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (100% met DSM-III criteria for ADD with hyperactivity) Age: mean 104.5 months (approximately 8.7 years) (range 6-10 years) IQ: mean 110.5 (SD 7.15) MPH-naive: 100% Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: central auditory processing disorder (80%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Male • 6-10 years of age • IQ > 85 • Clinical diagnosis of ADD from paediatrician and met DSM-III criteria for ADD on both Parent and Teacher Versions of the SNAP; scored ≥ 15 points on the Parent Version of the Abbreviated Conners' Rating Scale **Exclusion criteria** • Seizures • Cerebral palsy • Learning disabilities • Speech or language problems • Vision or peripheral hearing problems • Thought disorder • Abnormal auditory brainstem-evoked potentials • Previous drug treatment for ADHD
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Mean MPH dosage: 0.30 mg/kg (0.057) Administration schedule: not stated Duration of each medication condition: 3 weeks Washout before trial initiation: not relevant, 100% treatment-naive Medication-free period between interventions: minimum of 48 h between the 2 interventions Titration period: dose was titrated up to a maximum (MPH tablets or placebo tablets) over the first 3 weeks of the experimental period Treatment compliance: not stated
Outcomes	**ADHD symptoms**

Cook 1993 *(Continued)*

- SNAP: teacher- and parent-rated, only items on the Inattention and Impulsivity subdomains, measured at the end of each treatment condition
- ADD/H Comprehensive Teacher Rating Scale: measured at the end of each treatment condition
- Abbreviated Conners' Rating Scale: parent-rated, measured at the end of each treatment condition

Notes

Sample calculation: no information

Ethics approval: yes

Comment from trial authors

- Limitations: the conclusion should not be generalised to results obtained with measures other than the 3 behaviour rating scales. The sample is small. Stimulant treatment periods were brief, and results may not have been maintained at the same level if the trial had been conducted over a longer period

Comment from review authors

- Read relevant parts of Dr. Cook's Ph.D. dissertation to get additional information about the trial

Key conclusion of trial authors

- "The implications of these results are 3-fold. First, sustained attention is a critical feature of performance on tests of central auditory processing disorder, and current diagnostic criteria for central auditory processing disorder make clinical separation of the 2 disorders problematic. Second, stimulants appear to be a useful treatment for symptoms of both ADD and central auditory processing disorder. Third, tests of central auditory processing disorder may provide a useful measure of ADD symptoms and response to stimulants"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: supported by the Medical Center Rehabilitation Hospital Foundation and the School of Medicine, University North Dakota; the Veterans Hospital; the Dakota Clinic; and The Neuropsychiatric Institute, Fargo, North Dakota

Email correspondence with trial authors: September 2013. Emailed trial author requesting additional information about the trial and data. Dr. Cook referred to his Ph.D. dissertation, which we managed to get.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to groups by a table of random numbers known only to the pharmacist
Allocation concealment (selection bias)	Low risk	Drugs were coded and administered by a pharmacist, and clinical titration of dosage was done by the participant's paediatrician; neither practitioner was involved in data collection
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physician, audiologist, teachers and parents involved in behaviour ratings and participants themselves were blinded to assigned treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physician, audiologist, teachers and parents involved in behaviour ratings and participants themselves were blinded to assigned treatment

Cook 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Corkum 2008

Study characteristics	
Methods	3-week, blind medication trial with cross-over design, in which children were randomly assigned to the following: • LD-MDH; MD-MDH • placebo
Participants	Number of participants included: 28 Number of participants followed-up: 21 (15 boys, 6 girls) Number of withdrawals: 7 children excluded from final data analyses Diagnosis of ADHD: DSM-IV (combined type (52%), hyperactive-impulsive type (10%), inattentive type (38%)) Age: mean not reported (range 6 years 1 month-12 years 1 month) IQ: no intellectual disability MPH-naive: 100% Setting: outpatient clinic Country: Canada Ethnicity: all participants were white Comorbidity: learning disabilities (29%), ODD (10%), CD (0%), generalised anxiety disorder (0%), depression (0%) Comedication: not stated Other sociodemographics: predominantly middle-class families **Inclusion criteria** • Stimulant medication-naive • DSM-IV criteria for 1 of the 3 ADHD subtypes • Received a recommendation to initiate a trial of MPH following assessment • Parents/caregivers agreed to initiate a stimulant medication trial through the clinic paediatrician **Exclusion criteria** • IQ < 1 SD below the mean on the WISC-IV • Known neurological, metabolic or seizure disorder • Currently taking other psychotropic medications or medications for sleep disturbances • Symptoms of an intrinsic sleep disorder (i.e. sleep apnoea, restless legs syndrome or periodic limb movements in sleep) or a sleep-onset disorder based on parent report

Corkum 2008 *(Continued)*

	• Reached criteria for another mental health disorder that was considered primary to the ADHD diagnosis (e.g. autism)
Interventions	Participants were randomly assigned to 1 of 3 medication-dosing schedules, including 1 week of baseline, placebo and low and moderate IR-MPH (Ritalin) dose condition Children weighing ≤ 25 kg received 5-mg and 10-mg doses; children weighing > 25 kg received 10-mg and 15-mg doses. Children received medication 3 times/d (8:00 am, 12:00 pm, 4:00 pm) Duration of medication: 1 week of each dose Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS, CTRS - Revised, Short Form: rated weekly **Non-serious AEs** • Sleep Disturbances Scale for Children based on child's sleep over previous week: rated by parents • Actigraphy • Sleep diary
Notes	Sample calculation: not stated Ethics approval: yes **Key conclusion of trial authors** • "Based on findings from the current trial, we would encourage physicians and parents to closely monitor children's sleep when treating ADHD with stimulant medication, and to carefully weigh the benefits of improved behavioural functioning while taking medication against the potential negative consequences of sleep" **Comment from review authors** • Paper includes data on AEs: sleep disturbance (ActiGraph data, sleep diary data, Sleep Disturbances Scale for Children data) related to MPH treatment compared with placebo Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: research was supported by a grant from the Izaak Walton Killam IWK Health Centre in Halifax, Nova Scotia Email correspondence with trial authors: August-October 2013. We received supplemental information regarding additional data from trial authors, but we never received first-period data from the crossover trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Baseline data from 1 week were collected, followed by a 3-week medication trial with random assignment of children to 1 of 3 medication-dosing schedules. The original, fully randomised schedule was modified after a pilot trial, conducted before the current trial, indicated that children receiving MD-MPH before the LD-MPH reported increased side effects and were more likely to stop taking the third dose (4:00 pm) of medication

Corkum 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Pharmacy local to the ADHD clinic prepared both placebo and active medication, which were packaged into identical gelatin capsules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Child, family, school personnel and trial investigators were unaware of the randomisation schedule. This information was made available only to the paediatrician and the pharmacist
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Child, family, school personnel and trial investigators were unaware of the randomisation schedule. This information was made available only to the paediatrician and the pharmacist
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 children excluded from final data analyses for the following reasons: actigraphic problems (i.e. data failure/loss of ActiGraph/refusal to wear ActiGraph) (n = 5), withdrawal of consent due to marital discord (n = 1) and decision to try alternative medication immediately before the start of the medication trial (n = 1) Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Protocol received through correspondence with trial author. No indication of selective reporting.

Corkum 2020

Study characteristics	
Methods	A 4-week cross-over-trial with 2 arms: • 2 weeks of ER-MPH • 2 weeks of placebo Phases: 2 (baseline followed by 4-week, double-blind trial)
Participants	Number of participants screened: 32 Number of participants included: 26 (23 boys, 3 girls) Number of participants followed up: 26 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (combined type: 17 (65.4%), inattentive type: 9 (34.6%)) Age: mean 8 years and 8 months (SD 24.5 months, range 6-12 years) IQ: 95.6 (SD 31.6) MPH-naive: 100% Ethnicity: white (n = 23), Latin American (n = 2), Aboriginal (n = 1) Country: Canada Setting: outpatient and sleep laboratory Comorbidity: learning disorder (n = 8, 30.8%) Comedication: not stated

Corkum 2020 *(Continued)*

	Additional sociodemographics: socioeconomic status was calculated using the Boyd-NP scale and was in the average range (M 68.7, SD 23.2). Mean household annual income fell in the bracket of CAD 51,000 to CAD 60,000. **Inclusion criteria** • Medication-naïve • 6-12 years old • DSM-IV-TR diagnosis of ADHD **Exclusion criteria** • Full scale IQ falling > 1 SD below the mean according to the WISC-IV • Known neurological, genetic, metabolic, or seizure disorder • Previous diagnosis of a primary sleep disorder • Undergoing behavioural or pharmacological treatment for sleep problems • A diagnosis of another primary mental health disorder based on the clinical diagnostic procedures (excluding comorbid diagnoses of learning disabilities • Pubertal development beyond Tanner Stage 2 • Currently taking or had previously taken psychotropic medication • PolySomnography evidence indicative of a sleep breathing problem
Interventions	Participants were randomly assigned to 1 of 2 possible orders of placebo for 2 weeks and MPH (Biphentin) for 2 weeks. Children weighing < 20 kg received a 20 mg daily dose, children weighing 20-30 kg were given 30 mg, and children weighing > 30 kg were given 40 mg. Number randomised to each group: not stated Mean medication dosage: not stated Administration schedule: once daily within 1 h of waking Duration of each medication: 2 weeks (data related to sleep and daytime behaviour were collected during the 1st and 3rd weeks of this trial (i.e. after the 1st week of each condition). The 2nd and 4th weeks were used in situations in which the first week of a condition was not considered typical by the parent, e.g. child was ill) Washout before trial initiation: not necessary as all participants were medication-naive Medication-free period between interventions: none Titration period: none Treatment compliance: not measured. Parents reported informally to the paediatrician that the children had been adherent
Outcomes	**ADHD symptoms** • CPRS-Revised: Long Version assessed at week 1 and 3 • CTRS-Revised: Long Version assessed at week 1 and 3 **Non-serious AEs** • Sleep parameters assessed by polysomnography and actigraphy sleep onset latency, sleep efficiency, and total sleep time (also reported as sleep duration) assessed at week 1 and 3
Notes	Sample calculation: yes; "with an effect size (Cohen's f) of 0.18 and power set at 0.95 and an alpha of 0.05, 26 participants were determined to be the minimal sample size needed" Ethics approval: yes **Comments from trial authors**

Corkum 2020 *(Continued)*

- "It is likely that the inconsistencies in results between actigraphy and polysomnography are due to the fact that polysomnography is collected in a novel and controlled environment for one night compared to actigraphy that is collected at home over a number of nights."
- "Our trial also had an unequal sex distribution, but this is consistent with known differences in ADHD diagnoses in boys versus girls. Moreover, research indicates that there are no sex differences in terms of sleep problems in pre-pubertal children."

Key conclusion of trial authors

- The main finding of this trial was that based on actigraphy, MPH had a negative impact on total sleep time due to a 30-min increase in sleep onset latency.
- Increased sleep onset latency resulting in reduced total sleep time, which has been linked to poorer daytime functioning, is a potential AE of stimulant medication, which may require management to optimise outcome.

Comment from review authors

- It is not clear if another article is going to report on the full population of the trial or if Corkum 2020 is the main article, as there are some small discrepancies in the participant information between the 3 included articles.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no

Any withdrawals due to AEs: no

Funding source: Canadian Institutes of Health Research

Email correspondence with trial authors: August and September 2021. Trial authors were contacted for information regarding main article, risk of bias and first-period data through personal email in August and Semptember 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted using blocking on an online calculator (randomised in blocks of 10)
Allocation concealment (selection bias)	Low risk	The randomisation schedule was conducted through a third-party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The pharmacists prepared the medication and placebo by placing these in identical gelatin capsules so that children and parents could not identify whether capsules contained medication or the placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The randomisation schedule was conducted through a third-party, and the child, family, teachers, and trial staff were all blind to medication condition; only the trial paediatricians and pharmacists were aware of the medication status of the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Cox 2006

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, cross-over trial of adolescent drivers with ADHD who were assessed on a driving simulator after taking: • 72 mg of OROS-MPH • 30 mg of ER-MAS • placebo Phases: 3 (2 relevant phases)
Participants	Number of participants screened: not stated Number of participants included: 35 (19 boys, 16 girls) Number of participants followed up: 35 Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV (combined 21 (60%), hyperactive-impulsive 2 (6%), inattentive 12 (34%)) Age: mean 17.8 years (range 16-19) IQ: not stated MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: agoraphobia (2.9%), CD and marijuana abuse (2.9%), OCD (2.9%), OCD and hypomania (2.9%), nicotine dependence (5.7%) Comedication: 2 were taking no medication, 21 were taking MPH and 12 were taking amphetamine formulations at the start of the trial Other sociodemographics: none **Inclusion criteria** • Adolescent drivers • 16-19 years of age • ADHD according to DSM-IV. To meet inclusion criteria for a diagnosis of ADHD, adolescents first needed to surpass clinical cut-offs for ADHD on a commonly used parent rating scale, the ADHD-RS-IV • Psychiatrist confirmed ADHD diagnosis with the Standardized Interview for Adult ADHD (DSM-IV) • Positive history of stimulant responsiveness, as disclosed by adolescents and by parent reports; current licence to drive and reported daily driving activity **Exclusion criteria** • Adolescents were excluded when they had a history of tics or any adverse reaction to stimulant medication • History of substance abuse disclosed by patient or parent • Co-existing medical condition or medication usage known to interfere with safe administration of stimulant medications
Interventions	Participants were randomly assigned to 1 of 2 relevant drug condition orders of MPH and placebo

Cox 2006 *(Continued)*

	Mean MPH dosage: 72 mg/d Administration schedule: 2 overlaid capsules/tablets in blister packs each day on awakening Duration of each medication condition: 17 days Washout before trial initiation: not stated Medication-free period between interventions: 4-21 days between OROS-MPH and MAS Titration period: half dose (36 mg/d OROS-MPH) days 1-5, full dose (72 mg/d OROS-MPH) days 6-17 initiated after randomisation Treatment compliance: not stated. Pill counts were completed at each trial visit
Outcomes	**Non-serious AEs** • Throughout the trial, only 1 AE was reported - urinary difficulty. This AE occurred during treatment with 36 mg of OROS-MPH and was resolved after 2 days without discontinuation of the medicine • Self-Reported Stimulant Drug Side Effects Rating Scale on days 5 and 10
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • Automobile accidents are the leading cause of death among adolescents, and collisions are 2-4 times more likely to occur among adolescents with ADHD • Studies have demonstrated that stimulants improve driving performance • Results provide evidence supporting most literature on children with short-acting stimulants; longer-acting stimulants appear equally effective for female and male post-pubertal adolescents with ADHD • Limitation of this trial is that few participants with hyperactive subtype were included, limiting extrapolation of results to this subgroup **Key conclusions of trial authors** • This trial validates the use of stimulants to improve driving performance in adolescents with ADHD • In this trial, OROS-MPH promoted significantly improved driving performance compared with placebo and ER-MAS **Comments from review authors** • Effects of MPH were also measured, but not in comparison with placebo. Therefore, we could not use these data in the review • Some participants are > 18 years. However, as mean age is > 19 years, this trial is still included but was tested by sensitivity analyses Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; excluded if any history of AEs to stimulant medications Any withdrawals due to AEs: no Funding source: supported by funding from McNeil Pediatrics, a division of McNeil-PPC Incorporated Email correspondence with trial authors: February 2014. We received additional information from trial authors. Data from the Self-Reported Stimulant Drug Side Effects Rating Scale are no longer available (Krogh 2013b [pers comm]).

Risk of bias

Bias	Authors' judgement	Support for judgement

Cox 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Using a random-numbers table, each participant was assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatments were provided in different forms: "Participants took 2 overlaid capsules/tablets in blister packs each day on awakening". Participants and research assistants were blinded to medication conditions
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Participants were either tested on placebo or were not required to come in for testing". Participants and research assistants were blinded to medication condition
Incomplete outcome data (attrition bias) All outcomes	Low risk	Email correspondence with trial author: no dropouts and all were followed up (Krogh 2013b [pers comm]) Selection bias (e.g. titration after randomisation → exclusion): none described
Selective reporting (reporting bias)	Low risk	Email correspondence with trial author, who stated that all planned outcome measures and analyses are described in the papers (Krogh 2013b [pers comm])

CRIT124US02

Study characteristics	
Methods	An 8-week, cross-over trial of LA-MPH 20-60 mg/d with 2 arms • 4 weeks of MPH • 4 weeks of placebo Phases: unknown; mention of washout in Cortese 2018 (page 362 of appendix)
Participants	Number of participants screened: not stated Number of participants included: 109 (100% girls) Number of participants followed-up: 83 Number of withdrawals: 26 Diagnosis of ADHD: not stated (55% combined type, 0.9% hyperactive-impulsive type and 44% inattentive type) Age: mean 13.8 years (range 12-17) IQ: not stated MPH-naive: not stated Ethnicity: race: white (70%), black (20%), Asian (1%), other (9%) Country: USA Setting: not stated Comorbidity: not stated Comedication: not stated

CRIT124US02 *(Continued)*

	Additional sociodemographics: family history of ADHD: 38% no, 60% yes, 3% unknown **Inclusion criteria** • Girls aged 12-17 years • Diagnosis of ADHD confirmed by performance on the DISC-4 • Ability and willingness of a parent or other caregiver and the patient to complete questionnaires • Function at an age appropriate academic level **Exclusion criteria** • Medical condition interfering with trial participation • Pregnancy • Difficulty in swallowing capsules • Known sensitivity to the trial drug or other drugs in the same class • Use of any investigational medication in the past 30 days
Interventions	Participants were randomly assigned to 1 of 2 different medication orders of LA-MPH 20-60 mg/d or placebo for 4 weeks Number randomised to each group: not stated Mean medication dosage: not stated Administration schedule: once daily Duration of each medication: 4 weeks Washout before trial initiation: mention of washout in Cortese 2018 but not clear if before or in between interventions Medication-free period between interventions: mention of washout in Cortese 2018 but not clear if before or in between interventions Titration period: not stated Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS. No information on timing of outcome assessment for this outcome available • CASS:S. No information on timing of outcome assessment for this outcome available **Serious AEs** • Monitored and recorded. No information on timing of outcome assessment for this outcome available **Non-serious AEs** • Monitoring and reporting of AEs. No information on timing of outcome assessment for this outcome available
Notes	Sample calculation: 108 Ethics approval: not stated **Comments from review authors** • Length of cross-over as well as mention of washout period was found in review by Cortese 2018 Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no Any withdrawals due to AEs: no

CRIT124US02 *(Continued)*

Funding source: Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All capsules were over-encapsulated in a one-colour capsule of the same size
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout of > 20% of the participants Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, 10 withdrawals due to lack of efficacy
Selective reporting (reporting bias)	High risk	The results for vital signs, ECG, laboratory evaluations and physical condition and body weight are not reported.

Douglas 1986

Study characteristics

Methods	5-day cross-over trial with 2 interventions: • MPH (0.3 mg/kg capsules each dose, morning + afternoon) • placebo (100 mg lactose capsules) Phases • Screening session about a week before testing (given practice on all tasks in the test battery; appropriate level was established for each child on tasks graded for difficulty level) • 5 days of testing. Children received drug (D) or placebo (P) according to 1 of 4 possible orders: (1) PDDPP: (2) DPPDD; (3) DDPPD; (4) PPDDP. Testings were received each morning according to 4 test orders: (1) ABCDEF; (2) ACBEDF; (3) ADEBCF and (4) AEDCBF Before the trial was undertaken, 16 drug and test order combinations for the morning test battery were ordered randomly. As participants entered the trial, they were assigned to these drug-plus-test order combinations until all 16 participants had been assigned. The order of the 2 tests in the afternoon battery (arithmetic and word discovery) was alternated over children, and each child received tests in the same order over 5 days of testing
Participants	Number of participants screened: not stated Number of participants included: 16 (15 boys, 1 girl) Number of participants followed up: 16

Douglas 1986 *(Continued)*

Number of withdrawals: not stated

Diagnosis of ADHD: DSM-III (subtypes not stated)

Age: mean 9.2 years (range 6-11.6)

IQ: mean 103.19 (range 89-125)

MPH-naive: 13 (81%)

Ethnicity: not stated

Country: Canada

Setting: outpatient clinic

Comorbidity: not stated

Comedication: not stated

Other sociodemographics: children's families varied from I to V on the Hollingshead and Redlich Index (with most families falling within level III to IV (V being the poorest)

Inclusion criteria

- Met criteria for a DSM-III diagnosis of ADHD (American Psychiatric Association, APA 1980)
- Had to receive ratings > 1.5 (on a 0-3 scale) on the Hyperactivity Index of Revised Conners' Parent and Teacher Rating Scales

Participants were referred to the Hyperactivity Project at Montreal Children's Hospital by paediatricians or school personnel. Referral was based on presence of the following symptoms:

- inattentiveness
- impulsivity
- hyperactivity
- restlessness
- poor compliance and poor self control

Symptoms were of sufficient severity to prompt referring physicians to consider a trial on stimulant medication

Exclusion criteria

- Psychosis
- Serious visual, auditory or language deficits
- Diagnosed as brain damaged
- Restless behaviour attributable to emotional problems or a stressful home environment
- Appearance of symptoms before age 5 and evidence that symptoms were chronic and pervasive

Interventions	Participants were randomly assigned to 1 of 4 possible orders of drug (D) or placebo (P): (1) PDDPP; (2) DPPDD; (3) DDPPD; (4) PPDDP. On days when participants were assigned to active medication, they received a capsule containing the quantity of medication closest to a calculated dose of 0.3 mg/kg for each dose (morning and afternoon) Mean MPH dosage: not stated Administration schedule: morning capsule administered approximately 1 h after breakfast and 45 min before morning test battery was administered. Second capsule, identical to the morning capsule, administered before child left for lunch and returned to school. Time between morning and afternoon capsule was approximately 3½ h Duration of each medication condition: 1 day each; in all 2 or 3 days, depending on order of drugs assigned

Douglas 1986 *(Continued)*

	Washout before trial initiation: 24 h before screening, 48 h before first testing day Titration period: none Treatment compliance: capsule administered by examiner
Outcomes	**ADHD symptoms** • Hyperactivity Index from CTRS-R: examiner-rated, at end of each morning of individual testing • Hyperactivity Index from CTRS-R: teacher-rated, each afternoon Score for the Index is based on the mean of item ratings on a 4-point scale (0-3)
Notes	Sample calculation: no Ethics approval: yes **Key conclusions of trial authors** • Results indicate MPH-induced improvement in most measures • Drug-induced changes reflected increased output, accuracy and efficiency and improved learning acquisition. Evidence of increased effort and self-correcting behaviours was found • It is argued that review authors have underestimated the potential of stimulants to improve performance of ADD-H children on academic, learning and cognitive tasks Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: not stated Funding source: supported by grant number MA 6913, from the Medical Research Council of Canada Email correspondence with trial authors: July 2014. Emailed trial authors to ask for additional information. Received information on ethics approval, but first trial author was not able to provide additional data or information on the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	High risk	Capsule was administered by examiner
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In a few cases in which data were missing, scores from 1 or 2 days were used to compute means for drug and placebo conditions. No information on dropout rate Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no

Douglas 1986 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol obtained

Douglas 1995

Study characteristics	
Methods	8-day, double-blind, cross-over trial in which participants were randomly assigned to different doses of MPH and placebo: • 0.3 mg/kg MPH • 0.6 mg/kg MPH • 0.9 mg/kg MPH • placebo Phases • Assessment week 1: 4 different doses given on 4 different days • Assessment week 2: same structure as assessment week 1
Participants	Number of participants screened: not stated Number of participants included: 17 (16 boys, 1 girl) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-III-R. Also had to meet DSM-III criteria for ADD-H Age: mean 9 years 5 months (range 6 years 3 months-11 years 9 months) IQ: mean 104.3 (range 89.0-127) MPH-naive: 53% Ethnicity: not stated Country: Canada Setting: treatment centre (hospital) or outpatient clinic Comorbidity: ODD (71%), CD (18%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DMS-III-R criteria for ADHD • DSM-III criteria for attention deficit disorder with hyperactivity • Ratings from both mothers and teachers at or above a criterion score of 1.5 on the Hyperactivity Index of the Revised CRS **Exclusion criteria** • IQ < 85 • Serious visual, auditory or speech deficits • Evidence of organic damage

Douglas 1995 *(Continued)*

	• Evidence suggesting that symptoms could be attributed to emotional problems or a stressful home environment
Interventions	Participants were randomly assigned to 1 of 24 possible drug condition orders of MPH (0.3 mg/kg, 0.6 mg/kg, 0.9 mg/kg) and placebo Mean MPH dosage: 0.3 mg/kg: 9.71; 0.6 mg/kg: 19.42; 0.9 mg/kg: 29.14 Administration schedule: once daily Duration of each medication condition: 1 day; each child received each dosage twice during the trial (i.e. during first and second assessment weeks) Washout before trial initiation: in the case of children currently receiving stimulants, medication was discontinued ≥ 48 h before screening Titration period: none Treatment compliance: to ensure compliance, medications were administered at the laboratory
Outcomes	**Non-serious AEs** • Not described as a measure for the trial, but the Barkley Side Effects Rating Scale is mentioned
Notes	Sample calculation: no information Ethics approval: no information **Key conclusion of trial authors** • Under acute dosage conditions as used in this trial, MPH doses up to 0.9 mg/kg had an increasingly positive effect on measures of mental flexibility and other cognitive processes Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: grants from the Medical Research Council of Canada and by William T. Grant Foundation Faculty Scholar Program Email correspondence with trial authors: October 2013. Emailed last trial author twice to get supplemental information (protocol, ethics approval, data on side effects, etc.) but received no response. Therefore we included no data from this trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Drug order was determined by consecutive assignment to a randomly ordered list of 24 possible combinations of 4 medication levels for each of the 2 testing weeks
Allocation concealment (selection bias)	Low risk	Drug order was determined by consecutive assignment to a randomly ordered list of 24 possible combinations of 4 medication levels for each of the 2 testing weeks. To maximise blindness of examiners, all participants received a different drug order for assessment weeks 1 and 2
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medications containing active drug and placebo were prepared in identical opaque gelatin capsules and were administered in a double-blind fashion

Douglas 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	To maximise blindness of examiners, all participants received a different drug order during assessment weeks 1 and 2
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated whether any participants were LTFU Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

DuPaul 1996

Study characteristics	
Methods	4-week, double-blind, placebo-controlled, cross-over trial in which participants were randomly assigned to 3 doses of MPH: • 0.16 mg/kg • 0.29 mg/kg • 0.42 mg/kg • placebo
Participants	Number of participants screened: not stated Number of participants included: 24 (19 boys, 5 girls) Number of participants followed up: 24 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 11.09 years (range 9-15) IQ: > 70 MPH-naive: not stated Ethnicity: white (100%) Country: USA Setting: outpatient clinic Comorbidity: ODD (21%), CD (% not reported) Comedication: not stated Other sociodemographics: children were primarily from lower-middle class and middle class families **Inclusion criteria** • Parent and/or teacher referral to an outpatient ADHD clinic due to reported problems with inattention, impulsivity and/or overactivity • Parent interview indicating that child met DSM-III-R (American Psychiatric Association, APA 1987) criteria for ADHD • Independent diagnosis of ADHD by psychologist and paediatrician using DSM-III-R criteria for ADHD

DuPaul 1996 *(Continued)*

- Parent or teacher ratings on the Attention problem scale of the CBCL (Achenbach 1991), resulting in a T score ≥ 65 (i.e. 1.5 SD above the mean)
- ≥ 9 years old and able to read self-report questionnaires independently

Exclusion criteria

- Evidence of mental disability, gross sensory or motor disabilities, seizure disorder, autism, psychosis, tic disorders or Tourette's syndrome, or significant cardiac problems
- Currently receiving psychotropic medication

Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of low- (0.16 mg/kg; SD 0.08), moderate- (0.29 mg/kg; SD 0.11 kg) and high-dose (0.42 mg/kg; SD 0.14) MPH and placebo Administration schedule: twice/d, morning, noon Duration of each medication condition: 1 week Washout before trial initiation: not stated Titration period: none Treatment compliance: no participant was removed from the investigation for non-compliance (e.g. > 1 day of failure to administer medication as scheduled)
Outcomes	**ADHD symptoms** • ADHD-RS: teacher and parent ratings **Non-serious AEs** • Barkley Side Effects Rating Scale (17 items, 0 = absent, severity rated from 0-9): rated by participants at the end of each dosage condition
Notes	Sample calculation: no information Ethics approval: Human Subjects Research Board at the University of Massachusetts Medical Center **Comments from trial authors** • Conclusions based on present findings are limited by several factors • Among others, sample size may have diminished power to detect MPH effects on key variables, especially analyses of side-effect ratings • Also results are generalisable only to children with ADHD between 9 and 15 years of age Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not stated Email correspondence with trial authors: January 2013-August 2013. Emailed first trial author regarding additional information. Not able to get all data requested, as trial author no longer has these data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were randomly assigned to 1 of 6 possible orders of MPH dosage

DuPaul 1996 *(Continued)*

Allocation concealment (selection bias)	Low risk	Medication was prepared by the hospital pharmacy in increments of 5 mg and packaged within opaque gelatin capsules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, their parents and teachers and the research assistant in charge of collecting data were blinded to the order of medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, their parents and teachers and the research assistant in charge of collecting data were blinded to the order of medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	No Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of reporting bias. Analyses on all dependent measures in the trial are reported in the article

Duric 2012

Study characteristics	
Methods	RCT, parallel with 3 arms: • neurofeedback group • MPH group • MPH + neurofeedback group Phases: 2 (3 months with treatment in 3 arms. 6 months' follow-up with participants continuing on MPH)
Participants	Number of participants screened: 628 Number of participants included: 86 to relevant interventions (130 in all) Number of participants followed up: MPH 30 (23 boys, 7 girls), control 30 (22 boys, 8 girls) Number of withdrawals: MPH 14, control 12 Diagnosis of ADHD: ICD-10 (subtype not stated) Age: MPH 11.2 (SD 2.8), control 11.4 (SD 3.1) IQ: mean 87 Methyphenidate-naive: not stated Ethnicity: not stated Country: Norway Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: no significant differences in baseline demographics were noted between the 2 groups

Duric 2012 *(Continued)*

	Inclusion criteria • ICD-10 criteria for diagnosis of ADHD • 6-18 years of age • IQ > 70 **Exclusion criteria** • Involvement in another intervention group, including CBT and 'Stop Now And Plan' • the presence of co-morbid disorders other than ODD or anxiety disorder • the presence of a neurological and/or cardiovascular condition
Interventions	Partcipants were randomly assigned to MPH and neurofeedback (intervention group) or to neurofeedback (control group) Number of participants randomly assigned: MPH 44, control 42 MPH dosage: 20 mg daily to 60 mg daily. No placebo pill Administration schedule: twice/d Duration of intervention: 11-13 weeks (MPH continued the MPH interventions for 6 months) Titration period: not stated Treatment compliance: not stated
Outcomes	**ADHD symptoms** • 2 core ADHD symptoms – attention and hyperactivity, Assessment of Disruptive Behavior Disorders Rating Scale for parents: rated at baseline and 1 week after neurofeedback had been completed (between weeks 11 and 13 after start of intervention)
Notes	Ethics approval: yes **Comments from trial authors** • Factors that may result in ADHD symptom improvement: extraordinary amount of time spent with therapist during neurofeedback, better motivation for change in ADHD symptoms and cognitive-behavioural training induced under neurofeedback • For Attention rating, MPH + neurofeedback and MPH, no significant differences were noted between pre-treatment and post-treatment values Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: not stated Funding source: the Child and Adolescent Psychiatry Department of Helse Fonna Hospital Haugesund, Helse Fonna Trust Haugesund, Norway Email correspondence with trial authors: March-June 2013. Emailed first trial author. All questions were answered.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children with ADHD were randomly placed into 3 groups

Duric 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, as it is not a 'pure' placebo group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of parents
Incomplete outcome data (attrition bias) All outcomes	Low risk	No Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Outcomes reported according to protocol

Döpfner 2004

Study characteristics	
Methods	Randomised, double-dummy, double-blind, cross-over, multi-centre trial with 3 interventions: • IR-MPH 10 mg-40 mg • ER-MPH 10 mg-40 mg • placebo Phases: trial was subdivided into 5 stages: pre-screening, run-in phase (duration: 1 workday), trial phases 1 and 2 (duration in each case: 4 workdays plus weekend) and trial phase 3 (duration: 4 workdays). Participants also received a behavioural therapy intervention and social skills training at school.
Participants	Number of participants screened: not stated Number of participants included: 82 Number of participants followed up: 79 (71 boys, 8 girls) Number of withdrawals: 3 **Participants followed up** Diagnosis of ADHD: DSM-IV or ICD-10 (combined (92.4%), hyperactive-impulsive (0%), inattentive (7.6%)) Age: mean 10 years (range 6 to 16) IQ: 103 ± 10.4 MPH-naive: 0% Ethnicity: not stated Country: Germany Setting: outpatient clinic

Döpfner 2004 *(Continued)*

	Comorbidity: ODD/CD (44%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Meeting criteria for an ICD-10 diagnosis of Hyperkinetic disorder (F90) or for a DSM-IV diagnosis of ADHD • 8-15 years of age • MPH responders on the basis of clinical assessment and after careful titration • All patients had to be treated with IR-MPH at least twice daily or once daily with a retard preparation • During previous month, MPH dosage had to be unchanged. Daily MPH dosage was ≥ 10 mg • IQ ≥ 85 • Body weight > 20 kg • Written informed consent of parents and participants to join the trial **Exclusion criteria** • Patients attending schools for mentally handicapped, sensory handicapped or physically handicapped children • Patients who, during the past 4 weeks, were treated with other medication because of ADHD, apart from MPH • Diagnosis of a severe developmental disorder or psychosis • Previous convulsive disorder; EEG indicated susceptibility to convulsions • Case history of pathological changes in liver function or liver disease • Severe depressive disorder (CBCL, teacher-rated, > 70 on the Anxiety-depression scale) or a severe anxiety disorder according to clinical diagnosis
Interventions	Participants were randomly assigned to different orders of IR-MPH, ER-MPH and placebo Mean MPH dosage: 22 mg ± 6 mg. Dosage was identical in MPH groups but did not exceed 1 mg/kg body weight. Thus, 9 (11%) participants received a daily dose of 10 mg, 54 (68%) received 20 mg, 14 (17%) received 30 mg and 2 (3 %) received 40 mg Administration schedule: 9:00 am and 1:00 pm Duration of each medication condition: 4 days, and for trial phase 1 + 2 (also weekends) Washout before trial initiation: none Medication-free period between interventions: none Titration period: had to be oriented to the optimum individual dosage previously determined in clinical treatment trials initiated before randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP: rated by clinic personnel/caregiver staff for each child at 9:00 am, 11:00 am, 12:30 pm, 3:00 pm and 4.15 pm • Fremdbeurteilungsbogen für Hyperkinetische Störungen (3rd party assessment form for hyperkinetic disorders): staff/personnel-rated, at 1:00 pm and 4:45 pm **Non-serious AEs** • Questionnaire on side effects (Side Effects Rating Scale)
Notes	Sample calculation: not stated

Döpfner 2004 *(Continued)*

Ethics approval: approved by local university ethics committees

Comment from trial authors

- "Althogh the analogue classroom attempts to mimic many aspects of a regular school classroom, it represents a unique setting that may influence behaviour. Analogue assessments included only ADHD participants; no control or normal participants were available for comparison"
- Carry-over effect: as no evidence for possible carry-over effects was noted, no secondary analyses for carry-over effects were performed

Key conclusions of trial authors

- These data provide support for the benefit of this novel, once-daily MPH preparation for the treatment of ADHD
- On all measures analysed, both twice/d IR-MPH and ER-MPH produced significant improvement relative to placebo. Moreover, ER-MPH was not significantly different from twice/d, IR-MPH, even longer than 7 h after dosing
- Longer duration of action of Medikinet Retard has the potential to simplify psychostimulant treatment, thus reducing dose diversion and eliminating the need for in-school administration

Comments from review authors

- For the article in German (Döpfner 2003 in Döpfner 2004), only 1 review author who knew German extracted the data. All other articles were assessed for data by 2 review authors. We received Döpfner 2003 (Döpfner 2004) from HB Pharma
- 18 participants in the sample from Clinic for Neuropediatrics, University of Kiel, received response cost token-based behaviour training (RCT) (Gerber 2012 in Döpfner 2004)

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes; included only MPH responders

Any withdrawals due to AEs: no

Funding source: conducted and sponsored by MEDICE Arzneimittel Pütter GmbH & Co. KG as part of the drug approval process for Medikinet-Retard

Email correspondence with trial authors. We received some data from trial authors in July 2013. We sent 2 additional emails to different trial authors to request data in July 2014 but received no answer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Order in which participants were allocated to respective treatment arms was randomly assigned
Allocation concealment (selection bias)	Unclear risk	Order in which participants were allocated to respective treatment arms was randomly assigned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To guarantee a double-blind trial, the double-dummy method was used (i.e. participants took the capsule once/d and the tablets twice daily). Only 1 of the 2 galenical forms contained the active substance; the other form contained placebo. In the placebo group, participants took both placebo capsules and placebo tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Unclear risk	Not stated

Döpfner 2004 *(Continued)*

All outcomes		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol obtained

Epstein 2011

Study characteristics	
Methods	Cross-over trial with 2 interventions 3 preliminary phases to determine optimal dose followed by 2-phase trial of the following: • optimal dose of MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: not clear Number of participants followed up: 93 (numbers of boys and girls: not stated) Number of withdrawals: not clear Diagnosis of ADHD: DSM-IV (combined (n = 45), hyperactive-impulsive (n = 48), inattentive (n = 0)) Age: mean 8.1 years (range 7-11) IQ: mean 105.58 MPH-naive: 100% Ethnicity: white (75%), African American (22%), other (3%) Country: USA Setting: outpatient clinic Comorbidity: ODD (n = 34), CD (n = 4), anxiety disorders (n = 31), mood disorders (n = 2) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Children 7-11 years of age who met the diagnostic criteria for ADHD, plus 6 non-overlapping symptoms in a symptom domain on the Diagnostic Interview for Children - Parent Report and Vanderbilt Teacher Rating Scale; both parents and teachers reported ≥ 4 symptoms in that domain **Exclusion criteria** • Children with an IQ below 80 (on the WASI) or a score < 80 on the Reading or Numerical operations subtests of the Wechsler Individual Achievement Test or possible organic brain injury
Interventions	Participants were randomly assigned to an optimal dose of MPH and placebo Mean MPH dosage: 1.13 mg/kg Administration schedule: testing 1-4 h after medication ingestion

Epstein 2011 *(Continued)*

	Duration of each medication condition: 1 week Washout before trial initiation: no apparent washout Titration period: each of the 3 doses was trialled for 1 week before random assignment to identify an optimal dose Treatment compliance: not reported
Outcomes	**ADHD symptoms** • Vanderbilt ADHD-RS: completed by parents and teachers at the end of 1 week **Non-serious AEs** • Referred to the Pittsburgh Side Effects Rating Scale: completed by parents and teachers at the end of each week, but data were not reported
Notes	Sample calculation: not stated Ethics approval: not stated **Comments from trial authors** • "Although we used a placebo-controlled, double-blind titration trial to determine optimal dosage, the highest dosage used in this trial was 54 mg for children ≥ 25 kg and 36 mg for children < 25 kg" • "Also, a significant minority of children (24%) exited the titration trial, with the placebo dosage as their optimal dosage, which is comparable with the stimulant response rate in other studies. The fact that 19% of children in the optimal dose condition received the same stimulant dosage (i.e. placebo) as was received by the placebo control group may have affected the ability of this trial to detect between-group differences for some trial outcomes (e.g. accuracy)" **Key conclusion of trial authors** • None regarding our outcomes of interest Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: not stated Funding source: NIH and NIMH Email correspondence with trial authors: April 2014. We were able to obtain supplemental information regarding data (Storebø 2015b).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"; capsules were "identical" (p 2, p 1063)
Blinding of outcome assessment (detection bias)	Low risk	"Double-blind", capsules were "identical" (p 2, p 1063)

Epstein 2011 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear whether any participants were LTFU Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Fabiano 2007

Study characteristics	
Methods	Randomised, double-blind, within-participant design, cross-over trial with 2 interventions: • MPH • placebo Phases: 0.15 mg/kg, 0.30 mg/kg and 0.60 mg/kg. Medication was randomly assigned for each child and varied daily during a 9-week summer treatment programme
Participants	Number of participants screened: not stated Number of participants included: 48 (44 boys, 4 girls) Number of participants followed up: 47 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.35 years (SD 1.98, range 5-12) IQ: 106.33 (SD 14.61) MPH-naive: not stated Ethnicity: white (79%); African American (12.5%); Hispanic, Native American or mixed race (8.5%) Country: USA Setting: outpatient clinic (summer treatment programme) Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-IV, diagnostic criteria for ADHD • Estimated full-scale IQ ≥ 80 • No documented adverse response or non-response to MPH • No medical condition that would contraindicate use of MPH **Exclusion criteria** • None stated

Fabiano 2007 *(Continued)*

Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of IR-MPH (0.15 mg/kg, 0.30 mg/kg and 0.60 mg/kg) and placebo Mean MPH dosage: 5.03 mg (range 2.5-10), 10.8 mg (range 5-20) and 21 mg (range 12.5-30) Administration schedule: 3 times daily (7:45 am, 11:45 pm and 3:45 pm) Duration of each medication condition: varied daily Washout before trial initiation: none Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • IOWA CRS (inattention-impulsivity-overactivity): teacher- and observer-rated, daily **General behaviour** • IOWA CRS (oppositional defiance): teacher- and observer-rated, daily **Non-serious AEs** • Pittsburgh Side Effects Rating Scale: teacher-rated daily • Clinically significant AEs: observer-rated daily
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • "The study was conducted in an analogue classroom setting" (as opposed to a community classroom) • "The treatments used were of short duration" • "Observers and raters were blind to medication condition but not to behaviour modification conditions" • "Ratings from the Pittsburgh Side Effects Rating Scale were averaged across days within drug condition (regardless of behaviour modification condition) for the 47 children. One participant's medication was discontinued because of parental concerns about side effects (mainly buccal-lingual movements) after 2 days of treatment, and 1 child's afternoon dose was reduced on 0.60 mg/kg days because of parent-reported anxiety and mood symptoms. No other children had side effects rated by the teacher at an average level of moderate or severe" **Comments of review authors** • This trial of placebo versus MPH was conducted during different conditions of behaviour modification. We should consider whether to use only data from the non-behaviour modification condition or data from all conditions Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes Any withdrawals due to AEs: yes, 1 (withdrawn by parents due to concern about side effects and not included in the analysis) Funding source: NIMH grant MH62946 Email correspondence with trial authors: April 2014. We obtained supplemental information regarding risk of bias. No further information was received

Risk of bias

Fabiano 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation and allocation concealment were completed with a random number generator by a researcher not involved in treatment
Allocation concealment (selection bias)	Low risk	Randomisation and allocation concealment were completed with a random number generator by a researcher not involved in treatment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Medication assessment procedure was double-blinded" (p 201) "children, their parents, and all clinical staff members were blinded to medication condition" (p 202) Medication was prepared in opaque capsules by a pharmacist not otherwise involved in the trial. It was administered to children by research staff who were not involved in administration of behavioural treatment nor in daily activities
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observers and raters were blinded to medication conditions
Incomplete outcome data (attrition bias) All outcomes	High risk	One child's parents elected to stop medication for the child after 2 days because of their concerns about possible side effects of the medication. This child was not included in the analyses Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol/design was published

Findling 2006

Study characteristics	
Methods	3-week, randomised, double-blind, parallel trial with 3 arms: • IR-MPH (Ritalin) • MR-MPH (EqXL) • placebo
Participants	Number of participants screened: 346 Number of participants randomly assigned: 327 Number of participants included: 318; IR-MPH 133, MR-MPH (EqXL) 139, placebo 46 Number of participants followed up: IR-MPH 120, MR-MPH (EqXL) 120, placebo 39 (number in each arm is only per protocol population) Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (combined (71%), hyperactive-impulsive (6%), inattentive (23%)) Age: mean 9.5 years (range not reported) IQ: above 80 Sex: 252 boys, 66 girls

Findling 2006 *(Continued)*

	MPH-naive: 0% Ethnicity: white (86%), African Caribbean (5.2%), Asian (0.3%), Hispanic (1.6%), other (6.9%) Country: Australia, Canada, USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none. No significant differences in baseline demographics were noted between the 2 groups **Inclusion criteria** • Male and female children • 6-12 years of age • Stable dose of MPH 3 weeks before screening • Diagnosed with ADHD on the basis of DSM-IV criteria for any subtype and confirmed by administration of the K-SADS-PL at screening • Attending a school setting in which a single teacher could make morning and afternoon assessments of the child's behaviour **Exclusion criteria** • Girl who had experienced menarche • Comorbid psychiatric disorder requiring medication • History of seizure or tic disorder or family history of Tourette's disorder • IQ test score < 80, or functioning at a level of intelligence indicative of an IQ <80 • Use of unapproved medication(s) • Use of an investigational product within 30 days before trial entry • Concurrent chronic or acute illness, disability or medication that might confound the results of rating tests • Diagnosed with hyperthyroidism, glaucoma or eating disorder • Current substance abuse disorder or living with someone with a current substance abuse disorder • Demonstrated lack of response to MPH
Interventions	Participants were randomly assigned to IR-MPH, ER-MPH (EqXL) or placebo Mean MPH dosage: not stated Administration schedule: twice daily, morning and lunch Duration of intervention: 3 weeks Titration period: all participants were stable while taking MPH medication before randomisation Treatment compliance: not stated. Children with a previous total daily dose of 10 mg-20 mg IR-MPH or 20 mg ER-MPH were randomly assigned to receive 10 mg IR-MPH twice daily, 20 mg MR-MPH (EqXL) once daily or placebo; children given a previous total daily dose of 25 mg-40 mg IR-MPH or > 20 mg to < 40 mg ER-MPH were randomly assigned to receive 20 mg IR-MPH twice daily, 40 mg MR-MPH (EqXL) once daily or placebo; children given a previous total daily dose > 40 mg IR-MPH or < 40 mg ER-MPH were randomly assigned to receive 20 mg IR-MPH twice daily, 60 mg MR-MPH (EqXL) once daily or placebo
Outcomes	**ADHD symptoms** • SNAP-IV: teacher-rated at baseline and weekly • SNAP-IV: parent-rated at baseline and weekly, at the end of the child's day

Findling 2006 *(Continued)*

- IOWA CRS (Inattention-Impulsivity-Overactivity): teacher and parent

Serious AEs

- Only 1 serious AE (neutropenia) was reported during the trial in MR-MPH (EqXL) treatment, but the investigator considered it unlikely to be related to the trial medication

General behaviour

- IOWA CRS (oppositional defiance): teacher- and parent-rated, at baseline and weekly (2 h post-dose and -4 h post-lunch)

Non-serious AEs

- Barkley Side Effects Rating Scale: parent- and teacher-rated at baseline and weekly
- AEs, laboratory parameters, vital signs, physical exam, observer-rated, time point not specified

Notes

Sample calculation: yes

Ethics approval: yes; independent ethics committee at each clinical site before trial initiation

Key conclusion of trial authors

- MR-MPH (EqXL) given once daily was non-inferior to IR-MPH given twice daily. Both treatments were superior to placebo in reducing ADHD symptoms

Comment from review authors

- September 2013. Not possible to contact trial authors

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes

Any withdrawals due to AEs: yes, 14 placebo, 4 MPH-IR, 3 Equasym

Funding source: provided by Celltech Americas Incorporated, currently part of UCB (Union Chimique Belge)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" but did not state how
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both MR-MPH (EqXL) capsules and IR-MPH tablets were over-encapsulated in hard gelatin capsules identical to the placebo capsule
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Stated LOCF but primary efficacy population was the per protocol population, defined as participants who received trial treatment and had ≥ 1 efficacy measurement after the first dose

Findling 2006 *(Continued)*

		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol/design was published

Findling 2007

Study characteristics	
Methods	4-week, double-blind, randomised, placebo-controlled, cross-over trial with 4 interventions (MPH at 3 different doses, in the morning and at midday): • 5 mg • 10 mg • 15 mg • placebo Phases Participants were assigned to receive, at random, 1 of 6 possible dosing orders that included the following: • placebo, 5 mg, 10 mg, 15 mg • placebo, 10 mg, 15 mg, 5 mg • 5 mg, placebo, 10 mg, 15 mg • 5 mg, 10 mg, 15 mg, placebo • 10 mg, 15 mg, placebo, 5 mg • 10 mg, 15 mg, 5 mg, placebo Schedules were designed in such a way that participants did not receive the 15 mg dose before the 10 mg dose, so in the event that a participant experienced AEs while taking a lower dose, the 15 mg dose was not administered
Participants	Number of participants screened: not stated Number of participants included: 20 Number of participants followed up: 16 (12 boys, 4 girls) Number of withdrawals: 4 Demographic data regarding the 16 who completed the trial: Diagnosis of ADHD: DSM-IV (combined (94%), inattentive (6%)) Age: mean 10.43 years (range 5-17) IQ: > 70 MPH-naive: not stated Ethnicity: white (75%), African American (6%), Hispanic (19%) Country: USA Setting: outpatient clinic Comorbidity: bipolar (100%), ODD (50%), CD (25%), enuresis (12.5%), encopresis (12.5%)

Findling 2007 *(Continued)*

	Comedication: 100% divalproex sodium. Some received clonidine for sleep at night Other sociodemographics: none. No statistically significant differences in distribution based on sex, ethnicity, age group, rate/proportion of comorbid ODD or comorbid CD were found between 6 dosing order groups **Inclusion criteria** • 5-17 years of age • Individuals meeting DSM-IV criteria for a diagnosis of bipolar spectrum disorder and a comorbid diagnosis of ADHD were eligible for trial participation • Treated with fixed doses of mood stabilisers at the time of trial enrolment for ≥ 5 days before receiving trial medication • Eligible if trial physician's clinical assessment indicated the need for a psychostimulant for treatment of "dysfunctional residual symptoms of ADHD" **Exclusion criteria** • Mental disability • Pervasive developmental disorder • Inability to swallow pills • History of alcohol or other substance abuse or dependence within 6 months before enrolment • Active neurological or other medical condition suspected to be related to mood symptoms • Pregnant female patients, those intending to become pregnant and sexually active female patients who were using an inadequate form of birth control were not permitted to participate • Participation required a negative qualitative pregnancy test within 2 weeks of receiving the first dose of double-blind treatment for female patients of childbearing potential • Significant symptoms of mania (Young Mania Rating Scale score > 13) or depression (CDRS-R > 40) during the week before enrolment and anticipated dosing changes for mood-stabilising agents • Individuals receiving a tricyclic antidepressant or antipsychotic agent and those with symptoms of psychosis or suicidal ideation • Female patients nursing an infant and patients experiencing significant medical or neurological illness were not permitted to participate
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of MPH (5 mg twice/d, 10 mg twice/d, 15 mg twice/d) and placebo Mean MPH dosage: not provided, as the trial compares MPH at different doses Administration schedule: morning and midday Duration of each medication condition: 1 week Washout before trial initiation: not stated Medication-free period between interventions: between lunchtime dose and morning dose the following day Titration period: none. Dosing schedules were designed in such a way that patients did not receive the 15 mg dose before the 10 mg dose, so in the event that a participant experienced AEs while on a lower dose, the 15 mg dose was not administered Treatment compliance: 1 of 20 screened participants was withdrawn from the trial because of poor compliance. Among the 16 who participated, no compliance issues were reported
Outcomes	**ADHD symptoms** • ADHD-RS-IV: rated weekly by parents • CPRS (48-item): rated weekly **General behaviour**

Findling 2007 *(Continued)*

- CPRS, Conduct problem subscale

Non-serious AEs

- CDRS-R: rated weekly
- Young Mania Rating Scale: rated weekly.
- Side Effects/Behavior Monitoring Scale: rated weekly at the trial visit
- Resting BP and pulse recorded each week
- Weight documented at baseline and at end of trial

Notes

Sample calculation: yes

Ethics approval: yes

Comments from trial authors (limitations)

- Small sample size
- Full consideration of dosing order effects was not possible because of the modest size of this trial cohort

Key conclusion of trial authors

- Euthymic youths with bipolar disorder and ADHD may benefit from short-term concomitant treatment with MPH

Comment from review authors

- All participants have a bipolar disorder

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: yes; 2

Funding source: Stanley Medical Research Institute

Email correspondence with trial authors: November 2013. We wrote to the trial author twice to request a copy of the protocol and information about sample size and allocation concealment but have not received a response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random numbers table was generated and was used by a pharmacist to assign dose orders to participants. Counterbalancing was applied in such a way that as each dose order was used, its number was eliminated from the next dose order assignment.
Allocation concealment (selection bias)	Low risk	Placebo and MPH in identical capsules. No participants were discontinued from this trial because of broken integrity of the blind.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	At the conclusion of the 4-week trial, trial physician, participant and participant's guardian determined a "best dose week", taking into consideration behaviour ratings and reports of any AEs. After all assessments had been completed, the trial blind was broken to reveal the dose that had been prescribed during the previously identified best dose week. No participants were discontinued from this trial because of broken integrity of the blind.

Findling 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"After all of the assessments had been completed, the study blind was then broken to reveal the dose that had been prescribed during the previously identified 'best dose week'"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data present Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Findling 2008

Study characteristics	
Methods	7-week randomised, phase III, double-blind, multi-centre, parallel-group, placebo-controlled, naturalistic home and school trial with 3 arms: • MPH transdermal system patch + placebo capsule • OROS-MPH capsule + placebo patch • placebo capsule + placebo patch 5-week titration phase, 2-week maintenance phase
Participants	Number of participants screened: not stated Number of participants included: 282 (187 boys, 95 girls) Number of participants randomly assigned (and administered ≥ 1 dose of trial medication): MPH transdermal system 100, OROS-MPH 94, placebo 88 Number of participants followed up: MPH transdermal system 71, OROS-MPH 66, placebo 32 Number of withdrawals: MPH transdermal system 27, OROS-MPH 25, placebo 53 Diagnosis of ADHD: DSM-IV-TR (combined (80.5%), hyperactive-impulsive (1.4%), inattentive (17.0%), unclassified (1.1%)) Age: mean 8.8 years (range 6-12). MPH transdermal system 8.9, OROS-MPH 8.8, placebo 8.5 IQ: ≥ 80 MPH-naive: 86% Ethnicity: white (77.3%), African American (14.5%), Asian (0.7%), Hispanic (not stated), other (7.4%) Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: no significant differences in baseline demographics (age, sex, ethnicity, ADHD subtype, prior ADHD medication use) among the 3 groups **Inclusion criteria** • 6-12 years of age, inclusive

Findling 2008 *(Continued)*

- ADHD, DSM-IV-TR
- Stimulant-naive or known to be stimulant-responsive
- IQ ≥ 80
- Total score of 26 on ADHD-RS-IV, while unmedicated
- Normal laboratory parameters and vital signs, including ECG
- Female patients of childbearing potential must have a negative serum HCG pregnancy test at screening and a negative urine pregnancy test at baseline

Exclusion criteria

- Comorbid psychiatric diagnosis (except ODD)
- History of seizures during the past 2 years
- Tic disorder
- Any concurrent illness or skin disorder that might compromise safety or trial assessments
- Ingestion of clonidine, atomoxetine, antidepressants, antihypertensives, investigational medications, hepatic or cytochrome (p 450) enzyme-altering agents, medications with central nervous system effects, sedatives, antipsychotics or anxiolytics within the 30 days before trial entry
- Overweight (body mass index (BMI)-for-age > 90th percentile)

Interventions	Participants were randomly assigned to MPH patch, OROS-MPH or placebo Titration period: 5 weeks (after randomisation) of optimisation to 1 of 4 total daily dosage strength. OROS-MPH: 18 mg, 27 mg, 36 mg and 54 mg. MPH transdermal system and placebo transdermal system: 10 mg, 15 mg, 20 mg and 30 mg over a 9-h period in patches of 12.5 cm^2, 18.75 cm^2, 25 cm^2 and 37.5 cm^2, respectively Administration schedule: treatments were administered at approximately 7:00 am each morning; patches were applied to the hip area and were worn for approximately 9 h daily, different hip each day Mean patch wear time: 8.70 (0.51) to 9.46 (0.53) h Duration of intervention: 7 weeks Washout before trial initiation: up to 28 days if applicable Treatment compliance: mean compliance 97% to 99% during both trial phases
Outcomes	**ADHD symptoms** • ADHD-RS-IV: clinician-rated, weekly • CTRS: teacher-rated, twice weekly • CPRS: parent-rated, twice weekly **Non-serious AEs** • Evaluations for safety were performed at the end of each week during both dose-optimisation and dose-maintenance phases. Furthermore, AEs were spontaneously reported as coded via MedDRA (7.0) Adverse Event Dictionary • BP, pulse, oral temperature, weight: weekly • Laboratory parameters: week 7 • Sleep-related behaviours rated by parents each week using Childrens' Sleep Habits Questionnaire • Skin reactions due to the patch investigated each week; Dermal Response Scale • ECG: final dose-optimisation visit and final trial visit
Notes	Sample calculation: yes (258 participants) Ethics approval: yes **Comments from trial authors**

Findling 2008 *(Continued)*

- It is important to note, however, that effects reported are for baseline and endpoint reports of sleep problems; thus, these results may not generalise to the titration period. For example, sleep problems may have resulted in dosage adjustments and attenuation of sleep problems during titration
- Respondents did not enter the maintenance phase if spontaneously reported side effects could not be controlled by adjusting the dose. Thus, participants with extreme insomnia would not have entered the maintenance phase
- Rating scales for sleep problems may lack validity

Key conclusions of trial authors

- Results of this trial suggest that the MPH transdermal system is an efficacious treatment option for children with ADHD
- "Results of our analysis suggest that emergence or worsening of sleep problems in response to treatment of ADHD symptoms with OROS methylphenidate or methylphenidate transdermal system generally should not be a major concern to clinicians, children with ADHD or their parents after titration to an optimal dose, as described for this protocol. However, these suggestions should be considered in the light of other research that supports an effect of MPH on insomnia and other sleep difficulties, especially when MPH will be administered to children with pre-existing sleep difficulties. These findings should not be generalised to children who have not been titrated to an optimal dose."

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes. An inclusion criterion is that participants are stimulant-naive or stimulant-responsive

Any withdrawals due to AEs: yes; 11

Funding source: Shire Development Incorporated, Wayne, Pennsylvania

Email correspondence with trial authors. June-September 2013. We attempted to obtain supplemental efficacy and safety data from trial authors but without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers schedule
Allocation concealment (selection bias)	Low risk	Computer-generated random numbers schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy: participants received both a patch and a capsule to be administered each day. MPH and placebo capsules were over-encapsulated to blind the identity of the capsule's content
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT, LOCF Selection bias: yes; non-responders excluded during the trial. Participants who did not reach an acceptable condition by the final dose-optimisation visit (week 5) were withdrawn from the trial
Selective reporting (reporting bias)	Low risk	Outcomes reported according to protocol

Findling 2010

Study characteristics	
Methods	Phase IIIB, randomised, double-blind, parallel-group, placebo-controlled, multi-centre, dose-optimisation trial evaluating the efficacy and safety of the following in adolescents 13-17 years of age with ADHD: • MPH transdermal system (10 mg, 15 mg, 20 mg or 30 mg/9-h patches) • Placebo transdermal system **Double-blind RCT** consisted of 4 experimental periods • Screening and washout • Dose optimisation (5 weekly visits) • Dose maintenance (5 monthly visits) • 7-day post-treatment follow-up **Open-label extension** follow-up consisted of an open-label extension trial conducted to evaluate the safety and efficacy of the MPH transdermal system (10 mg, 15 mg, 20 mg or 30 mg/9-h patches) for participants who completed all required trial visits; consisted of 3 experimental periods
Participants	**Double-blind RCT** Number of participants screened: not stated Number of participants included: 217 (162 boys, 55 girls) Number of participants randomly assigned: MPH 145, placebo 72 Number of participants followed up (ITT population): MPH 143, placebo 72 Number of withdrawals: MPH 2, placebo 0 Number that completed 7-week dose-optimisation/dose-maintenance phase: MPH 95, placebo 72 Diagnosis of ADHD: DSM-IV (types not stated) Age: mean 14.6 years (SD 1.3, range 13-17) IQ: ≥ 80 MPH-naive: 122 (56%) Ethnicity: white (77%), African American (18%), Asian (0.5%), other (4.5%) Country: USA Setting: outpatient clinic Comorbidity: 0% Comedication: not stated Other sociodemographics: no significant difference in baseline demographics were noted between the 2 groups **Open-label extension (safety measures)** Number of participants included: 163 (previously taking MPH 110, placebo 53) Number of participants followed up: 162 (121 boys, 41 girls) Number of withdrawals: 1

Findling 2010 *(Continued)*

Diagnosis of ADHD: DSM-IV (types not stated)

Age: 14.5 years (SD 1.24, range 13-17)

IQ: ≥ 80

MPH-naive: 122 (56%)

Ethnicity: white (78%), African American (17%), Asian (0.6%), other (4.4%)

Country: USA

Comorbidity: 0 %

Comedication: not stated

Other sociodemographics: none

Inclusion criteria

- Male or female adolescents
- 13-17 years of age
- Primary diagnosis of ADHD according to DSM-IV
- IQ score > 80
- Total score ≥ 26 on the ADHD-RS-IV, at baseline
- Participants were required to have ECG results within normal range or variants that were not clinically significant, as judged by investigators in conjunction with the central laboratory
- BP measurements within the 95th percentile for age, sex and height
- No current or past skin disease or other skin problems, including sensitive skin or signs of skin irritation
- Female patients must have a negative urine pregnancy test at entry and must agree to use acceptable contraceptives throughout the trial period and for 30 days the last dose of IP
- Participant and parent of legally authorised representative are able, willing and likely to fully comply with trial procedures and restrictions

Open-label extension (6 months):

- participants must have completed all required trial visits or a 5-week dose-optimisation period without achieving an acceptable condition (i.e. ≥ 25% decrease from baseline in a participant's ADHD-RS-IV, score with minimal side effects)

Exclusion criteria

- CD or comorbid psychiatric illness (such as clinically significant OCD, depressive or anxiety disorder; PTSD; psychosis; bipolar illness; or pervasive developmental disorder); history of structural cardiac abnormality, cardiomyopathy, cardiac rhythm abnormalities or other serious cardiac problems; suicidal ideation; alcohol or other substance abuse (except caffeine or nicotine) within the past 6 months
- Seizures during the previous 2 years
- A history of being non-responsive to psychostimulant treatment
- Use of clonidine, atomoxetine, antidepressants, sedatives, antipsychotics, anxiolytics, P450 enzyme-altering agents or other investigational medications within 30 days before screening
- Female participant who is pregnant or lactating

Open-label extension (6 months):

- Participants were not eligible to participate in the extension trial if they were discontinued from the antecedent trial because of a protocol violation (including non-compliance) or had experienced an AE for which continued treatment would be medically contraindicated, or a serious AE
- Participants with considerable general medical illness (except mild, stable asthma) or an unstable medical condition, disability or other condition the investigator believed might interfere with or prevent completion of the trial

Findling 2010 *(Continued)*

Interventions	Participants were randomly assigned to MPH transdermal (patches) or placebo Mean MPH dosage at week 7: 10 mg (4.2%), 15 mg (16.7%), 20 mg (24.0%), 30 mg (55.2%); median exposure time: 48 days (range 4-57) Administration schedule: single patch in the morning, once daily for 9 h Duration of intervention: 7 weeks Titration period: 5 weeks, initiated after randomisation Treatment compliance: 124 fulfilled the protocol. However, it is not stated in the article how compliance regarding the medication had to be assessed to fulfil the protocol Mean MPH dosage at month 6: 10 mg (5.6%), 15 mg (7.9%), 20 mg (32.6%), 30 mg (53.9%); median exposure time: 168 days (range 3-200) Administration schedule: single patch in the morning, once daily for 9 h Duration of intervention: 6 months Titration period: 5 weeks of the 6 months Treatment compliance: not stated. 88 fulfilled the protocol. However, it is not stated in the article how compliance regarding the medication had to be assessed to fulfil the protocol

Outcomes	**7-week parallel trial (Double-blind RCT)**
	
	ADHD symptoms
	
	• ADHD-RS, Clinicians: rated baseline and weekly for 7 weeks (each trial visit)
	• CPRS-R, Parents: rated baseline and weekly for 7 weeks (each trial visit)
	
	Serious AEs
	
	• None
	
	Non-serious AEs
	
	• AEs monitored at each trial visit. All AEs were coded using the MedDRA, Version 7.0
	• Height measurements were performed at screening and at the final double-blind trial visit
	• Vital signs (SBP and DBP, pulse) and weight, at screening, at baseline and at each trial visit
	
	The investigator determined the clinical significance of any physical examination, height or vital sign measurement that was outside the normal range. Clinically significant deviations from measurements recorded at screening were reported as AEs. A 12-lead ECG evaluation was obtained at screening, at baseline, at week 5 and at the final double-blind trial visit. Dermal skin reaction: Dermal Scale was used to evaluate observed skin findings: range 0-7, where 0 shows no evidence of irritation
	
	Regarding 6-month open-label extension:
	
	• Dose optimisation (5 weekly visits); dose maintenance (5 monthly visits)
	  ◦ AEs were monitored at each trial visit and were assessed by an open-ended inquiry along with specific dermatological questions asked by an investigator or a qualified evaluator. AEs were considered treatment-emergent if they began or worsened on or after application of the first patch, and occurred before or at the same time as application of the patch. AEs coded and defined using the MedDRA, Version 7.03, at 7-day post-treatment follow-up
	  ◦ Height: measured at month 6 visit by the investigator
	  ◦ Weight: recorded at all visits (5) by the investigator
	  ◦ Vital signs (SBP, DBP, pulse): measured at all trial visits by the investigator. 12-Lead ECG performed at entry, week 4, month 3 and month 6 by the investigator
	  ◦ Blood and urine samples collected at entry, week 4, month 4 and month 6
	  ◦ Dermal skin reaction: measured by Dermal Scale at each trial visit

Findling 2010 *(Continued)*

- Sleep: measured by non-validated Post-Sleep Questionnaire. Measured at 6-month visit

Changes noted between evaluation data at trial entry and data obtained at schedule visits deemed to be clinically significant by the investigator were considered an AE

Notes

Sample calculation: yes. By using 85% power to detect an effect size of 0.5 between active treatment and placebo at the significance level of 5%, it was estimated that 112 participants were needed for MPH transdermal system groups and 56 for placebo transdermal system groups. Assuming a 20% dropout rate, ~ 210 participants (MPH transdermal system 140, placebo transdermal system 70) were required for the trial

Ethics approval: yes

Comments from trial authors

- Given the short duration of this trial, results do not characterise the long-term effects of treatment with MPH transdermal system
- It is important to note that participants who failed to respond to psychostimulants in the past and those with CD and other psychiatric comorbidity were excluded from the trial
- Regarding the 6-month trial: no clinically significant findings between laboratory evaluation parameters obtained post entry relative to screening values obtained at the antecedent trial
- Limitations: this trial used an open-label design; thus tolerability and effectiveness assessments are susceptible to observer bias. Another way in which results of long-term, open-label continuation studies may be biased is that participants who enrol in a trial after participating in an antecedent trial may represent that subset of patients who have had improvement in ADHD symptoms and/or who did not experience substantial AEs in the antecedent trial

Key conclusions of trial authors

- MPH transdermal system therapy was generally well tolerated and resulted in significantly greater improvement in ADHD symptoms among adolescents when compared with the placebo transdermal system
- Reported AEs included those typically observed for oral MPH, with the exception of generally mild application site erythema associated with transdermal delivery
- Regarding the 6-month open-label trial: MPH transdermal system was generally well tolerated, and AEs were generally typical of those associated with oral MPH, with the exception of application site reactions associated with transdermal delivery of MPH

Comments from review authors

- As already stated, people who earlier had failed to respond to psychostimulants were not included in the trial. Therefore, results can be generalised only to responders
- Risk of bias table done only for the 7-week parallel-group trial
- Regarding the 6-month open-label trial: participants who had not reached an acceptable response by the end of week 5 were withdrawn from the trial

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, participants were excluded if they had a history of being non-responsive to psychostimulant treatment

Any withdrawals due to AEs: yes, 10 (2 in placebo group, 8 on MPH group)

Fnding source: Shire Development Incorporated

Risk of bias

Bias	Authors' judgement	Support for judgement

Findling 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants were allocated the next sequential randomisation number and received treatment that corresponded with that randomised number as given by an interactive voice response system
Allocation concealment (selection bias)	Low risk	Randomisation schedule was produced by computer software that incorporated a standard procedure for generating random numbers
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no information on MPH and placebo blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Efficacy analyses were performed on the ITT population, defined as all randomly assigned participants who received ≥ 1 dose of trial medicine and ≥ 1 post-baseline primary efficacy assessment. Safety population was defined as all randomly assigned participants who received ≥ 1 dose of trial medicine. Selection bias (e.g. titration after randomisation → exclusion): yes. No further dose titration was permitted for any participant after week 5, and participants who had not reached an acceptable response by the end of week 5 were withdrawn from the trial
Selective reporting (reporting bias)	Low risk	No indication of selective reporting. Protocol registered 12 July 2007. First participant consent was obtained 29 August 2007 for the open-label trial

Fine 1993

Study characteristics	
Methods	3-week double-blind, cross-over trial with 2 interventions: • MPH twice/d (2 doses: 0.3 mg/kg and 0.6 mg/kg) • placebo twice/d Phases: medical trial or typical clinical procedure, concluded with recommendation for treatment, follow-up (6 weeks and 3 months)
Participants	Number of participants screened: 24 who were randomly assigned: 12 "typical clinical procedure", 12 "medical trial" Number of participants included: 12 (sex not stated). Participants in the medical trial group were randomly assigned to different possible drug condition orders Number of participants followed up: 12 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 101.58 months (approximately 8.5 years) (range 6-10 years) IQ: not stated MPH-naive: 12

Fine 1993 *(Continued)*

	Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: (socioeconomic status calculated using Blishen Index; lower score indicates higher socioeconomic status): medical trial: mean 3.42 (SD 0.90); typical clinical procedure: mean 3.50 (SD 1.88) **Inclusion criteria** • ADHD diagnosis. Parent interview with psychiatrist, several parent (mother and father) and teacher ratings. Included if any positive **Exclusion criteria** • Physical or mental disability • Tic disorders
Interventions	Participants in the medical trial group were randomly assigned to different possible drug condition orders of 0.3 mg/kg and 0.6 mg/kg MPH and placebo Mean MPH dosage: not stated Administration schedule: twice/d Duration of each medication condition: "the different interventions were randomly assigned across days" Washout before trial initiation: not stated Medication-free period between interventions: not stated Titration period: not stated Treatment compliance: missed pills mean 1.92 (SD 1.44). Furthermore, compliance was assessed by urine test. By 6-week follow-up, parent-reported compliance was 83%; by 3 months, it was 73%
Outcomes	**ADHD symptoms** • Abbreviated CRS: rated on weekdays by teachers and on weekends by parents • SNAP: rated daily, but not stated by whom **Non-serious AEs** • Side effects questionnaire: rated weekly by parents ("Across the 12 children, ratings were available from an average of 2.58 placebo days, 1.33 LD-MPH days and 1.75 high-dose MPH days")
Notes	Sample calculation: not stated Ethics approval: not stated **Comments from trial authors** • Small sample size • Rely on parent ratings to assess side effects **Key conclusions of trial authors**

Fine 1993 *(Continued)*

- Fine 1993: "Our analyses revealed that several side-effects appeared equally often on placebo as on active medication and the parents' reports of side effects are significantly related to reports of ADHD symptomatology" (p 28)
- Johnston 1993 (in Fine 1993): "In summary, this study finds mixed support for the prediction that medication trials would enhance acceptability, satisfaction, and compliance associated with MPH" (p 728)

Comments from review authors

- This trial aims to examine differences in attitudes of parents whose children participate in a medical trial or are subjected to "typical clinical procedure"
- Only the medical trial group represents a cross-over design
- Fine 1993 deals only with the medical trial group, and Johnston 1993 (in Fine 1993) deals with both

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: CIBA-GEIGY Canada

Email correspondence with trial authors: June 2014. Emailed trial authors for supplemental information and received the following response: "I did look at the questions, but unfortunately, given how long ago the study was conducted, I do not still have the data necessary to answer" (Krogh 2014b [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	24 children were matched in pairs on sex and age and then were randomly assigned to the medication trial or to the typical clinical procedure. Higher and lower doses of MPH and placebo were randomly assigned across days by the hospital pharmacy
Allocation concealment (selection bias)	Low risk	Higher and lower doses of MPH and placebo were randomly assigned across days by the hospital pharmacy. Active medication and placebo were packaged in capsule form to disguise taste and visual differences, and were dispensed in envelopes for daily use
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, teacher, child and resident were blinded to the daily medication status of the child. "Active medication and placebo were packaged in capsule form to disguise taste and visual differences, and were dispensed in envelopes for daily use". All evaluations were conducted by psychiatric residents blinded to the hypotheses of the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents, teacher, child and resident were blinded to the daily medication status of the child. All evaluations were conducted by psychiatric residents blinded to the hypotheses of the trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Across 12 children, ratings were available for an average of 2.58 placebo days, 1.33 LD-MPH days and 1.75 HD-MPH days. Ratings for each child were averaged across each of the 3 treatment conditions. Data for all participants were available for measures of missed pills and appointments. 1 participant was missing on measures of parent-reported compliance at 6-week follow-up, and 2 participants at 3-month follow-up. 3 participants lacked data for the number of missing envelopes. 4 participants did not provide urine for analysis, and 4 were missing physician reports of compliance (6-week and 3-month follow-ups). As the result of intervening school holidays, teacher reports of compliance are available for only 16 children (8 in each condition) at each follow-up.

Fine 1993 *(Continued)*

		MPH non-responders were not excluded. Did not state the method used to account for missing outcome data Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol was identified

Firestone 1981

Study characteristics	
Methods	3-month, randomised, double-blind, placebo-controlled, parallel trial, wherein participants were randomly assigned to 3 arms: • parent training + placebo (control group) • parent training + MPH (intervention group) • MPH
Participants	Number of participants screened: 91 Number of participants included: not stated (includes boys and girls) Number of participants followed up: intervention 18, control 13 Number of withdrawals: not stated Diagnosis of ADHD: DSM-III Age: mean 7.32 years (range 5-9) MPH-naive: not stated Ethnicity: not stated Country: not stated Setting: outpatient clinic Comorbidity: not stated Comedication: not stated IQ: 116 Other sociodemographics: all children living at home with ≥ 1 parent. No significant differences in age and IQ between treatment groups. No data on remaining parameters **Inclusion criteria** • 5-9 years of age • Fit DSM-III criteria for ADD-H, showing overactivity, short attention span, impulsivity, aggressiveness and oppositional behaviour, both at home and in school, since before 4 years of age • Hyperactivity Index of CTRS ≥ 15 • IQ > 85 **Exclusion criteria** • Brain damage • Epilepsy

Firestone 1981 *(Continued)*

	• Psychosis
Interventions	Participants were randomly assigned to MPH + parent training (intervention group) or to placebo + parent training (control group). After the titration period MPH was given only on school days Average MPH dosage: 22 mg/d (range 10 mg/d-30 mg/d) Titration period: first 3-4 weeks: MPH was titrated (after randomisation), starting with 5 mg twice/d (morning, noon), 7 days a week Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CTRS 2, CPRS subscale • Hyperactivity Index: rated by mothers post-treatment
Notes	Ethics approval: no information **Key conclusions of trial authors** • All groups showed improvement at home and in school; only with MPH administration were gains in measures of attention and impulse control also seen • Results also revealed greater improvement in academic achievement and in classroom behaviour in medication groups as compared with placebo groups • No evidence showed significant benefit from the addition of parent training to administration of medication **Comment from review authors** • First trial author has retired; we were not able to get data from him (e.g. protocol, randomisation method) Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes, 4 participants responded adversely and were dropped from the trial Funding source: Ministry of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were randomly assigned; no description of how
Allocation concealment (selection bias)	Unclear risk	No data
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, teachers, therapists and those testing the children were unaware of medication conditions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents, teachers, therapists and those testing the children were unaware of medication conditions
Incomplete outcome data (attrition bias)	Unclear risk	No data

Firestone 1981 *(Continued)*

All outcomes		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): none
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Fitzpatrick 1992a

Study characteristics	
Methods	Cross-over trial with 4 interventions 1. ER-MPH 2. Standard MPH 3. Combination 4. Placebo Phases: 4 pharmaceutical conditions, each lasting 2 weeks (including weekends), with different dosage schedules based on weight of child and type of intervention
Participants	Number of participants screened: not stated Number of participants included: 19 (17 boys, 2 girls) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADD: DSM-III during Diagnostic Instrument for Childhood and Adolescence (ADD with hyperactivity 16/19) (ADD without hyperactivity 3/19) Age: mean 8.71 years (SD 1.33, range 6.9 to 11.5) IQ: 114.11 (SD 13.34) MPH-naive: 18 Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: oppositional disorder (n = 12), oppositional + CD (n = 1), enuresis (n = 2), encopresis (n = 2), phobia (n = 1), overanxious (n = 1), adjustment disorder (n = 1) Comedication: not stated Other sociodemographics: middle class (Hollingshead 4-factor mean 38.11, SD 13.18) **Inclusion criteria** 1. Not explicitly stated **Exclusion criteria** 1. Not explicitly stated
Interventions	Participants were randomly assigned to 1 of 24 (3 MPH and 1 placebo) possible drug condition orders of ER-MPH (SR), standard MPH (SA), MPH combination and placebo

Fitzpatrick 1992a *(Continued)*

Mean MPH dosage: SRSA-MPH 17.1 mg (0.56 mg/kg), SASR-MPH 20 mg (0.67 mg/kg), combination 11.8 mg SA MPH + 20 mg SR MPH (0.38 mg/kg SA, 0.67 mg/kg SR)

Administration schedule: ER-MPH, mornings (8:00 am) daily, SA MPH morning (8:00 am) and noon daily

Duration of each medication condition: 2 weeks

Washout before trial initiation: not stated

Medication-free period between interventions: not stated

Titration period: not stated

Treatment compliance: parents phoned weekly to encourage compliance. School nurse contacted at the beginning of each individual's participation to promote co-operation and to check on compliance

Outcomes

ADHD symptoms

1. Conners' Hyperactivity Index: parent- and teacher-rated, weekly (although results were averaged over treatment phase)
2. IOWA Inattention/Overactivity and Aggression/Non-compliance Scales: parent- and teacher-rated, weekly
3. Hyperactivity, Attention and Aggression subscales of Loney's Time on Task Scale (TOTS): every 2 weeks

General behaviour

1. Selected items of Child Psychiatric Scale: observer, end of each laboratory session (i.e. after 14 days of treatment)

Non-serious AEs

1. Interviewed: 12 side effect symptoms: drawn from Subject's Treatment Emergent Symptom Scale, parents, end of each treatment phase
2. Body weight: start of each laboratory session

Notes

Sample calculation: not stated

Ethics approval: not stated

Key conclusions of trial authors

1. MPH conditions were superior to placebo and were comparable with one another
2. Findings suggest comparable effectiveness for ER and standard preparations of MPH
3. Improved behaviour and improved information processing under stimulant conditions

Comment from review authors

1. This trial was not actually randomised; therefore we cannot use data on ADHD symptoms and general behaviour - only data on AEs

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: not clear

Any withdrawals due to AEs: not clear

Funding source: National Institute of Mental Health (NIMH) grant MH38118

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Double-blind trial consisting of 4 pharmacological conditions, each lasting 2 weeks and ordered according to a Latin square (i.e. not randomly assigned)

Fitzpatrick 1992a *(Continued)*

Allocation concealment (selection bias)	High risk	Not randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Blindness was maintained by administering placebo tablets consisting of the vehicle for the SA and SR preparations, respectively, as appropriate for each condition
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data for 6 participants on Paired Associate Learning Test excluded, as they could not read well, but this was not 1 of our outcomes Selection bias (e.g. titration after randomisation): no, but because of emergent side effects, reductions of 2.5 mg SA MPH per dose were performed blindly for 1 participant in the combined condition. Similarly, blinded (but sham) adjustments of SA placebo were made for 2 participants in the placebo phase and for 1 in the SR condition
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Flapper 2008

Study characteristics	
Methods	4-week, double-blind, randomised, placebo-controlled, cross-over trial of MPH and placebo with weekly switches of 4 dosage levels; capsules of: • 0.5 mg/kg • 0.75 mg/kg • 1 mg/kg • placebo MPH-sensitive children continued in an open-label trial for 4 weeks
Participants	Number of participants screened: 80 Number of participants included: 30 (22 boys, 8 girls) Number of participants followed up: 30 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (37%), hyperactive-impulsive (7%), inattentive (57%)) Age: mean 105.2 months (approximately 8.8 years) (SD 25.1, range 7-12 years) IQ: > 70 MPH-naive: 100% Ethnicity: not stated Country: the Netherlands Setting: outpatient clinic

Flapper 2008 *(Continued)*

	Comorbidity: developmental co-ordination disorder (100%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD, DSM-IV • Developmental co-ordination disorder, DSM-IV • ADHD symptoms had to be severe for ≥ 6 items on the DSM-IV ADHD-RS, Parent Version, investigator administered and scored • Total score on the Movement Assessment Battery for Children below the 5th centile **Exclusion criteria** • Comorbid disorders (including pervasive developmental disorder) • Not medication-naive • IQ score below normal range (< 70), as assessed by the WISC–R (Dutch Edition)
Interventions	Participants were randomly assigned to possible drug orders of the 3 daily doses of MPH (0.5 mg/kg, 0.75 mg/kg, 1 mg/kg) and placebo Mean optimal dosage: 0.66 mg/kg/d (SD 0.22) Administration schedule: twice/d Duration of each medication condition: 1 week Washout before trial initiation: none. All were medication-naive Medication-free period between interventions: none Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • 18-Item ADHD-RS-IV: rated weekly (each Friday) by parents and teachers
Notes	Sample calculation: yes Ethics approval: procedures were performed in accordance with the ethical standards of the University Medical Centre, University of Groningen **Comment from trial authors** • One aim of the trial was to investigate the effectiveness of MPH in improving the fine motor performance of children with ADHD and developmental co-ordination disorder (DCD). To prevent confounding by fluctuations in ADHD symptoms, these had to be reduced by selecting MPH-sensitive children **Key conclusions of trial authors** • Children with ADHD/DCD and their parents rated overall quality of life as poorer than for healthy controls, manifested in domains of motor and autonomic functioning, as well as cognitive and psychosocial functioning • "In our trial, significant improvements in health-related quality of life were noted after treatment with MPH, as was improvement in symptoms of ADHD and motor functioning" • Fine motor performance in children with ADHD-DCD was poorer before use of MPH than afterwards • Impairment in manual dexterity and poor quality of handwriting and drawing improved after MPH use, but performance remained poorer than in the control group

Flapper 2008 *(Continued)*

Comment from review authors

- Only data from the 4-week cross-over trial are useful for the review; therefore all data extracted were derived from the cross-over period

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: none (no funding was available). This double-blind placebo-controlled trial of MPH was performed as a clinical treatment program as best clinical practice to determine the effects of MPH and optimal dose compared with placebo

Email correspondence with trial authors: August 2013-January 2014. We obtained supplemental information regarding participant demographics and efficacy data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random order by pharmacist
Allocation concealment (selection bias)	Low risk	Medication codes were broken at time 2 (endpoint)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, teachers, children and paediatrician were kept blinded to the child's drug condition and dosage level
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents, teachers, children and paediatrician were kept blinded to the child's drug condition and dosage level
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant withdrew; no ITT was needed. 7 children whose ADHD symptoms were not sensitive enough to MPH (effect < 25%) were excluded from the 4-week open-label period. However, as we are using in this review only data from the preceding cross-over period, exclusion of these children does not cause high risk of bias Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of reporting bias

Forness 1992

Study characteristics

Methods	Double-blind, placebo-controlled, cross-over trial with 2 interventions: • MPH • placebo Phases: 4

Forness 1992 *(Continued)*

Participants	Number of participants screened: 82 Number of participants included: 71 (all boys) Number of participants followed up: CTRS (n = 47), CPRS (n = 69) Number of withdrawals: CTRS 33.8%, CPRS 12.6% Diagnosis of ADHD: DSM-III-R (hyperactive-impulsive (100%)) Age: mean 9.3 years (range 7-11) IQ: mean 106.2 (range 67-137) MPH-naive: 100% Ethnicity: ethnic minority (11.3%) Country: USA Setting: outpatient clinic Comorbidity: CD (30/71) Comedication: no; had no psychotropics for a month before Other sociodemographics: all participants were middle to upper class **Inclusion criteria** • Boys • 7-11 years of age • Recruited from referrals to 2 clinics: University of California, Irvine Child Development Center for Children with ADD, and University of California, Los Angeles Child Psychiatry Outpatient Department for children with psychiatric disorders • Meet cut-off for inattention/overactivity **Exclusion criteria** • IQ < 85
Interventions	Participants were randomly assigned to different possible drug condition orders of 0.3, 0.6 and 1.0 mg/kg MPH (unless dosages would exceed 20 mg, so LD would be 0.15 mg/kg) 3 times/d and placebo Mean MPH dosage: not stated Administration schedule: 3 times/d – 7:30 am, 11:30 am, 3:30 pm Duration of each medication condition: 7 days Washout before trial initiation: not stated Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CRS: teachers and parents
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusion of trial authors**

Forness 1992 *(Continued)*

- At the very least, teachers may be cautious about optimistic claims of positive response to MPH

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: unclear

Funding source: NIMH grant MH38686

Email correspondence with trial authors. Emailed trial authors to ask for additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as double-blind but not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as double-blind but not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion): no, but high loss to follow-up for teachers' scores on CTRS Washout period between medication conditions: unclear
Selective reporting (reporting bias)	Unclear risk	Not protocol identified

Froehlich 2011

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, cross-over trial of multiple MPH doses in stimulant-naive school-aged children Phases: 3 active dosage weeks and 1 week of placebo
Participants	Number of participants screened: 162 Number of participants included: 105 Number of participants followed up: 89 (65 boys, 24 girls) Number of withdrawals: 16 Diagnosis of ADHD: DSM-IV (combined (48%), hyperactive-impulsive (0%), inattentive (52%))

Froehlich 2011 *(Continued)*

	Age: mean 8.13 years (range 7-11) IQ: mean: 105.34 ± 12.65 MPH-naive: 100% Ethnicity: white (79%), African American (18%), Hispanic (2%), other (1%) Country: USA Setting: outpatient clinic Comorbidity: anxiety disorder (17%), mood disorder (2%), disruptive behaviour disorder (36%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD according to DSM-IV criteria for onset age, pervasiveness and impairment, inattentive or combined type • Stimulant-naive • 7-11 years of age • 6 non-overlapping symptoms in a symptom domain (as per DISC, and VADTRS), and both parent and teacher reported ≥ 4 symptoms in that domain **Exclusion criteria** • Hyperactive-impulsive-type participants • IQ ≤ 80 • Mania/hypomania • Comorbid ODD, CD, depression and anxiety, if they were determined to be the primary cause of ADHD symptoms, or required different treatment • Medical history suggesting significant brain injury
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of OROS-MPH (18 mg, 27 mg, 36 mg for children ≤ 25 kg; 18 mg, 36 mg or 54 mg for children > 25 kg; sample mean maximum dose 1.57 mg/kg/d) and placebo Administration schedule: once daily Duration of each medication condition: 1 week Washout before trial initiation: drug-naive Medication-free period between interventions: not stated Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Parents and teachers: VAPRS/VADTRS: completed at baseline and each week of the trial
Notes	Sample calculation: yes Ethics approval: yes; Cincinnati Children's Hospital Institutional Review Board **Comments from trial authors**

Froehlich 2011 *(Continued)*

- "Additional limitations include restricted duration of follow-up and heterogeneity of our sample due to recruitment from a variety of sources. Further, our sample had more inattentive (52%) than combined subtype (48%) participants"
- "Although consistent with subtype distribution in many epidemiological samples, this differs from clinic settings, where combined type is most common"

Key conclusions of trial authors

- "Results of this double-blind, placebo-controlled, ADHD pharmacogenetic trial of psychostimulant-naive school-aged children suggest that dopamine active transporter (DAT) and dopamine receptor (DR) D4 variations may be associated with unique MPH dose-response curves"
- "Children lacking the DAT 10-repeat allele and those with the DRD4 4-repeat allele had a more robust MPH response compared with those of alternate genotypes, consistent with improved response for the ADHD susceptibility low-risk alleles"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: NIMH and Cincinnati Children's Hospital Center for Education and Research Therapeutics Award

Email correspondence with trial author: October/November 2013. Contacted trial author to obtain mean and SD for ADHD symptoms. Never received additional data. Therefore no further email correspondence regarding allocation concealment, randomisation, etc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned to different drug orders. No description about how
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial medication consisted of identical capsules filled with an inert white powder (placebo) or prescribed dose of Concerta over-encapsulated to preserve double-blind Double-blind, but not specified who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial medication consisted of identical capsules filled with an inert white powder (placebo) or prescribed dose of Concerta over-encapsulated to preserve double-blind Double-blind, but not specified who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided on 89 participants who completed the trial Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	Not able to find protocol or trial identifier

Froehlich 2018

Study characteristics	
Methods	A 4-week cross-over trial with 4 arms • 1 week of LD-LA-OROS-MPH (Concerta) • 1 week of MD-LA-OROS-MPH (Concerta) • 1 week of HD-LA-OROS-MPH (Concerta) • 1 week of placebo Phases: 1
Participants	Number of participants screened: 194 met inclusion criteria Number of participants included: 171 (122 boys, 49 girls) Number of participants followed-up: 168 (154 for sleep outcomes) Number of withdrawals: 3 (found from table on ClinicalTrials.gov) (14 further for sleep outcomes) Diagnosis of ADHD: DSM-IV (45 combined, 0 hyperactive-impulsive and 126 inattentive) Age: 8.4 (SD 1.3, range 7-11) IQ: inattentive-type: 107.8 (SD 13.3), combined-type: 105.6 (SD 12) MPH-naive: 100% Ethnicity: white (n = 139), black (n = 21), Hispanic/Latino (n = 4), other (n = 3) Country: USA Setting: outpatient Comorbidity: comorbid ODD, CD, depression, and anxiety disorders were allowed unless determined to be the primary cause of ADHD symptomatology or necessitating different treatment. Anxiety disorder = 2, mood disorder = 2, disruptive behavior disorder = 45 Comedication: no medication for psychological or psychiatric problems Additional sociodemographics: none **Inclusion criteria** • Consent: the family must provide signature of informed consent by a parent or legal guardian. Children must also assent to trial participation • Age at screening: 7.0 years-11.9 years, inclusive • Sex: includes male and female children • ADHD diagnostic status: meets DSM-IV criteria for ADHD, predominantly inattentive or combined subtype with CGI-S rating corresponding to at least "moderately ill" • Cognitive functioning: IQ > 80 as estimated by Vocabulary and Block Design subtests of the WISC-IV, or an IQ of ≥ 80 when administered the Full Scale Version of the WISC-IV • Absence of learning disability: on the abbreviated Wechsler Individual Achievement Test-2nd edition Reading and Math subtests, participants must score > 80. However, children may also be included if they receive a score of ≥ 75 on the Word Reading and/or Math subtests, as long as this score is not a significant discrepancy from their full-scale IQ score (e.g. a difference of > 1 SD or 15 points). • School: enrolled in a school setting rather than a home-school programme **Exclusion criteria** • Understanding level: participant and/or parent cannot understand or follow trial instructions • Psychiatric medications: current or prior history of taking any medication for psychological or psychiatric problems

Froehlich 2018 *(Continued)*

- Behavioral interventions: current active participation in ADHD-related behavioral interventions or counselling
- Exclusionary psychiatric conditions: children with mania/hypomania and/or schizophrenia will be excluded. The following comorbid diagnoses will not be excluded unless they are determined to be the primary cause of ADHD symptomatology (see below for description of this decision process): PTSD, phobias and anxiety disorders, OCD, major depression/dysthymia, eating disorders, elimination disorders, trichotillomania, tic disorder, ODD, CD
- Organic brain injury: history of head trauma, neurological disorder, or other organic disorder affecting brain function
- Cardiovascular risk factors: children with a personal history or family history of cardiovascular risk factors will be excluded, or given the option of participating in the trial after obtaining an ECG and a signed letter from a paediatric cardiologist verifying the safety of their participation in a trial of MPH. In this case, families will be responsible for the costs of ECG and cardiologist evaluation. If for any reason a family is unable to assume the cost of the ECG and cardiologist evaluations but still wishes for their child to participate, trial staff will determine on a case-by-case basis whether the trial budget allows the trial to offer financial assistance to the families for these evaluations.

Interventions	Participants were randomly assigned to 1 of 6 different medication orders, of 3 different medication weeks of OROS-MPH (Concerta) at a high, medium and low dose, and 1 week of placebo. Number randomised to each group: not stated Mean medication dosage: 18 mg, 27 mg, 36 mg for children ≤ 25kg; 18 mg, 36 mg or 54 mg for children > 25kg; sample mean maximum dose = 1.57 mg/kg/d) Administration schedule: not stated Duration (of (each) medication): 3 weeks of OROS-MPH (Concerta), 1 week at each dose, 1 week of placebo Washout before trial initiation: not applicable, all were MPH-naive Medication-free period between interventions: not stated Treatment compliance: not stated
Outcomes	**ADHD symptoms** • VADPRS • VADTRS Data on ADHD symptoms were not reported in a way that could be used for this review. Trial authors were contacted, but no data were received. **Serious AEs** • Spontaneous reporting **Non-serious AEs** • Parent-completed Pittsburgh Side Effect Rating Scale (including sleep outcomes)
Notes	Sample calculation: no Ethics approval: institutional Review Board-approved protocol **Comments from trial authors** • "Our trial limitations include its short-term nature, so we are unable to comment on the longer-term persistence of the documented MPH response patterns." • "In addition, in accordance with usual clinical practice, we depended on parent and teacher ADHD symptom ratings to determine MPH response, rather than using direct behavioral observations or neuropsychological measures."

Froehlich 2018 *(Continued)*

Key conclusion of trial authors

- No factors have been identified that consistently predict MPH response in children with ADHD.
- There is growing interest in a new ADHD-related phenotype called sluggish cognitive temp (SCT), and the relationship between SCT symptomatology and medication response.
- Higher levels of specific SCT symptoms related to being sleepy and slow moving were linked to a diminished MPH response in this trial.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no

Any withdrawals due to AEs: not stated

Funding source: data collection for the project was supported by the NIMH (Bethesda, MD) by R01MH074770 [Epstein] and K23MH083881 [Froehlich], while investigators' time on the project was funded by NIMH K24MH064478 [Epstein], K23MH083027 [Brinkman], and R01MH070564 [Stein]).

Email correspondence with trial authors: August and November 2021 We received supplemental information regarding risk of bias through personal email correspondence with the trial authors in August 2021 (Storm 2021b [pers comm]). Inquiries for outcome data was also made but no answer was received in either September and November 2021.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list was used to randomise participants equally to one of 6 dosing schedules
Allocation concealment (selection bias)	Low risk	Trial medication consisted of identical capsules filled with either an inert white powder (placebo) or the prescribed dose of OROS-MPH (Concerta_ over-encapsulated to preserve double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial pills were identical capsules filled with either an inert white powder (placebo) or the prescribed dose of MPH over-encapsulated to preserve the blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Yes, outcome assessors were blind to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 participants did not complete the medical trial. 17 missing data for sleep outcomes, LOCF (high risk of bias for this particular outcome) Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	Family satisfaction with medication trial not reported

Gadow 1990

Study characteristics

Methods	6-week double-blind, cross-over trial in which participants received the following in random order:

Gadow 1990 *(Continued)*

- LD-MPH
- MD-MPH
- placebo

Furthermore, a single case report from the trial is described

Participants	Number of participants screened: not stated Number of participants included: 11 (11 boys, 0 girls) Number of participants followed up: between 9 and 10, depending on ratings Number of withdrawals: 1-2 Diagnosis of ADHD: DSM-III (type not stated) Age: mean not reported (range 5.9-11.9 years) Case report: 10 years of age IQ: > 75 Stimulant-naive: 6 Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: disruptive behaviour disorder Comedication: not reported Other sociodemographics: children represented a full range of socioeconomic backgrounds **Inclusion criteria** • Boys • 5-12 years of age • ADHD diagnosis according to DSM-III • Scored above research cut-off (> 7) on the Aggression scale of IOWA CTRS, or were considered aggressive by their classroom teacher and were above cut-off on ≥ 1 other conduct problem scale • Scored ≥ 15 on the Abbreviated Teacher Rating Scale • Above cut-off on the Oppositional DIsorder or CD Index of the Parent or Teacher Version of the Stony Brook Child Psychiatric Checklist, Version 3 **Exclusion criteria** • IQ < 70 • Psychosis, pervasive developmental disorder, dangerous to self or others • Seizure disorder, major organic brain dysfunction, medical illness, contraindication to medication treatment
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of LD-MPH (0.3 mg/kg) and MD-MPH (0.6 mg/kg) (upper limit 25 mg) and placebo Mean MPH dosage: not stated Administration schedule: twice/d, morning, noon, 3.5 h apart, 7 d/week Duration of each medication condition: 2 weeks

Gadow 1990 *(Continued)*

	Washout before trial initiation: yes Titration period: when MD was not preceded by LD condition, the child was gradually built up to MD. Data from these titration days were excluded from the analyses Treatment compliance: pill count, no further information
Outcomes	**ADHD symptoms** • Conners' Abbreviated Teacher Rating Scale • Conners' Abbreviated Parent Rating Scale **Non-serious AEs** • Stimulant Side Effects Checklist: rated systematically
Notes	Sample calculation: no information Ethics approval: no information **Comment from trial authors** • Sample size was small, which decreased the probability of detecting clinically significant group differences between treatment conditions **Key conclusion of trial authors** • Results of this trial indicate that MPH-induced improvements in the classroom behaviour of aggressive hyperactive boys are associated with concomitant changes in the demeanour of classmates sitting in close proximity to the drug-treated child Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: Ciba Pharmaceutical Company supplied MPH placebo Email correspondence with trial authors: July 2013. Emailed first trial author twice to get additional information (funding, ethics approval, etc.) and data from the trial. Trial authors not able to provide us with additional data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Dose schedules were assigned on a random basis
Allocation concealment (selection bias)	Low risk	Medication and placebo pills were identical and were dispensed to parents and school nurses in dated, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, teachers, observers, treating physicians and children were blinded to dose and order
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents, teachers, observers, treating physicians and children were blinded to dose and order

Gadow 1990 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	For classroom analyses, data on 10 boys were analysed, and for lunch room analyses, data on 9 boys were analysed Selection bias (e.g. titration before randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified. Email sent to first trial author. No answer; therefore not able to get information

Gadow 1995

Study characteristics	
Methods	Randomised, placebo-controlled, double-blind, cross-over trial with 2 interventions: • MPH in 2 or 3 dosages • Placebo Phases • Washout if medications before trial • 8-week RCT with 2 weeks on each arm • Open-label follow-up at 24 months
Participants	Number of participants screened: not stated Number of participants included: 34 (31 boys, 3 girls) Number of participants followed up: RCT 34, minimal effective dose, after RCT 27; 12-month follow-up 30; 18-month follow up 26; 24-month follow-up 26 Number of withdrawals: RCT: 0 Diagnosis of ADHD: DSM-III-R (subtypes not stated) Age: mean 8 years and 10 months (range 6.1 years-11.9 years) IQ: mean 105.9 (SD 13.7, range no information) MPH-naive: 24 (71%) Ethnicity: white (85%), African American (3%), Asian (3%), Hispanic (9%), other (0%) Country: USA Setting: outpatient clinic Comorbidity: data from only 21 children from Gadow 1995: tics (100%); anxiety or depressive disorder, or both (8/21; 38%); OCD (3/2; 14%); most of the children also had ODD or CD and academic problems Comedication: not during RCT. 4 children were treated with an anti-tic medication in combination with MPH at some time during the course of follow-up (neuroleptic 3, clonidine 1) Other sociodemographics: none **Inclusion criteria** • Meet DSM III-R diagnostic criteria for ADHD and chronic motor tic disorder or Tourette's disorder • ADHD had to be a primary reason for seeking clinical services • In general, had to be above the cut-off on 2 or 3 parent- and teacher-rated hyperactivity and/or ADHD behaviour rating scales

Gadow 1995 *(Continued)*

- Written signed statement from parents consenting to their child's participation

Exclusion criteria

- Dangerous to self or others
- Tics: the major clinical management concern
- Psychosis
- IQ < 70
- Seizure disorder
- Major organic brain dysfunction
- Major medical illness
- Contraindications to medication (other than tics)
- Pervasive developmental disorder

Interventions	Participants were randomly assigned to 1 of 4 possible drug condition orders of doses: 0.1 mg/kg (mean 4.4 mg), 0.3 mg/kg (mean 9.0 mg) and 0.5 mg/kg (mean 14.0 mg) of MPH and placebo Upper dosage limit was 20 mg. When the 0.5-mg/kg dose was not preceded by a LD condition, the child was gradually built up to MD. Build-up days occasionally fell on scheduled school observation days. Observers were unaware of these days and observations were conducted as usual, but these data were excluded from the analyses Administration schedule: twice/d (or 3 times/d) at morning and noon, approximately 3.5 h apart, 7 d/week Duration of each medication condition: 2 weeks Washout before trial initiation: MPH 1 week, antipsychotic 3 weeks, clonidine 2 weeks Medication-free period between interventions: none Titration period: none Treatment compliance: parents and nurses were asked to return unused medication envelopes, which allowed researchers to assess compliance. No further information was provided in the paper Regarding 24-month follow-up: total daily dose of MPH, minimal effective dose - after RCT mean 16.5 mg (range 5 mg-40 mg); second visit mean 28.5 mg (range 15 mg-60 mg); third visit mean 29.2 mg (range 10 mg-90 mg); and 4th visit mean 34.5 mg (range 15 mg-92 mg)

Outcomes	**During 8-week RCT**
	
	ADHD symptoms
	
	• Parents
	  ◦ Abbreviated CPRS: rated Saturday and Sunday each week
	  ◦ Mothers' Objective Method for Subgrouping: rated by parents Saturday and Sunday each week
	• Teachers
	  ◦ Abbreviated CTRS, 10-item: rated 2 d/week for each intervention period
	  ◦ IOWA CTRS: rated 2 d/week for each intervention period
	
	General behaviour
	
	• Peer Conflict Scale: parent- and teacher-rated, 2 times/week
	• Classroom Observation Code: observer-rated, 4 days for each treatment condition
	• ADHD School Observation Code: observer, 3-4 days for each treatment condition
	• Code for Observing Social Activity: observer, lunch and playground, 20-30 min, 4 days for each treatment condition
	
	Non-serious AEs

Gadow 1995 *(Continued)*

- Side Effects Checklist: 13 items, rated by parents on Saturday and Sunday and rated by teacher twice/week
- Global Tic Rating Scale: rated by parents on Saturday and Sunday and rated by teacher twice/week
- Motor and vocal tic category: observers coded presence or absence of tics in the classroom, lunchroom or playground, 4 times for each medication condition

Physician evaluations

- YGTSS: rated every second week
- Tourette Syndrome Unidentified Rating Scale: rated every 2nd week
- Global Tic Rating Scale (assessed in only 22 participants): rated every 2nd week
- Shapiro Tourette Syndrome Severity Scale (assessed in only 22 participants): rated every 2nd week
- Motor tic frequency tics: rated in 180 5-s intervals in a simulated classroom; tics were coded as present or not present in each interval, rated every 2nd week
- Weight: assessed every 2nd week
- Heart rate: assessed every 2nd week
- BP: assessed every 2nd week

During 24-month follow-up

Physician evaluations

- All rated at minimally effective dose (right after RCT) 6 months, 12 months, 18 months and 24 months
- YGTSS
- Shapiro Tourette Syndrome Severity Scale
- 3 subscales from Tourette Syndrome Unified Rating Scale
- Total number of tics
- Number of tics observed in 2 min of quiet conversation with physician
- LeWitt Disability Scale, which assesses tics and symptoms of comorbidity
- Global Tic Rating Scale
- BP
- Heart rate
- Pulse
- Weight

Parent ratings

- Based on last 2 weeks and rated at minimal effective dose (right after RCT) 6 months, 12 months, 18 months and 24 months
- Stimulant Side Effects Checklist
- Global Tic Rating Scale

Notes

Sample calculation: yes

Ethics approval: no information

Comments from trial authors

- "Magnitude of clinical improvement associated with 0.3 mg/kg dosage vs 0.5 mg/kg dosage was generally trivial for many children"
- "0.5 mg/kg dosage was associated with more side effects, but fortunately they were generally of limited clinical significance"
- "Generalisability of findings from this trial is subject to several qualifications. First, our data pertain to observed treatment effects over an 8-week period and therefore cannot address the issue of tic exacerbation as a function of long-term drug exposure. Furthermore, the findings pertain only to children with ADHD with tics of mild to moderate severity that occur frequently enough to be observed during 15-minute intervals"

Gadow 1995 *(Continued)*

Key conclusions of trial authors

- "During the course of this short-term drug evaluation, physician, teacher and parent ratings were in agreement that MPH did not lead to worsening of the severity of children's tic disorders"
- "MPH is an effective drug for the treatment of ADHD and oppositional and aggressive behaviour"
- "Follow-up trial showed that long-term treatment with MPH seems to be safe and effective for the management of ADHD behaviours in many (but not necessarily all) children with mild to moderate tic disorders. Nevertheless, careful clinical monitoring is mandatory, to rule out the possibility of drug-induced tic exacerbation in individual patients"

Comments from trial authors (limitations)

- 2-year follow-up component was not blinded. Although obstacles to creating and maintaining a long-term double-blind trial with a placebo group are daunting, failure to do so does introduce the possibility of bias
- Absence of a no-treatment group does not allow inferences about natural changes in tic status over time

Comments from review authors

- Well-designed trial
- No exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH. 26 children received stimulant medication throughout the follow-up interval; of these children, 1 was switched to dextroamphetamine. However, we have chosen to use in our analyses results for all 26
- All included articles include a mix of different protocols, so total numbers of included participants differ from article to article

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no; children were not excluded from participation in the trial if they had prior experience with stimulant drug therapy, or if such therapy purportedly had exacerbated their tics

Any withdrawals due to AEs: no

Funding source: research grants from the Tourette Syndrome Association and the NIMH

Email correspondence with trial authors: April 2013. We emailed trial authors for supplemental information regarding cross-over data. Data were not available. Also no further data for the interventions were available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Dose schedules were counterbalanced and assigned on a random basis
Allocation concealment (selection bias)	Low risk	Medication and identically matching placebos were dispensed to parents and school nurses in dated, sealed envelopes at 2-week intervals
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, teachers, participants, observers and physicians were blinded to the identity of those conditions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medication was administered under double-blind conditions (i.e. no one involved in clinical management of the participant, data collection or interaction with the school knew the identity of treatment conditions)
Incomplete outcome data (attrition bias)	Low risk	Trial describes how many people were included in the different analyses

Gadow 1995 *(Continued)*

All outcomes		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified or received

Gadow 2007

Study characteristics	
Methods	Double-blind, randomised, cross-over trial with interventions: • MPH • placebo Phases • Washout if previously medicated • 8-week trial, 2 weeks on each arm. Performed in 2 cohorts (several years apart, same personnel)
Participants	Number of participants screened: not stated Number of participants included: 71 (39 + 32, cohorts 1 and 2, respectively) Number of participants followed up: 71 (57 boys, 14 girls) Number of withdrawals: not stated Diagnosis of ADHD: DSM-III-R or DSM-IV (subtype not stated) Age: mean: 8.9 ± 1.9 years (range 6-12) IQ: mean 103.8 MPH-naive: not stated Ethnicity: white (87%), African American (6%), Asian (1%), Hispanic (6%) Country: USA Setting: outpatient clinic Comorbidity: Tourette's syndrome (96%), chronic motor tic disorder (4%), ODD (56%), CD (7%), overanxious or generalised anxiety (30%), simple phobia (7%), OCD (11%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-III-R or DSM-IV diagnosis of ADHD • Chronic motor tic disorder or Tourette's syndrome • ADHD clinical criteria at both school and home **Exclusion criteria** • Too severely ill (dangerous to self or others) • Psychotic • IQ < 70 • Seizure disorder

Gadow 2007 *(Continued)*

- Major organic brain dysfunction
- Major medical illness
- Medical or other contraindication to medication (other than tics)
- Pervasive developmental disorder
- Tics so severe at intake that the parent or the child requested immediate intervention
- Extremely mild tics at intake

Interventions	Participants were randomly assigned to 1 of 4 possible drug condition orders of placebo or IR-MPH (0.1 mg/kg (mean 4.5 mg; SD 1.6), 0.3 mg/kg (mean 9.3 mg; SD 3.0) and 0.5 mg/kg (mean 14.3 mg; SD 3.3)), twice/d for 2 weeks, each under double-blind conditions. Upper limit was 20 mg/d Administration schedule: twice daily, 3.5 h apart. Most days, a morning dose and a noon dose, 7 days/week Duration of each medication condition: 2 weeks Washout before trial initiation: minimum washout periods for children receiving medication at referral were as follows: 1 week for stimulants (n = 10), 3 weeks for neuroleptic or SSRI (n = 2) and 2 weeks for clonidine (n = 1) Medication-free period between interventions: none Titration period: none Treatment compliance: not stated

Outcomes	**ADHD symptoms**
	
	• Teachers
	  ◦ Abbreviated Teacher Rating Scale (total score (Hyperkinesis Index) and ADHD (factor 1) and Emotional lability (factor 2) subscales)
	  ◦ IOWA CTRS (Inattention-Impulsivity-Overactivity and Oppositional Defiant subscales): twice/week, weekdays
	• Parents
	  ◦ Abbreviated Parent Rating Scale (total score (Hyperkinesis Index) and ADHD (factor 1) and Emotional lability (factor 2) subscales): Saturdays and Sundays, every week
	
	General behaviour
	
	• IOWA CTRS (Oppositional Defiant subscale)
	
	Non-serious AEs
	
	• Physician
	  ◦ Assessment of clinical status and heart rate, BP and weight: biweekly (n = 57)
	  ◦ Tics: YGTSS (includes 4 behaviourally anchored subscales: total Motor Tic score, Total Phonic Tic score, Overall Impairment Rating and Global Severity score), completed for all but the first 12 participants. Additional measures: Shapiro Tourette Syndrome Severity Scale (tic frequency, severity and impairment), Global Tic Rating Scale and Two-Minute Tic and Habit Count, completed for first 12 participants only. Both rated at 2-week intervals
	• Parents and teachers
	  ◦ Global Tic Rating Scale: twice a week for each week of the trial
	  ◦ Stimulant Side Effects Checklist: rated twice a week

Notes	Sample calculation: no Ethics approval: yes **Comment from trial authors**

Gadow 2007 *(Continued)*

- Children were not excluded if previous treatment with stimulants had purportedly induced or exacerbated their tics

Key conclusion of trial authors

- In this trial, IR-MPH was found to be a safe and effective short-term treatment for ADHD in children with chronic tic disorder, but complete normalisation of all problem behaviours often is not achieved at acceptable doses

Comments from review authors

- Given our concern about the possibility of a type II error (i.e. erroneously concluding that MPH did not have an adverse effect on tics), we performed follow-up repeat-measure ANOVAs on each respondent category, even when the main effect of dose was not significant
- Use of a cross-over design may result in carry-over effects. However, differences in change scores for tic frequency (simulated classroom) and severity (YGTSS - Global Severity score), respectively, between baseline and placebo in children who received placebo first and last were non-significant and minuscule (i.e. effect size = 0.08 and 0.19, respectively)

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: this trial was supported in part by a research grant from the Tourette Syndrome Association Incorporated, and by Public Health Service (PHS) grant number MH45358 from NIMH

Email correspondence with trial authors: April 2014. We obtained supplemental information from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Dose schedules were counterbalanced and assigned on a random basis
Allocation concealment (selection bias)	Low risk	Medication was administered twice daily, approximately 3.5 h apart, 7 d/week, and was dispensed in dated, sealed envelopes at 2-week intervals
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind conditions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	None required withdrawal of medication Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Gadow 2011

Study characteristics	
Methods	8-week, placebo-controlled, cross-over trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 54 (42 boys, 12 girls). Participants were randomly assigned to the different possible drug condition orders: ADHD without anxiety 37, ADHD with anxiety 17 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-III-R or DSM-IV (subtype not stated) Age: ADHD without anxiety 8.9 years, ADHD with anxiety 9.1 years (range 7-12) IQ: ADHD without anxiety mean 103.5, ADHD with anxiety mean 103.1 MPH-naive: 48 (89%) Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: Tourette's (n = 52), chronic multiple tic disorder (n = 2), anxiety (n = 17), major depressive episode or dysthymia (n = 11), overanxious disorder or generalised anxiety disorder (n = 12), separation disorder (n = 6), social phobia (n = 1), ODD (n = 36), CD (n = 4) Comedication: not stated Other sociodemographics: ADHD without anxiety 37.1, ADHD with anxiety 35.4 (according to Hollingshead) **Inclusion criteria** • DSM-III-R or DSM-IV diagnostic criteria for ADHD • Chronic multiple tic disorder or Tourette's disorder according to research diagnostic criteria • Each child met ADHD clinical criteria at both school and home (the "and rule") **Exclusion criteria** • Tics were the major clinical management concern • Too severely ill (dangerous to self or others) • Psychotic • Mentally disabled (IQ < 70) • Seizure disorder • Major organic brain dysfunction • Major medical illness • Medical or other contraindication to medication (other than tics) • Pervasive developmental disorder
Interventions	Participants were randomly assigned to different possible drug condition orders of 0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg MPH and placebo Mean MPH dosage: 4.7 mg, 9.5 mg, 14.5 mg

Gadow 2011 *(Continued)*

	Administration schedule: "administered twice daily, approximately 3.5 hours apart, 7 days a week" Duration of each medication condition: 2 weeks Washout before trial initiation: not stated Medication-free period between interventions: none Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Abbreviated Teacher/Parent Rating Scale • IOWA CTRS • CPRS (48-item) • Mothers' Objective Method for Subgrouping • Parent and Teacher Versions of the Child Symptom Inventory **General behaviour** • IOWA CTRS (Oppositional Defiant subscale) **Non-serious AEs** • Stimulant Side Effects Checklist • YGSS, which includes 4 behaviourally anchored subscales: total Motor Tic score, Total Phonic Tic score, Overall Impairment Rating and Global Severity score
Notes	Sample calculation: not stated Ethics approval: yes; approved by a university Institutional Review Board (IRB) **Comments from trial authors** • No evidence suggested that IR-MPH exacerbated tics in children with anxiety • Teacher ratings actually indicated improvement in motor and vocal tic frequency with medication (placebo > 0.5 mg/kg) **Key conclusions of trial authors** • Findings suggest that the co-occurrence of diagnosed chronic multiple tic disorders and ADHD with anxiety represents a particularly troublesome clinical phenotype, at least in the home setting • Comorbid anxiety disorder was not associated with a less favourable response to IR-MPH in children with ADHD and chronic multiple tic disorder, but replication with larger samples is warranted before firm conclusions can be drawn about potential group differences Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: NIMH and the Tourette Syndrome Association Incorporated. CIBA Pharmaceutical Company supplied MPH placebos. Novartis supplied IR-MPH Email correspondence with trial authors: May 2015. Emailed trial authors requesting additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement

Gadow 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Dose schedules were counterbalanced and were assigned on a random basis
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...dispensed in dated, sealed envelopes at two-week intervals"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	"In order to increase sample homogeneity, an additional 3 children with diagnosed specific phobia (n = 2) or major depressive episode without comorbid anxiety disorder (n = 1) were excluded from data analyses"

Garfinkel 1983

Study characteristics	
Methods	Double-blind, randomised, placebo-controlled, cross-over experiment with 4 arms: • MPH • clomipramine • desipramine • placebo Trial lasted 20 weeks; first and last 2 weeks were baseline periods during which no medication was given. Different interventions lasted 3 weeks each (Monday to Friday) with a 7-day washout between changes in drugs
Participants	Number of participants screened: not stated Number of participants included: 12 (all boys) Number of participants followed up: 12 Number of withdrawals: 0 Diagnosis: DSM-III Age: mean 7.3 years (range 5.9-11.6) IQ: > 70 MPH-naive: 50% Ethnicity: not stated Country: USA

Garfinkel 1983 *(Continued)*

	Setting: outpatient clinic and patient ward. 8 participants were day hospital patients and 4 were inpatients Comorbidity: no Comedication: no comedication during trial period Other sociodemographics: children presented with remarkably similar clinical, family and educational histories. None of the children had localising neurological signs or met criteria for other psychiatric diagnoses **Inclusion criteria** • ADD according to DSM-III **Exclusion criteria** • None mentioned directly
Interventions	Participants were randomly assigned to the different possible drug condition orders of MPH, clomipramine, desipramine and placebo Mean MPH dosage: 18 mg/d Administration schedule: twice/d, morning and lunch Duration of each medication condition: 3 weeks Washout before trial initiation: 2 weeks before trial entry and 7 days between drug conditions Titration period: first week of the drug condition after randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CTRS: rated daily by care workers (in settings away from the classroom) and teachers (in classroom) **General behaviour** • Werry-Weiss-Peters Activity Rating Scale: rated daily by parents for day patients and by evening child care staff for fully hospitalised children **Non-serious AEs** • DBP and SBP, measured by the nurse while participants were sitting and standing at 09.00 am and 12.00 pm • Apical pulse, morning and afternoon
Notes	Sample calculation: no information Ethics approval: no information **Key conclusions of trial authors** • MPH was significantly better for improving classroom and behavioural manifestations of ADD as compared with placebo, desipramine and clomipramine • Tricyclic antidepressants may have a significant therapeutic effect as indicated by mood elevation and amelioration of non-classroom behaviour in the evenings • Results encourage further clinical and pharmacological investigation of ADD using various alternative treatments **Comment from review authors** • Only information and data extracted from the MPH group and the placebo group

Garfinkel 1983 *(Continued)*

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: Ontario Mental Health Foundation

Email correspondence with trial authors. October 2013. We obtained supplemental information regarding number of dropouts and SD for CRS. We also wanted other data but were not able to obtain these, as the trial took place several years ago and the data are no longer available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were randomly given MPH, desipramine, clomipramine, placebo. A Latin square was followed to control for the order of presentation of drugs
Allocation concealment (selection bias)	Low risk	Children were randomly given MPH, desipramine, clomipramine, placebo. A Latin square was followed to control for the order of presentation of drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, parents, attending physicians, teachers, nursing staff and child care workers did not know which medication the child received, ensuring the double-blind procedure. Medication was added to lactose powder and was placed in identical-appearing gelatin capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, parents, attending physicians, teachers, nursing staff and child care workers did not know which medication the child received, ensuring the double-blind procedure. Medication was added to lactose powder and was placed in identical-appearing gelatin capsules
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of reporting bias

Gonzalez-Heydrich 2010

Study characteristics

Methods

Cross-over trial with 2 interventions:

- OROS-MPH
- placebo

Phases: number of phases varied by dose group. For all dose groups, after completing first phase, participants were on a 1-week washout period before cross-over. Participants assigned to 1 of 3 maximum OROS-MPH dose groups in randomly assigned order

- Group 1: 1 week LD-MPH, 1 week placebo
- Group 2: 1 week LD-MPH, 1 week MD-MPH, 1 week placebo
- Group 3: 1 week LD-MPH, 1 week MD-MPH, 1 week HD-MPH, placebo

Participants assigned to next group after 3 participants have successfully completed preceding group with no side effects

Gonzalez-Heydrich 2010 *(Continued)*

Participants	Number of participants screened: 40 Number of participants included: 33 (19 boys, 14 girls) Number of participants followed up: 33 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-R (combined (51.1%), inattentive (48.5%)) Age: mean 10.5 years (SD 3.0, range 6.4-17.5) IQ: mean 89.7 (SD 16.9, range 59-123) MPH-naive: not stated Ethnicity: not stated Country: USA Setting: hospital ward Comorbidity: epilepsy (100%), others (not stated) Comedication: yes, continuation of previous medication allowed. All participants were currently on a stable dose of antiepileptic medication. Other sociodemographics: none **Inclusion criteria** • Speaks English • IQ > 35 and score > 35 on Scales of Independent Behavior Revised (SIB-R) Broad Independence Scale (both IQ and adaptive functioning at the moderate mental disability level or higher) • Diagnosis of epilepsy by International League Against Epilepsy criteria 26 (repeated, afebrile, unprovoked seizures with a seizure within the past 5 years) • DSM-IV-R diagnosis of ADHD • Score ≥ 4 on CGI severity scale for ADHD • Score > 90% on ADHD-RS, Parent Version; investigator scored for age and sex on inattentive, hyperactive-impulsive or total score at first visit • Has not taken stimulants or alpha-adrenergic medications for > 2 weeks before trial entry • If taking antidepressants, neuroleptics or lithium, doses have been stable for > 4 weeks • Currently on an antiepileptic drug regimen with stable doses for > 4 weeks before trial entry • Seizure-free for > 1 month before trial entry • Prescribing clinician for epilepsy anticipates the need for a stable antiepileptic drug regimen for the duration of the trial • Guardian gives permission for trial personnel to communicate with prescribing epilepsy clinician • Teacher agrees to fill out ADHD-RS at baseline and at the end of each arm of the trial **Exclusion criteria** • Has had a seizure within the month preceding trial entry • Change in antiepileptic drug regimen or dose within 4 weeks of trial entry • History of moderate or severe AE related to MPH • History of any psychotic disorder • Current acute major depression or bipolar mania • Current psychiatric disorder requiring pharmacotherapy (other than ADHD) • Unstable significant medical condition other than epilepsy • Any known conditions that may make treatment with MPH medically inadvisable • Not currently working with a physician for epilepsy treatment

Gonzalez-Heydrich 2010 *(Continued)*

- Previously participated in a trial that provided adequate treatment with ER-MPH
- Weighs < 9 kg
- Pregnant
- Unwilling to use an effective form of contraception
- Child has taken a stimulant (MPH, an amphetamine preparation or pemoline), an alpha-adrenergic (clonidine or guanfacine) or other ADHD medication within 2 weeks of the screening telephone interview (children will not be withdrawn from psychotropic medications to be enrolled in the trial)

Interventions	Participants were randomly assigned to different possible drug condition orders of MPH and placebo. Each child was given 5 mg of IR-MPH in the morning and at noon for 1 day. If this dose was tolerated, 18 mg of OROS-MPH was administered in the morning for the remaining 6 days of the 1st week. For group 1, maximum dose remained 18 mg, and MPH and placebo arms lasted 1 week. For group 2, a further 1 week of OROS-MPH at a dose of 36 mg was given in the morning for 1 week; this group was also administered placebo for 2 weeks. For group 3, maximum dose was 54 mg in the morning, and each arm of the cross-over lasted 3 weeks Mean MPH dosage: 11 participants < 1 mg/kg/d, 13 participants 1-1.5 mg/kg/d, 9 participants 1.5-2 mg/kg/d Administration schedule: 1 dose in the morning Duration of each medication condition: 1 week Washout before trial initiation: participants were not allowed to have taken ADHD medication within 2 weeks before the telephone interview screening Medication-free period between interventions: yes; 1 week Titration period: no Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV, Observer, Parent, Teacher Version; CGI-ADHD-Severity: clinician-rated at baseline and at end of each cross-over week **Serious AEs** • Seizure Classification Interview: observer, baseline and during trial **Non-serious AEs** • Barkley Side Effects Checklist - Modified: observer, each trial visit
Notes	Sample calculation: no Ethics approval: not stated **Comment from trial authors** • "Considering exposure time, we observed increased daily risk of seizures with increasing dose of OROS methylphenidate, suggesting that potential safety concerns require further trial" **Key conclusions of trial authors** • No serious AEs and no carry-over effects were noted in the cross-over trial • A larger trial is needed to assess the effect of OROS-MPH on seizure risk • Cross-over design, including participants with frequent seizures, could maximise power and address high participant heterogeneity and recruitment difficulties Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes

Gonzalez-Heydrich 2010 *(Continued)*

Any withdrawals due to AEs: no

Funding source: supported by NIMH grant, Number K23 MH066835

Email correspondence with trial authors: April 2014. We obtained supplemental efficacy data from trial authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation lists for each maximum-dose group were prepared by a statistician and maintained by the research pharmacist
Allocation concealment (selection bias)	Low risk	Randomisation lists for each maximum-dose group were prepared by a statistician and maintained by the research pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were randomly assigned to take OROS-MPH or placebo. Principal investigator was blind to medication status. In cases of seizure worsening... Data and Safety Monitoring Board (DSMB) and Institutional Review Board (IRB) were informed of these seizures. trial personnel, the DSMB and the IRB were not unblinded through this process, as the participant would not be exposed again to the same condition
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Principal investigator was blinded to medication status
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 participants discontinued treatment while taking placebo and 14 while taking OROS-MPH; however, all were included in all analyses Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	All outcomes reported referred to parent- and teacher-rated versions of ADHD-RS-IV, and to clinician-rated ADHD Severity measured weeks 1 to 4 in the protocol. Barkley Total scores (although significantly different) were not reported, although individual effects were reported

Gorman 2006

Study characteristics

Methods	Participants with ADHD took part in a randomly ordered, double-blind, cross-over clinical drug trial comprising 21 consecutive days of: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 43 Number of participants followed up: 41 (21 boys, 20 girls) Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV (combined (n = 22), hyperactive-impulsive (n = 0), inattentive (n = 19))

Gorman 2006 *(Continued)*

	Age: mean 9.08 years (range 6.26-12.55) IQ: mean 107.66 MPH-naive: 37 (out of 41, 90%) Ethnicity: white (92.67%) Country: USA Setting: outpatient clinic Comorbidity: > 2 anxiety disorders (12.16%), lifetime affective disorder (2.46%), ODD or CD (49.28%) Comedication: 0% Other sociodemographics: mean 50.43 (range 22-66) (Hollingsworth socioeconomic status) **Inclusion criteria** • 6-12 years of age • Diagnosis of ADHD according to DSM-IV, and based on a combination of the Parent Interview for Child Symptoms-4 and a semi structured interview • IQ > 80 • Normal or corrected vision and hearing • No current use of medicine **Exclusion criteria** • Physical disabilities; history of neurological disorder, chronic medical illness, bipolar disorder, schizophrenia or pervasive developmental disorder; and an episode of major depressive disorder within at least 6 months
Interventions	Participants were randomly assigned to 1 dose of MPH and placebo Mean MPH dosage: final daily dose 33.12 mg ± 1.36 (SE), range 25-50 mg/d (0.94 ± 0.02 mg/kg) Administration schedule: twice/d Duration of each medication condition: 21 days Washout before trial initiation: not stated Medication-free period between interventions: from lunch to the following morning Titration period: 0.25 mg/kg twice/d (breakfast and lunch) on days 1-2; 0.25 mg/kg twice/d, plus 0.125 mg/kg at 4:00 pm on days 3-7; 0.3 mg/kg twice/d and 0.15 mg/kg at 4:00 pm on days 8 to 14; and 0.4 mg/kg twice/d, and 0.2 mg/kg at 4:00 pm on days 15-21. All dosages were administered to the nearest 2.5 mg Titration: took place after randomisation Treatment compliance: not stated. 4 participants with ADHD had undergone previous trials of stimulant therapy ranging from 2 weeks to 7 months
Outcomes	**ADHD symptoms** • IOWA CTRS and IOWA CPRS: at the end of each treatment period (around day 21) **Serious AEs** • 5 participants with 'serious side effects' were referred to, but no further information was given **Non-serious AEs**

Gorman 2006 *(Continued)*

- Barkley and Murphy Side Effects Rating Scale, rated by an investigator, at the end of each treatment
- Weight, in street clothes and without shoes on a professional scale, at the end of each treatment period

Notes

Sample calculation: not described

Ethics approval: yes

Comment from trial authors

- "The unusually high proportion of girls reflects increasing sensitivity by clinicians to the identification of girls with ADHD as well as the awareness of our referring sources that we were trialling sex differences in ADHD"

Key conclusions of trial authors

1. ADHD subtypes benefited comparably from MPH treatment with respect to inattention
2. Children with ADHD-combined subtype underwent greater reductions in hyperactivity/impulsivity, but children with ADHD-inattentive subtype also benefited in this respect
3. Only children with ADHD DSM-IV combined displayed a reduction in externalising problems under MPH. ADHD subtypes reacted comparably with stimulant treatment with respect to arithmetic performance, valence of teacher and parent comments and task-incompatible behaviours - all measures that do not distinguish between inattention, hyperactivity/impulsivity or oppositionality
4. Somatic effects of treatment were comparable for subtypes

Comment from review authors

- Chang et al. 2001 (in Gorman 2006) is a PhD thesis; the other 2 articles are based on data from this. We have not had access to the full thesis

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: not stated

Funding source: NIMH

Email correspondence with trial authors: January 2014. We obtained supplemental information from trial authors. Trial authors do not have the files anymore; therefore we are not able to obtain all of the data requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Answer from trial author: "Table of random numbers were used to make the allocation process, such that numbers ending in an even digit corresponded to one order and those ending in an odd digit to another" (Krogh 2014c [pers comm]
Allocation concealment (selection bias)	Low risk	Answer from trial author: "Table of random numbers were used to make the allocation process, such that numbers ending in an even digit corresponded to one order and those ending in an odd digit to another" (Krogh 2014c [pers comm]
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo capsules, identical in appearance and taste to those containing MPH, and administered on the same schedule
Blinding of outcome assessment (detection bias)	Low risk	Second author blinded. Placebo capsules, identical in appearance and taste to those containing MPH, and administered on the same schedule

Gorman 2006 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	When parents reported serious side effects (n = 5), their children's dosages were reduced, or planned increments were omitted. However, trial authors noted "eliminating participants who could not tolerate their assigned dosage might potentially skew the sample" Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	Answer from trial author: "Event related potentials and performance measures on a cognitive task were not reported (I didn't attempt to publish the ERP data because the analyses I conducted did not yield significant results) - And since we do not look at this outcome, we see it as low" (Krogh 2014c [pers comm])

Green 2011

Study characteristics	
Methods	1-day, randomised, parallel trial with 2 arms: • IR-MPH • placebo 6-month follow-up of trial participants continuing MPH treatment
Participants	Number of participants screened: not stated Number of participants included: 34 (20 boys, 14 girls) Number of participants followed up: 34 Number of patients continuing MPH treatment beyond the 1-day trial: 16 Number of participants followed up: 15 Number of withdrawals from extension trial: 1 **Patients participating in the 1-day trial** Diagnosis of ADHD: DSM-IV-TR (combined (33.3%), hyperactive-impulsive (not stated), inattentive (50%), not otherwise specified (17.7%)) Age: mean 11.1 years (range 5-20) IQ: mean: 81.4 MPH-naive: 61.8% Ethnicity: not stated Country: Israel Setting: hospital/outpatient clinic Comorbidity in total sample: velocardiofacial syndrome (100%), ODD (23.5%), specific phobia (26.5%), generalised anxiety disorder (11.8%), social phobia(11.8%), dysthymic disorder (8.8%) and separation anxiety (5.9%) Comorbidity in MPH group: congenital anomalies of the heart and great vessels (54.5%) Comedication: no other psychotropic medication during the trial

Green 2011 *(Continued)*

	Other sociodemographics: none. The 2 groups had similar baseline demographics **Inclusion criteria** • Not stated **Exclusion criteria** • Not stated
Interventions	RCT: participants were randomly assigned to MPH or placebo Number randomised to each group: MPH 22, placebo 12 Mean MPH dosage: 15.7 ± 5.6 mg (0.5 mg/kg) Administration schedule: once Duration of intervention: 1 day Titration period: no mention, none Washout before trial initiation: 3 days Treatment compliance: not stated Follow-up: some participants continued MPH treatment beyond the RCT Mean MPH dosage: not stated Administration schedule: not stated Duration of treatment: 6 months Treatment compliance: 1 withdrew because of poor compliance
Outcomes	**Non-serious AEs** • Cardiologic evaluation (ECG, heart rate and BP): immediately before taking the pill (MPH or placebo), and again after 90 min • Barkley Side Effects Rating Scale (modified Hebrew Version), parent-rated: 24 h after MPH administration and at 6-month follow-up
Notes	Sample calculation: not stated Ethics approval: trial protocol was approved by the Institutional Review Board of the Rabin Medical Center **Comments from trial authors** • "We found that all participants (100%) with velocardiofacial syndrome treated with MPH exhibited ≥ 1 side effect" • "Rate of all side effects immediately observed following initiation of treatment remained similarly high after 6 months of treatment" • "According to our findings, it seems that children with velocardiofacial syndrome did not develop tolerance to MPH side effects" • None of the children withdrew because of side effects • Limitations: short duration of parallel-group trial and relatively small sample size **Key conclusions of trial authors** • Use of MPH in children with velocardiofacial syndrome appears to be effective and relatively safe • Comprehensive cardiovascular evaluation for children with velocardiofacial syndrome before and during stimulant treatment is recommended

Green 2011 *(Continued)*

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: The Basil O'Connor Starter Scholar Research Award of the March of Dimes, NARSAD (National Alliance for Research in Schizophrenia and Affective Disorders) Young Investigator Award, the Marguerite Stolz Award from the Sackler Faculty of Medicine and the National Institute on Drug Abuse (NIDA)

Email correspondence with trial authors: November 2013. We obtained supplemental information regarding ADHD diagnostic criteria from trial authors. Furthermore, we received safety data from the trial sample, excluding participants > 18 years or with IQ < 70 (or both), but we decided not to use these data in our analyses, as data were missing for 60% of the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomly assigned to drug or placebo in a 2:1 ratio, according to their order of recruitment
Allocation concealment (selection bias)	High risk	Participants were randomly assigned to drug or placebo in a 2:1 ratio, according to their order of recruitment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and their parents were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting. Trial authors have confirmed that planned outcomes for the 1-day RCT were measured and reported

Greenhill 2002

Study characteristics

Methods	3-week, randomised, double-blind, 32-site, parallel trial with 2 arms: • MR-MPH • placebo
Participants	Number of participants screened: 507 Number of participants included: 321 (257 boys, 57 girls) Number of participants followed up: MPH 141, placebo 135 Number of withdrawals: MPH 17, placebo 28

Greenhill 2002 *(Continued)*

Diagnosis of ADHD: DSM-IV (combined subtype or predominantly hyperactive-impulsive subtype)

Age: mean 9 years (range 6-15)

IQ: > 80

ADHD treatment-naive: 36%

Ethnicity: white (71%), African American (15%), Hispanic (10%), other (4%)

Country: USA

Setting: outpatient clinic

Comorbidity: none

Comedication: concomitant use of clonidine, anticonvulsant drugs and medications known to affect BP and heart rate was not allowed

Other sociodemographics: no significant differences in baseline demographics were noted between the 2 groups

Inclusion criteria

- 6-16 years of age
- Primary diagnosis of ADHD, combined subtype or predominantly hyperactive-impulsive subtype, as defined in DSM-IV
- Did not respond to placebo with a reduction of ADHD symptoms during washout period
- First-grade or higher school setting in which a single teacher could assess behaviour
- BP, heart rate and oral temperature had to be within normal range

Exclusion criteria

- Comorbid psychiatric diagnosis
- History of seizure or tic disorder
- Family history of Tourette's syndrome
- IQ < 80
- Inability to follow or understand trial instructions
- Female patient who had undergone menarche
- Use of amphetamines, pemoline or an investigational drug within 30 days of trial entry
- Concomitant use of clonidine, anticonvulsant drugs or medications known to affect BP, heart rate or CNS function
- Hyperthyroidism or glaucoma
- Concurrent chronic or acute illness (e.g. allergic rhinitis, severe cold) or disability that could confound trial results
- Failed a previous trial of stimulants for ADHD
- Requiring a third daily dose in the afternoon or evening
- Documented allergy or intolerance to MPH
- Living with anyone who currently had substance abuse disorder (excluding dependency)

Interventions	Participants were randomly assigned to MR-MPH or placebo Number randomised to each group: MPH 158, placebo 163 Mean MPH dosage: 40.7 mg/d (1.28 mg/kg/d) Administration schedule: once daily Duration of intervention: 3 weeks Titration period: none

Greenhill 2002 *(Continued)*

	Treatment compliance: medication counts showed satisfactory adherence in both groups
Outcomes	**General behaviour** • CGI - teacher version: rated twice daily (morning and afternoon), 3 times a week • CGI - parent version, 1 day of each weekend during the morning, afternoon and evening **Non-serious AEs** • Pittsburgh (11-item) Side Effects Questionnaire: parent- and teacher-rated weekly • Teachers completed a similar side effect questionnaire
Notes	Sample calculation: no Ethics approval: yes; probably approved by an institutional review board **Comments from trial authors** • "Because no dose-response curves were collected on children in the trial, we could not determine whether effects of modified-release methylphenidate were dose-related." • Trial inclusion and exclusion criteria were selected for milder cases of ADHD • Lower scores in this trial mean that findings may not be generalisable • 3-week duration of the trial did not allow investigators to determine whether dual-phase effects of MR-MPH persist with long-term treatment • Trial design limited generalisability of the results because it excluded acute placebo responders and those who had failed to respond to any MPH treatment before the start of the trial • Parents were aware that researchers had the option of stepping up the "dose" of placebo each week **Key conclusion of trial authors** • MR-MPH administered once daily in the morning was well tolerated and was significantly more effective in a double-blind comparison with placebo in controlling ADHD symptoms throughout the school day Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; participants with a documented allergy or intolerance to MPH were excluded Any withdrawals due to AEs: yes, 2 Funding source: Celltech Pharmaceuticals Incorporated Email correspondence with trial authors: November and December 2013: not possible to get supplemental information regarding the trial through personal email correspondence with trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "randomised". Stratification based on previous treatment before randomisation ensured equal distribution across the 2 treatment groups
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical appearing MR-MPH and placebo capsules were packaged in blister cards
Blinding of outcome assessment (detection bias)	Unclear risk	Stated "double-blinded"

Greenhill 2002 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	316 were included in the safety population, and 314 in the ITT efficacy population. All statistical summaries and analyses were conducted for the ITT population using the LOCF approach for children who withdrew prematurely Selection bias (e.g. titration after randomisation → exclusion): yes; exclusion of placebo responders
Selective reporting (reporting bias)	Unclear risk	No protocol available

Greenhill 2006

Study characteristics	
Methods	7-week multi-centre, randomised, double-blind, placebo-controlled, parallel trial with 2 arms: • ER-d-MPH • placebo To compare the efficacy and safety of ER-d-MPH vs placebo in paediatric patients with ADHD Pre-randomisation phase of up to 2 weeks followed by double-blind treatment phase for 7 weeks (5 weeks of dose titration followed by 1 week of optimal constant dose)
Participants	Number of participants screened: not stated Number of participants included: 103 (66 boys, 37 girls) Number of participants followed up: MPH 48, placebo 37 (ITT analyses: MPH 52, placebo 45) Number of withdrawals: MPH 5, placebo 13 Diagnosis of ADHD: DSM-IV (combined (83%), hyperactive-impulsive (1.9%), inattentive (15.1%)) Age: mean MPH 9.6 years, placebo 10.4 years (range 6-17) IQ: > 70 (age-appropriate functioning levels academically) MPH-naive: 40 Ethnicity: white (60%), African American (23.3%), other (16.5%) Country: USA Setting: classroom setting Comorbidity: no psychiatric comorbidity Comedication: not stated Other sociodemographics: no significant difference in baseline demographics was noted between the 2 groups. See Tables 1 and 2 **Inclusion criteria** • ADHD diagnosis as per DSM-IV • Baseline age of 6-17 years • Conners' ADHD/DSM-IV Scales - Teacher, for boys 6-8 years ≥ 27, 9-11 years ≥ 24, 12-14 years ≥ 19, 15-17 years ≥ 14

Greenhill 2006 *(Continued)*

- Conners' ADHD/DSM-IV Scales - Teacher, for girls 6-8 years ≥ 16, 9-11 years ≥ 13, 12-14 years ≥ 12; 15-17 years ≥ 6
- Age-appropriate functioning levels academically
- Negative pregnancy test and adequate contraception

Exclusion criteria

- Clinically significant abnormalities in vital signs, physical examination findings or laboratory test results
- History of seizures or use of anticonvulsant medication
- Comorbid psychiatric conditions (obtained by clinical interview)
- Any medical condition that could interfere with trial participation or assessments, or that may pose danger with administration of MPH
- Psychotropic medications
- Initiation of psychotherapy within the past 3 months
- Positive urine drug screen
- History of poor response or intolerance to MPH
- Pregnant or nursing
- Any other investigational drug within 30 d of trial entry

Interventions	Participants were randomly assigned to an ER formulation of d-MPH or placebo. Permitted doses were 5 mg/d for the 1st week; 5 or 10 mg/d for the 2nd week; 5 mg/d, 10 mg/d or 15 mg/d for the 3rd week; 5 mg/d, 10 mg/d, 15 mg/d or 20 mg/d for the 4th week; and 5 mg/d, 10 mg/d, 15 mg/d, 20 mg/d or 30 mg/d for the 5th through 7th weeks Number randomised to each group: MPH 53, placebo 50 Mean final MPH dosage: 24.0 ± 7.1 mg/d Administration schedule: once daily in the mornings Duration of intervention: 5-week titration period plus 2 weeks at a constant dose Titration period: initiated after randomisation Treatment compliance: at each trial visit, compliance was assessed by investigator and trial staff on the basis of pill count and participant report
Outcomes	**ADHD symptoms** • Conners' ADHD/DSM-IV Scales - Teacher: rated weekly by teachers • Conners' ADHD/DSM-IV Scales - Parent: rated weekly by parents Serious AEs • Spontaneous reporting recorded weekly: no deaths or serious AEs **Quality of life** • Child Health Questionnaire, Parent Form 50: parent-rated at final visit **Non-serious AEs** • Vital signs were rated weekly • Spontaneously reported AEs were recorded weekly
Notes	Sample calculation: assumptions for sample size and power included treatment difference of 9.0 and SD of 13.5 Ethics approval: no information provided **Comments from trial authors**

Greenhill 2006 *(Continued)*

- "It is of interest that no participant who received extended-release dexmethylphenidate discontinued the trial because of an AE. This may result in part from the fact that more than one-third of participants in each treatment group had prior experience with ADHD medications (mainly methylphenidate and dexmethylphenidate) and in part from the flexible-dose design of the trial"
- "Another possible limitation is that patients with previous methylphenidate or dexmethylphenidate experience were enrolled only if they had not experienced moderate to severe adverse reactions. By excluding patients who could not tolerate methylphenidate or dexmethylphenidate, investigators may have inflated the apparent safety and tolerability of extended-release dexmethylphenidate. However, only about one-fourth of the participants in each treatment group had prior experience with methylphenidate or dexmethylphenidate, so this factor probably had little impact on AE rates during the trial"

Key conclusions of trial authors

- "In conclusion, results of this trial indicate that extended-release dexmethylphenidate administered once daily in doses of 5 mg to 30 mg is safe and effective for treatment of paediatric patients with ADHD symptoms, as reflected by its significant superiority over placebo on Conners' ADHD/DSM-IV Scales - Teacher, Conners' ADHD/DSM-IV Scales - Parent, CGI - Improvement Scale and CGI - Severity Scale, and in the Child Health Questionnaire Psychosocial Component score."
- "Extended-release dexmethylphenidate was well tolerated and had a safety profile consistent with those of other methylphenidate or dexmethylphenidate formulations, resulting in appetite reduction and reduced weight in some patients."

Comments from review authors

- Statistically significant treatment by centre interaction in primary efficacy analysis
- Trial authors defined baseline scores on Conners' ADHD/DSM-IV Scales - Teacher (to be included) as different scores for different age groups, but they informed efficacy as the difference from baseline to endpoint in all medicated individuals
- As precise information on dose (mg/kg/d) was lacking, it is difficult to evaluate whether 24 mg/d was enough for participants in this age range (6-17 years)

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; participants with history of poor response or intolerance to MPH were excluded

Withdrawals due to AEs: MPH 0, placebo 1

Funding source: Novartis

Email correspondence: July 2014. Wrote to Novartis to request additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further description provided
Allocation concealment (selection bias)	Unclear risk	No description provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, no further description provided
Blinding of outcome assessment (detection bias)	Unclear risk	Double-blind, no further description provided

Greenhill 2006 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Trial used an ITT analysis. LOCF analysis was used to impute missing values for all final visit analyses Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	Trial authors defined baseline scores on Conners' ADHD/DSM-IV Scales - teacher-rated, as inclusion criteria (different scores for age groups), but they informed efficacy as the difference from baseline to endpoint for all medicated individuals

Gruber 2007

Study characteristics	
Methods	14-day, double-blind, placebo-controlled, cross-over trial with 2 interventions: • placebo • MPH
Participants	Number of participants screened: not stated Number of participants included: 37 (31 boys, 6 girls) Number of participants followed up: 37 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (70%), hyperactive-impulsive (11%), inattentive (19%)) Age: mean 9.2 years (range 6-12) IQ: mean 96.7 MPH-naive: not stated Ethnicity: white (94%), other (6%) Country: Canada Setting: outpatient clinic Comorbidity: ODD (30%), CD (46%), major depressive disorder (5%), general anxiety disorder (3%) Comedication: no Other sociodemographics: none **Inclusion criteria** • ADHD according to DSM-IV • Patient at the Disruptive Behavior Disorders Program and in the outpatient department of Douglas Mental Health University Institute in Montreal • Between 6 and 12 years of age **Exclusion criteria** • Score < 80 on the WISC-III • Diagnosis of psychosis

Gruber 2007 *(Continued)*

- Diagnosis of Tourette's syndrome
- Pervasive developmental disorder
- Taking any medication other than MPH
- Previous intolerance/allergic reaction to any psychostimulant

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Mean MPH dosage: 0.5 mg/kg/d Administration schedule: twice daily, morning and noon Duration of each medication condition: 7 days Washout before trial initiation: no Medication-free period between interventions: no Titration period: none Treatment compliance: not stated
Outcomes	**General behaviour** • CBCL, daily **Non-serious AEs** • Sleep assessment using miniature Antigraphs, measured daily
Notes	Ethics approval: trial was approved by the Research Ethics Board of Douglas Mental Health University Institute **Key conclusion of trial authors** • "Findings of the present trial support the hypothesis that sleep moderates performance on the Continuous Performance Test in children with ADHD receiving placebo or MPH" **Comment from review authors** • Unfortunately, the data are not useable because of how the trial is set up Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes (see exclusion criteria) Any withdrawals due to AEs: no Funding source: this was not an industry-supported trial Email correspondence with trial authors: February and March 2014. Emailed trial author twice but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Order of administration (MPH or placebo) was determined by random assignment
Allocation concealment (selection bias)	Unclear risk	No information

Gruber 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"MPH and placebo were prepared in identical coloured gelatin capsules by the hospital's clinical pharmacist, who was not involved in the study in any other way. Capsules were sealed in individual, daily-dose envelopes to help control accurate administration"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Hale 2011

Study characteristics	
Methods	Cross-over trial with 2 interventions: • MPH • placebo Phases: baseline, placebo, LD-MPH and HD-MPH for 4 weeks per medication phase
Participants	Number of participants screened: 65 Number of participants included: 56 (39 boys, 17 girls) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV-TR (combined (58.9%), hyperactive-impulsive (7.1%), inattentive (33.9%)) Age: mean 120.84 months (approximately 10.1 years) (SD 30.85 months, range 6-16 years) IQ: mean 99.56 (SD 6.84, n = 41) MPH-naive: number not stated ("All participants were either medication-naive or received an appropriate wash-out period") Ethnicity: European American (82%), African American (18%) Country: USA Setting: outpatient clinic Comorbidity: specific learning disability (n = 13), ODD/CD (n = 11), anxiety/depression (n = 6) Comedication: not stated Other sociodemographics: middle class (n = 44), lower class (n = 12); urban (n = 36), suburban (n = 13), rural (n = 7) **Inclusion criteria**

Hale 2011 *(Continued)*

- Diagnosis based on DSM-IV-TR criteria by referring physician - independent confirmation by licensed and/or certified psychologist
- Demonstrated significant attention, hyperactivity and/or impulse control problems interfering with major life function in both home and school settings
- ≥ 1.5 SD above the mean on ≥ 1 of the attention problems on the CBCL, Teacher Report Form; Inattention and/or Hyperactive-Impulsive subscales of the CPRS - Revised and Long; or CTRS - Revised

Exclusion criteria

- ≥ 1 comorbid secondary diagnosis
- History of mental disability
- Seizure disorder - brain injury
- Other medical condition affecting cognitive or neuropsychological performance - missing or different instruments for measuring MPH response (i.e. missing data)

Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of MPH (0.15 mg/kg, 0.30 mg/kg) and placebo Mean MPH dosage: not stated Administration schedule: twice daily Duration of each medication condition: 4 weeks Washout before trial initiation: 2 days Medication-free period between interventions: no Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CTRS - Revised and Long: teacher-rated at baseline and at treatment follow-up **General behaviour** • Schools Situation Questionnaire - Revised: teacher-rated at baseline and at treatment follow-up **Non-serious AEs** • Side Effects Rating Scale, unclear who rated: at baseline and at treatment follow-up
Notes	Sample calculation: no Ethics approval: not stated **Comment from trial authors** • Several trial limitations are worth noting. First. age limitations. Second, neuropsychological tests that were not counterbalanced and analysed for order effects. Third, inter-rater reliability during MPH trials. 4th, intelligence/cognitive screening **Key conclusion of trial authors** • "Robust cognitive and behavioural MPH response was achieved for children with significant baseline executive working memory/self regulation (EWM/SR) impairment, yet response was poor for those with adequate EWM/SR baseline performance. Even for strong MPH responders, the best dose for neuropsychological functioning was typically lower than the best dose for behaviour. Findings offer 1 possible explanation for why long-term academic MPH treatment gains in ADHD have not been realised" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Hale 2011 *(Continued)*

	Any withdrawals due to AEs: not stated Funding source: research part funded by the Neuropsychiatric Research Institute, Fargo, North Dakota, USA Email correspondence with trial authors: June-August 2014. Emailed trial authors twice to request additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All medications and placebos were prepared by the trial pharmacist, who randomly assigned children to 1 of 6 trial orders in placebo (P), low-dose (L) and high-dose (H) conditions (P-L-H, P-H-L, L-P-H, L-H-P, H-L-P, H-P-L)
Allocation concealment (selection bias)	Low risk	Research assistants, teacher, parents and participants were blinded to the order of conditions. Ground MPH tablet was placed in lactose-filled opaque capsules for active drug conditions, with lactose included only for the placebo condition, and was administered twice per day
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Research assistants, teacher, parents and participants were blinded to the order of conditions. All medications and placebos were prepared by the trial pharmacist. Ground MPH tablet was placed in lactose-filled opaque capsules for the active drug condition, with lactose included only for the placebo condition
Blinding of outcome assessment (detection bias) All outcomes	Low risk	After results were analysed, the order of conditions was revealed
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants for whom data were missing or different instruments were used for MPH response were excluded Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Hawk 2018

Study characteristics

Methods	A 3-day cross-over-trial with 3 arms • 1 day LD-MPH • 1 day HD-MPH • 1 day of placebo Phases: 2 (1 day baseline day, then cross-over-trial)
Participants	Number of participants screened: not stated Number of participants included: 84 Number of participants followed-up: 82 (74% boys, 26% girls). Trial authors provided data for 80 participants

Hawk 2018 *(Continued)*

	Number of withdrawals: 2 (AE: moderate motor ticks at the 0.3 mg/kg dose, which led to exclusion) Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 10.8 years (SD 1.1, range 9-12) IQ: 103 (SD 14) MPH-naive: 21% Ethnicity: white (81%), black (12%) other (7%) Country: USA Setting: outpatient clinic Comorbidity: ODD (44%), CD (27%) Comedication: no psychotropic medication Additional sociodemographics: none **Inclusion criteria** • DSM-IV diagnosis of ADHD • 9-12 years of age **Exclusion criteria** • Full-scale IQ < 80 • History of seizures, neurological disorders and other medical problems • Contraindicating psychostimulant treatment • Current use of non-ADHD psychotropic medications • History or concurrent diagnosis of pervasive developmental disorder or psychosis, and sensory problems that would make it difficult to complete the task
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders different orders of LA-MPH in 2 different doses (OROS-MPH; Concerta) and placebo, receiving each drug for a single day. • 1 (LD) provided equivalent effects to 3 times/d IR-MPH at 0.3 mg/kg dose, producing a total daily dose of 0.9 mg/kg • The other (HD) was equivalent to 3 times/d IR-MPH 0.6 mg/kg dose, producing a total daily dose of 1.8 mg/kg Number randomised to each group: dosing order was counterbalanced among participants Mean medication dosage: doses ranged from 27-90 mg (dose was capped at 90 mg for safety reasons). Mean low and high doses were 1.06 mg/kg (SD 0.12) and 2.02 mg/kg (SD 0.23), respectively Administration schedule: once daily, morning, 90 min before trial Duration of each medication: 1 day Washout before trial initiation: 24 h Medication-free period between interventions: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Teacher ratings of Inattention/Overactivity on the Modified-IOWA Scale. No information on timing of outcome assessment for this outcome available

Hawk 2018 *(Continued)*

Serious AEs

- None reported

Non-serious AEs

- Daily assessments of BP and heart rate

Notes

Sample calculation: no

Ethics approval: yes; all procedures were approved by the University at Buffalo Children and Youth Institutional Review Board

Comments from trial authors

- "The majority of children had a history of well-tolerated treatment with stimulant medication, and the trial was not adequately powered to evaluate the possible moderating role of treatment history."
- "Data were collected in a summer research camp with clinical outcomes focusing on an analogue classroom. This permitted strong experimental control but does not reflect the environments in which children's behaviour is most problematic."
- "We examined a narrow range of clinical outcomes, which limits generalisability."
- "It is critical to determine whether our findings for acute intervention (one day per treatment condition) generalise to more ecologically valid treatment durations, as well as varying combinations of medication and behavioral intervention."

Key conclusion of trial authors

- "Building upon decades of largely independent literatures demonstrating the clinical and cognitive effects of stimulants among children with ADHD, the present work provides the first evidence that stimulant effects on specific cognitive processes (namely working memory and inhibitory control) actually account for, or partially mediate, individual differences in clinical response to stimulants."

Comments from review authors

- The 24 stimulant-naïve children, as well as an unnumbered amount of children who usually took a low dose of MPH were always allocated to receive 1 day LD-MPH before HD.
- While trial authors were able to supply us with additional information regarding risk of bias and teacher rated ADHD symptom data, side-effects data were unfortunately not available.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no

Any withdrawals due to AEs: yes, 2

Funding source: supported by grants from the NIMH and from the National Institute on Drug Abuse (NIDA)

Email correspondence with trial authors: August and October 2021. Trial authors supplied us with information regarding risk of bias and teacher ratings of inattention on the modified IOWA scale through personal email in August and October 2021 (Storm 2021c [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Nothing stated
Allocation concealment (selection bias)	Low risk	Meds were dispensed by a pharmacist who was otherwise uninvolved with trial procedures

Hawk 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medication and placebo were administered in identical opaque capsules by trial staff upon arrival to camp
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Ratings were made blind to treatment condition and were aggregated across classes within condition
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were reported for the 80 participants who were not withdrawn due to AEs. Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, the high medication dose was withheld from 2 participants who experienced AE's at the low dose. These 2 participants were excluded from the analysis.
Selective reporting (reporting bias)	High risk	No trial protocol available While the Pittsburgh Side Effect Rating Scale, which inquires about common side effects seen with stimulants (rated none to severe) was used during the trial, no side effect data are available.

Heriot 2008

Study characteristics	
Methods	3-month, parallel trial with 4 arms • MPH and parent training programme • MPH and supportive non-training parent group • Placebo and parent training • Placebo and supportive non-training parent group
Participants	Number of participants screened: 93 Number of participants included: 20-26 (13 boys, 3 girls) (6 withdrew, but unclear whether before or after random assignment) Number of participants followed up: MPH + parent training 4, MPH + no training 4, placebo + training 4, placebo + no training 4 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (combined (25%), hyperactive-impulsive (56%), inattentive (19%)) Age: mean 4.78 years (range 3-6) IQ: mean 97 (range 80-123) MPH-naive: 100% Ethnicity: not stated Country: New Zealand Setting: outpatient clinic Comorbidity (type: ODD 5/31%)

Heriot 2008 *(Continued)*

	Comedication: no Other sociodemographics: No significant differences in baseline demographics were noted between the 4 intervention groups. **Inclusion criteria** • Between 3.0-5.9 years of age • Resident with a primary caregiver for ≥ 6 months • Meet diagnostic criteria for ADHD as defined in DSM-IV • Features of ADHD had to be present for ≥ 12 months and to a degree that was considered to be developmentally inappropriate and functionally inappropriate and functionally impairing across settings • Above the 93rd percentile on the Global Index subscale of the CRS **Exclusion criteria** • Currently in hospital • Currently in another treatment trial • Currently receiving treatment • Full scale IQ < 80 • Pervasive developmental disorder or psychosis • Major neurological or medical illness that would interfere with participation or require medications incompatible with MPH • Chronic serious tics or Tourette's disorder • History of child abuse • Inability of parent to understand English
Interventions	Participants were randomly assigned to MPH + parent training, MPH + no parent training, placebo + parent training or placebo + no parent training Number randomised to each group: not stated Mean MPH dosage: 0.3 mg/kg Administration schedule: twice/d - morning and lunchtime Duration of intervention: 3 months Titration period: dosage was built up over the 1st week Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV Parent and Teacher versions: data not reported in an useable form - not possible to obtain data from trial author • CPRS - Revised, Long Version: no data provided in the article • CTRS - Revised, Long Version: no data provided in the article **Non-serious AEs** • Stimulant drug, Barkley Side Effects Rating Scale
Notes	Sample calculation: no Ethics approval: yes; obtained from the University of Waikato, Department of Psychology Ethical Review Committee and the Waikato Ethics Committee for Waikato Hospital **Comments from trial authors** • 7 of the 16 children no longer met DSM-IV (1994) diagnostic criteria for ADHD at the end of the trial

Heriot 2008 *(Continued)*

- Ethnicity did not appear to affect outcomes, although it was unclear whether the content of the programme was equally appropriate for all ethnic groups
- Limitations
  - Small number of participants
  - Of those willing to participate, only 43% met eligibility criteria for the trial
  - No follow-up data

Key conclusion of trial authors

- Children were more likely to improve when treatment involved ≥ 1 active component (medication or parent training). However, variability in individual parental and child participant responses to all treatment conditions was notable, indicating the importance of interaction between treatment variables and other factors. Findings are discussed within the framework of a transactional model, and inferences are drawn about limitations of the idea that a "best treatment" exists that is universally applicable. Although improvement among children receiving treatment with MPH was greater than for others, it is notable that all treatments were associated with improvement in some children.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: unclear

Funding source: no funding to conduct the trial was received from any party

Email correspondence with trial authors: January, February and May 2014. Emailed trial author but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were allocated to conditions sequentially, using RAND function (SPSS) to generate the sequence. Each parent was randomly assigned to attend the training programme group or the support group.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Throughout the period of data collection, participants and therapist were blinded to medication status
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Throughout the period of data collection, participants and therapist were blinded to medication status. All parents and teachers were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Only data for completing participants were reported Selection bias (e.g. titration after randomisation → exclusion): unclear. 4 were excluded after randomisation because of "treatment integrity problems"
Selective reporting (reporting bias)	Unclear risk	We were unable to identify a protocol

Hicks 1985

Study characteristics	
Methods	Double-blind, cross-over trial with 2 interventions: • LD-MPH and HD-MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 44 Number of participants followed up: 44 (36 boys, 8 girls; 20 inpatients, 24 outpatients) Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 8.4 years (SD 1.75, range not reported) IQ: mean 98.31 (SD 12.96) MPH-naive: not stated Ethnicity: white (68.2%), African American (31.8%) Country: not stated Setting: outpatient clinic and patient ward Comorbidity: not stated Comedication: not stated Other sociodemographics: mean 3.59 (SD 1.29) (Hollingshead 2-factor socioeconomic status index) **Inclusion criteria** • Diagnosis of ADHD according to DSM-III **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned to different orders of MPH (LD 0.3 mg/kg, HD 0.6 mg/kg) and placebo Mean MPH dosage: not stated Administration schedule: twice/d, morning and noon Duration of each medication condition: 12 for inpatients, 19 for outpatients Washout before trial initiation: not stated Medication-free period between interventions: 68 h Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS: rated weekly • CTRS: rated weekly

Hicks 1985 *(Continued)*

Non-serious AEs

- Pulse, measured once in each treatment condition, before and 1 h after treatment
- BP, measured once in each treatment condition, before and 1 h after treatment
- Blood samples, measured once in each treatment condition, before and 1 h after treatment, including growth hormone, prolactin, thyroid-stimulating hormone

Notes

Sample calculation: not stated

Ethics approval: yes

Key conclusion of trial authors

- "MPH appears able to engage homeostatic mechanisms which take over and operate to return functioning to a more normal level"

Comment from review authors

- Trial participants are both inpatients and outpatients; therefore the sample group is highly heterogeneous

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: NIH

Email correspondence with trial authors: March 2014. We obtained from trial authors supplemental information regarding funding and ethics. Not able to obtain additional data as they are no longer available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Hoeppner 1997

Study characteristics	
Methods	Double-blind, cross-over trial with 2 interventions: • HD-MPH • LLD-MPH • placebo 4 orders • Placebo, LD-MPH, HD-MPH • HD-MPH, placebo, LD-MPH • Placebo, HD-MPH, LD-MPH • LD-MPH, placebo, HD-MPH
Participants	Number of participants screened: 95 Number of participants included: 50 Number of participants followed up: 50 (39 boys, 11 girls) Number of withdrawals: none Diagnosis of ADHD: DSM-III-R Age: mean 9.6 years (range 6-18.1) IQ: not stated MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Meeting DSM-III-R ADHD, DSM-III ADD or DSM-III-ADD/H criteria • Score ≥ 1½ SD above the norm on the CPRS or the CTRS **Exclusion criteria** • No information
Interventions	Participants were randomly assigned to different possible orders of HD-MPH (0.3 mg/kg), LD-MPH (0.15 mg/kg) and placebo (doses rounded up to the nearest 2.5 mg) Mean MPH dosage: not stated Administration schedule: twice/d, 8:00 am and 12:00 pm Duration of each medication condition: 1 week Washout before trial initiation: "received an appropriate wash-out period" Medication-free period between interventions: from lunchtime until next morning, 20 h

Hoeppner 1997 *(Continued)*

	Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS, CTRS: completed daily
Notes	Sample calculation: no Ethics approval: no information **Comments from trial authors** • Dependent measures in this trial often failed to detect significant dose-response effects when analysed individually, and placebo effect were found for 4 of the 9 measures. Although ratings from the Conners' Parent and Teacher Rating Scales were sensitive to dose-response effects, findings were not uniform across raters and did not correspond with cognitive response • Small sample size **Key conclusion of trial authors** • According to cognitive rank order ratings, linear and quadratic MPH response patterns were identified, with the best dose for each group significantly different from that obtained for all other conditions Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: March 2014. Emailed trial authors to request additional information but have received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Pharmacists randomly assigned participants to 1 of 4 trial sequences
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo consisted of an opaque capsule filled with lactose; active drug consisted of the same lactose-filled capsule, to which MPH was added
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo consisted of an opaque capsule filled with lactose; active drug consisted of the same lactose-filled capsule, to which MPH was added
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of reporting bias

Horn 1991

Study characteristics	
Methods	12-week, double-blind, randomised, parallel trial with 6 arms: • placebo • LD-MPH • HD-MPH • Placebo + behavioural parent training + child self control instruction • LD-MPH + behavioural parent training + child self control instruction • HD-MPH + behavioural parent training + child self control instruction 9-month follow-up
Participants	Number of participants screened: 117 Number of participants included: 107 (83 boys, 24 girls) Number of withdrawals after randomisation: 18 Number followed up: at end of trial (12 weeks) 78, 9 months after termination of trial 71 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 8.27 years (range 7-11) IQ: > 70 MPH-naive: not stated Ethnicity: white (84.9%), African American (9.4%), Hispanic (3.8%), Asian American (1.9%) Country: USA Setting: outpatient clinic Comorbidity: CD (7.5%), disruptive oppositional disorder (15%), ODD (43%) Comedication: not stated Other sociodemographics: mean yearly family income USD 25,019. No significant differences in baseline demographics were noted between treatment groups or between treatment groups and treatment dropouts in any of the following parameters: child's age, grade, sex, IQ; parental marital status, annual family income and maternal education and age. However, a significantly greater number of non-white children were included in the placebo-alone condition than in remaining treatment conditions or among treatments dropouts **Inclusion criteria** • 7-11 years of age • Exact agreement between a licensed clinical psychologist and a board certified paediatrician with respect to diagnosis of ADHD according to DSM-III-R criteria • Score on Hyperkinesis Index of the CPRS or CTRS ≥ 2 SD above published means • Current psychostimulant therapy required to be withdrawn for the course of the trial **Exclusion criteria** • Comorbid anxiety, depressive disorder or both • Gross physical impairments, intellectual deficits or psychosis in child or parents

Horn 1991 *(Continued)*

Interventions	Participants were randomly assigned to 1 of 6 treatment conditions, including placebo, LD-MPH (0.4 mg/kg) and HD-MPH (0.8 mg/kg) No of participants assigned to each group: 16 to each arm Administration schedule: daily Duration of intervention: 12 weeks Washout before trial initiation: 2 weeks before initial diagnostic evaluation Titration period: no Treatment compliance: 87.39% of parents in the non-placebo medication conditions group reported anonymously that their child took the medications almost every day, whereas the remainder of families reported usage an average of 3 to 4 days a week. Stimulant medication was withdrawn immediately after post-test assessments
Outcomes	**ADHD symptoms** All dependent measures were administered at pre-test, post-test (within 1 week or 2 weeks of the end of the treatment phase of the trial) and follow-up • CBCL • SNAP • CTRS **AEs** • Medication side effects, monitored by a board certified paediatrician
Notes	Sample calculation: no information Ethics approval: no information Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes, 3 Funding: not declared Email correspondence with trial authors: August 2013. Not possible to receive supplemental information or data through personal email correspondence with trial authors. They do not recommend inclusion of the trial in this review because of problems with the design and methods used at the time the trial was carried out (Ramstad 2013a [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	2 of 12 families were randomly assigned to each of the 6 treatment conditions. This procedure was repeated 8 times, so that by the end of the trial, 16 families were randomly assigned to each of the 6 treatment conditions, for a total of 96 families
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	Low risk	Double-blind

Horn 1991 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Note that assessors were blinded to treatment status at all times
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were conducted on 4 samples: (1) participants completing the entire trial and followed up at 9 months (n = 71), (2) participants completing the entire trial (n = 78), (3) participants completing the entire trial + participants completing ≥ 6 weeks (n = 90) and (4) all of the above + those who dropped out immediately after initiating treatment (n = 96). When no post-test and/or follow-up data were available for dropouts, pre-test values or post-test values, or both, were substituted. Given that analyses produced essentially the same results, only the analyses that include completers are reported Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Huang 2021

Study characteristics	
Methods	A 2-week 2-way cross-over trial with 2 arms: • LA-MPH formulation (ORADUR-MPH) • placebo Phases: 3 (open-label titration period (2–4 weeks), double-blinded and placebo-controlled 2-way cross-over treatment phase (4 weeks), and follow-up phase (2 weeks))
Participants	Number of participants screened: 110 participants entered the open-label period Number of participants included: 103 randomised. Participants were randomly assigned to 1 of 2 possible drug condition orders. Number of participants followed up: 100 (ITT population: 99; 72.2% boys, 28.8% girls) Number of withdrawals: 5; 3 withdrew after randomisation, 2 withdrew after the 1st treatment periods (1 in each group) Diagnosis of ADHD: DSM-5 (of the ITT population 75% were combined type and 25% were inattentive type) Age: mean: LA-MPH, placebo: 9.16 years (SD 2.42); placebo, LA-MPH: 8.96 years (SD 2.39) (range 6-18) IQ: < 80 was an exclusion criterion, no further information MPH-naive: not stated Ethnicity: not stated Country: Taiwan Setting: outpatient Comorbidity: no Comedication: concomitant medication was an exclusion criterion

Huang 2021 *(Continued)*

Additional sociodemographics: parental education level

- Father's education level: senior high or below: LA-MPH, placebo 19 (38%), placebo, LA-MPH 21 (42%). College or above: LA-MPH, placebo 30 (60%), placebo, LA-MPH 28 (56%)
- Mother's education level: senior high or below: LA-MPH, placebo 20 (40%), placebo, LA-MPH 16 (32%). College or above: LA-MPH, placebo 29 (58%), placebo, LA-MPH 31 (62%)

Inclusion criteria

- 6-18 years
- Clinical diagnosis of ADHD according to the DSM-5 criteria within the last year
- Able to swallow the trial-specific capsule (18 mm) without difficulty
- Ability to provide written informed consent by participants and their parents/guardians

Exclusion criteria

- ADHD treatment for > 1 year or ADHD treatment within 30 days before the trial treatment initiation
- Participants that by investigator's evaluation are very anxious, tense or agitated
- Known allergies to any of the LA-MPH ingredients
- Estimated IQ < 80
- Taking a concomitant medication (e.g. MAOI) that is likely to interfere with safe administration of MPH within 14 days prior to the trial treatment initiation
- Joining other clinical studies and receiving any other investigational medical products within 30 days prior to the trial treatment initiation
- Glaucoma (narrow angle glaucoma), ongoing seizure disorder or any systemic disease
- Any disorder involving tics, Tourette's syndrome, or a family history of Tourette's syndrome
- Any psychotic disorders
- Clinically significant gastrointestinal problems, including narrowing of the gastrointestinal tract
- If participants or their caregiver(s) (in the case of participants whose parents/caregivers were to fill out the trial questionnaires) had exhibited drug or alcohol abuse/dependence within the last 6 months
- Psychological, familial, sociological, or geographical condition potentially hampering compliance with the trial protocol and follow-up schedule
- By the investigators' discretion, participants with serious or unstable medical illness that will interfere with the evaluations of trial efficacy and safety
- In the investigators' opinion, participants cannot understand or follow the instructions given in the trial

Interventions	Participants were randomly assigned to 1 of 2 possible orders of 2 weeks of LA-MPH (22 mg/d, 33 mg/d or 44 mg/d depending on optimal dose) and 2 weeks of placebo Number randomised to each group: LA-MPH, placebo 50, placebo, LA-MPH 50 Mean medication dosage: of the 99 who received 2 weeks of LA-MPH: 30.56 mg/d (SD 8.40 mg/d, range 22–44 mg/d) and 0.92 mg/kg/d (SD 0.28 mg/kg/d, range 0.42–1.90 mg/kg/d) Administration schedule: once daily in the morning, 20 min after breakfast Duration (of (each) medication): LA-MPH 2 weeks, placebo 2 weeks Washout before trial initiation: medication within the past 30 days was an exclusion criterion. There was minimum 1 week treatment at optimal dosage before randomisation. No washout period between open-label and blinded trial period Medication-free period between interventions: no washout period between interventions Titration period: 2-4 weeks, where each participant was titrated to their optimal dosage of either 22 mg/d, 33 mg/d or 44 mg/d Participants who were unable to tolerate 22 mg of MPH were withdrawn. After optimisation, each participant had 1 additional week at their optimal dosage Treatment compliance: pill count and parental reporting. No information on adherence

Huang 2021 *(Continued)*

Outcomes	**ADHD symptoms** • Chinese SNAP-IV-Parent • Chinese SNAP-IV-Teacher • K-SADS-E - Chinese • CTRS Revised: Short) - Chinese version **Serious** AEs • Spontaneous reporting **Non-serious AEs** • Open-ended questions during an initial clinical interview at each visit by the investigators • A structured interview by the investigators based on a standard questionnaire that includes all potential adverse effects • BP measure • Heart rate measurement • Body weight assessment • Physical examination findings
Notes	Sample calculation: yes; "By assuming that the mean difference between MPH and the placebo in terms of the SNAP-IV total score at 2 weeks was to be −6.0, the individual standard deviations (SDs) would have been 10.0. Based on such information, the total sample size was estimated using a one-sided significance level of 2.5% and a power of 80%. If an 18% dropout rate is included, then we need to recruit at least 110 subjects to this trial to obtain a target sample size of 90 for evaluation." Ethics approval: yes **Comments from trial authors** • "The small sample size may partially explain the low power to detect group differences" • "[…] [limitations] include the short treatment period, the lack of control regarding the time of day that reports are completed, the exclusion of ADHD patients with comorbidities such as other psychiatric disorders, the fact that the recruited population consisted largely of male subjects, and the lack of either a parallel placebo-controlled trial or a head-to-head comparison with standard psychopharmacotherapic treatment for ADHD." • "[…] MPH gives rise to several easily recognizable AEs, one such being decreased appetite; such well-known adverse effects may lead to a loss of blinding and thus influence rating of symptom, particularly when this is carried out by parents and assessors who have knowledge of reported adverse effects." **Key conclusion of trial authors** • "Our findings indicate that ORADUR-MPH [LA-MPH] is an efficacious, safe, and well-tolerated medication for treating children and adolescents with ADHD and that it does this by reducing their ADHD core symptoms without serious AEs. It provides another treatment option for patients with ADHD." Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes, during an open-label titration phase before randomisation Any withdrawals due to AEs: yes, 1 Funding source: this work is supported by Orient Pharma Co, Ltd. Email correspondence with trial authors: August and October 2021. We contacted the trial authors for information regarding risk of bias and first period data through personal email in August and October 2021, but no answer was received.
Risk of bias	

Huang 2021 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Based on a computer-generated random sequence, the trial participants were randomly assigned into either the LA-MPH or the placebo parts of the trial at a 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Nothing stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded, no mention of method "[…] methylphenidate gives rise to several easily recognizable AEs, one such being decreased appetite; such well-known adverse effects may lead to a loss of blinding and thus influence rating of symptom, particularly when this is carried out by parents and assessors who have knowledge of reported adverse effects."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants withdrew during the double-blind phase (2 of them were included in the ITT sample). Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	Conners' Continuous Performance Test (CPT-II) performance in LA-MPH vs. placebo is mentioned in protocol, but no outcomes are reported

Ialongo 1994

Study characteristics	
Methods	14-week, parallel trial with 3 arms: • placebo • LD-MPH (stimulant therapy) • HD-MPH (stimulant therapy)
Participants	Number of participants screened: not stated Number of participants included: 48 (35 boys, 13 girls). A sample of 21 non-clinical controls (13 boys and 8 girls) was also included in the trial Number of withdrawals: 7 families dropped out from pre-test to post-test: HD-MPH 3, placebo 4 Numper of participants followed up: LD-MPH 16, HD-MPH 13, placebo 12 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 7.97 years (SD 1.4, range 7-11) IQ: ≤ 70 MPH-naive: 98% Ethnicity: white (78.0%), African American (12.2%), Hispanic (9.8%)

Ialongo 1994 *(Continued)*

	Country: USA Setting: outpatient clinic Comorbidity: CD 5, ODD 12 Comedication: no Other sociodemographics: middle-income families. No significant differences between treatment groups or between treatment groups and dropouts in any participant and/or demographic characteristics at pre-test, with the exception of ethnicity. A significantly greater proportion of African American children were included in the placebo condition than in the high-dose condition **Inclusion criteria** • Diagnosis of ADHD according to DSM-III-R • Exact agreement between 2 assessors (paediatrician and psychologist) with respect to ADHD diagnosis • Score on Hyperkinesis Indices of the CPRS and CTRS ≥ 2 SD above published means **Exclusion criteria** • Comorbid anxiety and/or depressive disorder • Gross physical impairment • Intellectual deficits • Psychosis in child or parents • IQ < 70 (measured with the Peabody Picture Vocabulary Test - Revised)
Interventions	Participants were randomly assigned to 3 treatment conditions: medication placebo alone (n = 16), LD-MPH (0.4 mg/kg) stimulant therapy (16) or HD-MPH (0.8 mg/kg) stimulant therapy 16 Duration of intervention: 14 weeks Titration period: no Treatment compliance: 1 check on medication compliance consisted of periodic dispensing of medication over the course of the trial during follow-up visits to staff paediatricians. In addition, a medical compliance questionnaire was completed anonymously by parents 1 month after post-test assessments. 91.9% of parents in the medication conditions indicated that their child took the stimulant medication almost every day throughout the trial, whereas nearly all remaining families reported average usage of 3-4 days a week
Outcomes	**ADHD symptoms** • CPRS • CTRS **General behaviour** • CTRS, Conduct problems
Notes	Sample calculation: no information Ethics approval: no information **Key conclusion of trial authors** • In contrast to placebo, although MPH resulted in significantly greater amelioration of many of the core features of ADHD, we found no evidence of a decrease in perceived competence, or of an increase in external or unknown explanations of control or dysphoria at post-test (i.e. 14 weeks later) Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Ialongo 1994 *(Continued)*

Any withdrawals due to AEs: yes, 7 families dropped out due to intolerable side effects or lack of treatment efficacy

Funding source: not declared

Email correspondence with trial authors: August 2013 and January 2014. We emailed trial authors to request a copy of the protocol and additional information on, for example, the randomisation procedure and funding (Ramstad 2013a [pers comm]).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All medication was dispensed in a double-blinded fashion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All medication was dispensed in a double-blinded fashion
Incomplete outcome data (attrition bias) All outcomes	High risk	No description of imputation method Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Jacobi-Polishook 2009

Study characteristics

Methods	Single-day, randomised, controlled, parallel, double-blind trial with 2 arms investigating postural stability in 24 children with ADHD: • MPH • placebo
Participants	Number of participants screened: 80 Number of participants included: 24 (22 boys, 2 girls) Number of participants followed up: 24 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: MPH mean 10.06 years (range 7-16), placebo mean 10.88 years (range 7-16) MPH-naive: 0%

Jacobi-Polishook 2009 *(Continued)*

	Ethnicity: not stated Country: Israel Setting: outpatient clinic Comorbidity: not stated Comedication: no IQ: > 70 Other sociodemographics: none No significant difference in baseline demographics were noted between the 2 groups **Inclusion criteria** • DSM-IV diagnosis • 7-16 years of age • MPH treatment on a daily basis for the past 3 months • Only MPH responders (improvement in ADHD symptoms after MPH treatment according to parent and teacher reports on the ADHD-RS-IV, and according to paediatric neurologist follow-up) • IQ > 70 • ADHD symptoms had to be severe for ≥ 6 items on the DSM-IV ADHD-RS (ADHD RS-IV), Parent Version **Exclusion criteria** • Neurological, orthopaedic or psychiatric diagnoses according to DSM-IV criteria that can affect motor control and postural stability: cerebral palsy, neuropathic disease, limb fracture or head trauma during the previous year • Use of any medication other than MPH during the trial period
Interventions	Participants were randomly assigned to 5 mg of SA-MPH or 5 mg placebo Number randomised to each group: MPH 12, placebo 12 Mean medication dosage: not stated Administration schedule: 5 mg x 1 (single dose) Duration of intervention: 1 day Washout before trial intervention: 24 h Titration period: none Treatment compliance: 100%
Outcomes	**Serious AEs** • No serious AEs of drug treatment were experienced **Non-serious AEs** • No non-serious AEs of drug treatment were experienced
Notes	Sample calculation: yes Ethics approval: no information **Key conclusions of trial authors**

Jacobi-Polishook 2009 *(Continued)*

- MPH improves postural stability in ADHD, especially when an additional task is performed, probably through enhanced attention abilities, thus contributing to improved balance control during performance of tasks that require attention
- MPH remains to be studied as a potential drug treatment to improve balance control and physical functioning in other clinical populations

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; see 'Inclusion criteria'

Any withdrawals due to AEs: no

Funding source: not declared

Any withdrawals due to AEs: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using a table of random numbers
Allocation concealment (selection bias)	Low risk	Placebo pill was identical in appearance to the MPH pill
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and tester administering the examination were blinded to group assignments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and tester administering the examination were blinded to group assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts in either group Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Outcomes reported according to protocol

Jensen 1999 (MTA)

Study characteristics

Methods

14-month multi-centre, randomised, parallel clinical trial with 4 arms:

- medication management
- behavioural treatment
- combined treatment (medication management + behavioural treatment)
- community care (control group)

Phases: for the 2 groups receiving medication, an initial 28-day titration period was provided. This titration phase was carried out as a randomised, double-blind, placebo-controlled, cross-over trial with daily switching of MPH doses (placebo, low, middle and high). Once delivery of randomly assigned treatments by trial staff stopped at 14 months, the trial became an observational trial in which participants and families were free to choose their own treatment, but in the context of availability and barriers to

Jensen 1999 (MTA) *(Continued)*

	care existing in their communities. The following follow-up assessments took place after completion of the RCT at 10 months' follow-up (24 months after randomisation), 3-year follow-up, 8-year follow-up and 10-year follow-up In our review, we will compare combined behavioural treatment (RCT) according to our protocol and will look at the medication treatment group as a cohort (observational)
Participants	Number of participants screened: 4541 Number of participants included: 579 Number of participants randomly assigned to MPH + behavioural treatment (combined treatment): 145, MPH 144, behavioural treatment 144 Number of participants followed up: combined treatment 142; medication 136; behavioural treatment 141 Number of withdrawals/dropouts: combined treatment 3; medication 8; behavioural treatment 3 **Demographic data for combined treatment, behavioural treatment and medication management** • Diagnosis of ADHD: DSM-IV (combined (100%)) • Age: mean 8.4 years (range 7-9.9) • IQ: mean 100.4 • Sex: 346 boys, 87 girls • MPH-naive: 177 • Ethnicity: white (60.3%), African American (20.6%), Hispanic (8.8%), other (10.4%) • Country: USA and Canada • Setting: outpatient clinic • Comorbidity: anxiety disorder (35.1%), CD (14.1%), ODD (38.8%), affective disorder (3.5%), tic disorder (10.2%), mania/hypomania (3%) • Comedication: not stated • Other sociodemographics: 130 families on welfare. Population ranges widely in socioeconomic status. No significant differences in baseline demographics were noted between the 3 groups **Inclusion criteria** • Boys and girls • 7-9. 9 years of age • Grades 1 through 4 • In residence with the same primary carer(s) for the past 6 months or longer • Meeting DSM-IV criteria for ADHD, combined type **Exclusion criteria** • Child currently in hospital • Child currently in another trial • < 80 on all WISC-III, and on Severe Impairment Battery (SIB) (bipolar disorder, psychosis or personality disorder) • Chronic serious tics or Tourette's syndrome • OCD serious enough to require separate treatment • Neuroleptic medication in previous 6 months • Major neurological or medical illness • History of intolerance to trial medications • Ongoing or previously unreported abuse • Missed one-4th of school days in previous 2 months • Same classroom as child already in trial • Parental stimulant abuse in previous 2 years • Non-English-speaking primary carer

Jensen 1999 (MTA) *(Continued)*

- Another child in same household in trial
- No telephone
- Suicidal or homicidal

Interventions	Participants were randomly assigned to medication management, behavioural treatment or combined treatment Mean MPH dosage during main trial: combined treatment 31.2 mg/d, medication management: 37.8 mg/d Administration schedule: 3 times/d - breakfast, lunch and in the afternoon Duration of intervention: 14 months Titration period: 4 weeks. After randomisation. Participants randomised to receive medication or combined treatment underwent a 4-week, double-blind titration phase. Treatment compliance: monthly pill counts, intermittent saliva measurements to monitor intake of MPH and encouragement for families to make up missed visits. "The study achieved a high degree of adherence to protocol." NB! For participants not attaining an adequate response to MPH during titration, alternate medications were titrated openly in the following order until a satisfactory choice was found: dextroamphetamine, pemoline, imipramine and others, if necessary approved by a cross-site panel. Thus, 256 participants successfully completed titration; of these, 198 of 256 participants were assigned to an individually titrated best dose of MPH, and 26 were titrated to dextroamphetamine. 32 were given no medication because of a robust placebo response
Outcomes	**ADHD symptoms** • SNAP Inattention and Hyperactivity-Impulsivity subscale, both parent and teacher: assessed at baseline and at 3, 9 and 14 months • SNAP Oppositional Defiant Disorder subscale, both parent- and teacher-rated: assessed at baseline and at 3, 9 and 14 months. • Abikoff Classroom Observational System (ADHD and oppositional/aggressive symptoms): blind ratings by blind observers **Serious AEs** • 6 of 11 reported severe side effects could have been due to non-medication factors • 3 deaths were recorded among ADHD participants during 10 years of observation: a suicide at age 14 (participant was taking MPH), a fatal car accident at age 17 (participant was the driver and was taking MPH) and sudden unexplained death at age 17 (participant was found dead in bed; no specific cause of death could be determined; he had been treated previously with MPH and had been off medication for > 1 year when he died) **Non-serious AEs** Participants were provided up to 8 additional sessions when needed to address clinical emergencies or instances of possible trial attrition • Pittsburgh Side Effects Rating Scale: monitored monthly, reviewed by the pharmacotherapist • Internalising symptoms (anxiety and depression): measured with an internalising subscale from parent- and teacher-completed Social Skills Responsive Scale, measured at baseline and at 3, 9 and 14 months • Children's self-ratings on the Multidimensional Anxiety Scale for Children: assessed at baseline and at 3, 9 and 14 months For analysis of stimulant treatment duration in relation to substance use at 8-year follow-up, the primary outcome was the number of substances used in the past 6 months, to ensure that most stimulant treatment received would have preceded substance use. Component variables included the following: "drunk" once or more or drank alcohol ≥ 3-4 times; ≥ 1 cigarettes/d in the past month (time frame exception specific to tobacco); marijuana ≥ 2 times; and any other illicit drug use or prescription medication misuse. Secondary analyses explored each class of substances separately. For analysis of stim-

Jensen 1999 (MTA) *(Continued)*

ulant treatment exposure over time in relation to substance use at 8-year follow-up, the primary outcome variable was substance use disorder in the past year for any substance (excluding tobacco). Secondary analyses explored alcohol and marijuana/other drug use disorders separately

Notes

Sample calculation: yes; power analysis, with 576 participants required

Ethics approval: yes; approved by both local institutional review boards and NIH Office for Protection From Research Risk

Comments from trial authors

- Recruitment, screening and selection procedures aimed to collect a carefully diagnosed sample of impaired children with ADHD and a wide range of comorbid conditions and demographic characteristics representative of patients seen in clinical practice
- The design did not include a no-treatment or placebo group
- More than 3-4ths of participants given behavioural treatment were successfully maintained without medication throughout the trial. Consequently, it should not be concluded that behavioural treatment interventions did not work
- Combined treatment and medication management were clinically and statistically superior to behavioural treatment and community care in reducing children's ADHD symptoms. (...) For other areas of function (oppositional/aggressive behaviours, internalising symptoms, social skills, parent-child relations and academic achievement), few differences among our treatments were noted, and when found, were generally of smaller magnitude
- Significantly lower total daily dose of MPH in the combined treatment arm is noteworthy but was not unforeseen. The importance of this finding is unclear, and a rigorous test of the question would likely require a different design

Key conclusions of trial authors

- For ADHD symptoms, our carefully crafted medication management was superior to behavioural treatment and to routine community care that included medication. Our combined treatment did not yield significantly greater benefits than medication management for core ADHD symptoms but may have provided modest advantages for non-ADHD symptoms and positive functioning outcomes

Comments from review authors

- Trial authors have written > 70 articles describing different outcomes and challenges of the trial. We have included only those found through our comprehensive literature search and others that we found relevant to include upon looking through article reference lists
- We have discussed whether to include this trial, as not all participants randomly assigned to medication (combined treatment and medication management group) received MPH. Those who did not have an adequate response to MPH were given other medication (e.g. dextroamphetamine, pemoline, imipramine) or no medication. Furthermore, some participants in the behavioural group were also medicated during the 14-month randomisation phase. From all other studies in this review, we have included only receivers of pure MPH. Furthermore, lots of participants did not have an ADHD diagnosis at follow-up assessment. At 8-year follow-up, only 30% of remaining participants still had a diagnosis of ADHD. However, we have chosen to use the data from this trial, as it is such a large and well-known trial. All trial analyses will be included in the review as sensitivity analyses
- Regarding Molina 2013 (secondary reference under Jensen 1999 (MTA)) (substance use): we have included/asked for additional data from this trial, even though the medicated group received medication for a mean of only 2071.10 (SD 728.87) days of the 8 years the follow-up took place
- The following articles from the trial have been assessed by only 1 review author: Pelham 2000, Carey 2000, Swanson and Hinshaw 2007, Galanter 2003, Hinshaw 1997, Molina 2013 (secondary references under Jensen 1999 (MTA))

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, see exclusion criteria

Any withdrawals due to AEs: 4 participants were removed during the lead-in (titration period) because of prohibitive side effects: 1 child with buccal movements; another with skin picking; a third with de-

Jensen 1999 (MTA) *(Continued)*

pression, crying, sleep delay and appetite loss; and a 4th who was anorexic, listless and emotionally constricted

Funding source: this trial was supported by several grants from the NIMH, Bethesda, Maryland

Email correspondence with trial authors: January 2014-June 2014. We sent several emails to the MTA group to request additional information. However, we were not able to obtain additional data. We did receive an email from Dr. Hinshaw confirming that the data on ADHD symptoms, parent-rated, were wrong - instead of a mean of 1.85, the correct mean was 0.85 for combined treatment after 14 months. We also received an email from Dr. Swanson in June 2014 stating that he would help with data collection. We wanted to conduct a reanalysis of data excluding those few participants not receiving MPH. Dr. Swanson provided several helpful comments on this and enclosed published articles, but we did not receive additional data, in part because of the time frame of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done centrally by the NIMH Data Center, stratified by site in blocks of 16 (4 to each group). Stratified by 6 sites. Sealed, ordered envelopes were sent to sites for successive entries
Allocation concealment (selection bias)	Low risk	Sealed, ordered envelopes were sent to sites for successive entries. Treatment assignment was concealed until the family confirmed agreement to accept randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment assignment was concealed until the family confirmed agreement to accept randomisation. After agreement on best dose, the blind was broken, and the agreed-on dose (if not placebo) became the participant's initial maintenance dose
Blinding of outcome assessment (detection bias) All outcomes	High risk	After agreement on best dose, the blind was broken, and the agreed-on dose (if not placebo) became the participant's initial maintenance dose. However, for some outcome measures, 3 strategies were devised to enlist blinded raters and objective observations
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analyses. Despite high compliance, we checked whether compliance with assessments (i.e. missing data) could have changed our findings. We completed random-effects regression analyses 2 ways: once with inclusion of all participants, and then including only participants who provided data over multiple time points during the trial. No differences emerged from these 2 sets of analyses. Of 289 participants randomly assigned to medication treatments, 33 (11%) did not finish titration. 17 refused medication and 1 moved away. 4 participants were removed during lead-in because of prohibitive side effects: 1 child with buccal movements; another with skin picking; a 3rd with depression, crying, sleep delay, and appetite loss, and a 4th who was anorexic, listless, and emotionally constricted. Even though they did well in lead-in, 7 additional participants stopped in the middle of titration because they could not follow titration procedures and 4 had excessive missing data and were not included. The remaining 256 participants (88.6%) successfully completed titration. Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, for participants not attaining an adequate response to MPH during titration, alternate medications were titrated openly in the following order until a satisfactory choice was found: dextroamphetamine, pemoline, imipramine and others, if necessary approved by a cross-site panel. Thus, 256 participants successfully completed titration; of these, 198 of 289 participants were assigned to an individually titrated best

Jensen 1999 (MTA) *(Continued)*

		dose of MPH, and 26 were titrated to dextroamphetamine. 32 were given no medication because of a robust placebo response
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Johnston 1988

Study characteristics	
Methods	2-week cross-over trial with 3 interventions: • MPH • placebo • ER-MPH (we do not report on this group here) Phases: to define rebound effects in 21 boys 4-10 years of age, with a DSM-III diagnosis of ADD and treated with MPH some days, and placebo other days
Participants	Number of participants screened: not stated Number of participants included: 21 Number of participants followed up: 21 (21 boys, 0 girls) Number of withdrawals: 0 Diagnosis of ADD: DSM-III-R (subtype not stated) Age: mean 7 years 7 months (range 4-10 years) IQ: mean 101 (range 79-120) MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic (summer treatment programme) Comorbidity: CD (n = 2), ODD (n = 17), learning disability (n = 9) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-III-R diagnosis of ADD **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to different drug condition orders of: 0.3 mg/kg MPH, 0.6 mg/kg MPH, 20 mg ER-MPH, or placebo. Number randomised to each group: 0.3 mg/kg MPH twice daily: 21, 0.6 mg/kg MPH twice daily: 16 of the same 21 participants who received 0.3 mg/kg MPH, 20 mg ER-MPH: 8, placebo, not stated. Within-participant random sequence, condition varied daily

Johnston 1988 *(Continued)*

	Mean MPH dosage: not stated Administration schedule: twice daily, at breakfast and just before lunch Duration of intervention: 2 weeks. Note: it is not clear for how many days each boy received either of the MPH doses or placebo Washout before trial initiation: not stated Medication-free period between interventions: not stated Titration period: not stated Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Modified Conners' Scale Parent, daily, and Teacher-rated ACRS, 2-3 ratings per treatment condition. Daily reports of social and academic behaviour. Not stated who did the rating for these reports • SNAP, teacher-rated • Abbreviated CRS • IOWA CTRS **Non-serious AEs** • Rebound/Modified Conners' Scale, Parent, for rebound effect assessment • Specific Behaviour Ratings by parent (5, specific individual problem behaviours, rated every night)
Notes	Sample calculation: none Ethics approval: no information **Comment from review authors** • Non-validated endpoints used. No definition (defined cut-off score on scales) of what the authors considered to be 'rebound' Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: not stated Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: emailed trial authors to request additional information. Also asked whether this trial includes the Pelham 1989 reference. No answer from trial author, so we extracted data as from 2 different studies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Order of drug condition for each child was randomly assigned over days
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Child, parent, teacher and programme counsellors were blinded to the condition. Active medication and placebo were disguised in gelatin capsules and pre-packaged in individually dated envelopes

Johnston 1988 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Kaplan 1990

Study characteristics	
Methods	3 open trials, then a placebo-controlled, double-blind, cross-over trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: 6. Number of participants followed up: 6 (all boys) Number of withdrawals: 0. 3 outpatients were studied in an open-label design Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 14.4 years (range 13-16) IQ: mean 86 (range 76-97) MPH-naive: 5 (55%) Ethnicity: not stated Country: USA Setting: outpatient clinic and inpatient ward Comorbidity: aggressive CD (100%) Comedication: yes; diphenhydramine 50 mg Other sociodemographics: none **Inclusion criteria** • Meeting DSM-III criteria for both ADHD and aggressive CD **Exclusion criteria** • Consent from parent or custodial social service agency • Psychosis or drug abuse history
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.6 mg/kg, with 30 mg as a ceiling for MPH and placebo Administration schedule: twice/d, 8:00 am and noon

Kaplan 1990 *(Continued)*

	Mean MPH dosage: 0.47 mg/kg Duration of each medication condition: 3 weeks Washout before trial initiation: 1 week Medication-free period between interventions: 20 h Titration period: 1 week after randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CTRS: completed weekly by classroom teachers • In addition, for inpatients, CRS was completed weekly by the unit nurse • **Non-serious AEs** • Treatment Emergent Side Effect Scale: completed weekly by treating psychiatrists • Dizziness, appetite loss and headache were reported in 3 of the 9 youngsters
Notes	Sample calculation: no Ethics approval: no information **Comment from trial authors** • As the result of an oversight, assignment to MPH-first or placebo-first condition was made in the absence of a specific randomisation formula. 5 of the 6 participants received placebo for the first condition and MPH for the second condition **Key conclusion of trial authors** • Findings provide preliminary evidence of the efficacy of MPH in reducing aggression among aggressive conduct-disordered adolescents also diagnosed with ADHD Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: March 2014. Emailed trial author twice to request additional information but have not received a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	As the result of an oversight, assignment to MPH or placebo as the first condition was made in the absence of a specific randomisation formula. 5 of the 6 participants received placebo for the first condition and MPH for the second condition
Allocation concealment (selection bias)	Low risk	Assignment to order condition was determined with no knowledge of the particular participants involved; thus participants did not receive 1 condition or the other based on symptoms or any other systematic bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information

Kaplan 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In 2 cases, school vacation at the inpatient setting prevented teacher ratings from being obtained during 1 condition of the trial. In those 2 instances, the decision was made to use Conners' ratings obtained from the unit nurse for both the condition for which no teacher ratings were provided and the condition for which teacher ratings were given; thus comparisons were consistent in terms of rater. Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Kelly 1989

Study characteristics	
Methods	Double-blind, cross-over trial with 2 interventions: • MPH • placebo Followed by long-term follow-up of 12 children out of 21 who continued to receive MPH. Follow-up for an average of 16 months Phases • Baseline • Cross-over trial • Follow-up
Participants	**Cross-over trial** Number of participants screened: not stated Number of participants included: 21 (18 boys, 3 girls). 26 were initially included, but 5 children dropped out, 3 were removed by parents and 2 were disqualified because of a death in the family in 1 and a protocol procedural error in the other Number of participants followed up: 21, plus 2 participants who had been withdrawn but returned later for follow-up Number of withdrawals to follow-up: 0, but data for a few variables were not obtained for all participants Diagnosis of ADHD: DSM-III Age: mean 9.3 years (range 8-12) IQ: mean 100.7 MPH-naive: 100% Ethnicity: white (62%), Hispanic/oriental [Asian]/black (14%), mixed race (24%) Country: USA

Kelly 1989 *(Continued)*

	Setting: outpatient clinic Comorbidity: oppositional disorder (14%), enuresis (38%) Comedication: not stated Other sociodemographics: 2-parent household (95%) **Inclusion criteria** • ADHD diagnosis according to DSM-III • IQ > 80 • Free of major health problems, neurological disorders or psychosis **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned to MPH or placebo MPH dosage: between 0.3 and 0.6 mg/kg/d in the short-term phase Administration schedule: 2 time points/d Duration of each medication condition: not stated Washout before trial initiation: from noon to the following morning (i.e. the next day) Titration period: no
Outcomes	**ADHD symptoms** • ACTerRS: ADD/H: rated before diagnosis, at cross-over, at the conclusion of the short-term protocol and again during long-term follow-up • Conners' Parent Questionnaire: rated before diagnosis, at cross-over, at the conclusion of the short-term protocol and again during long-term follow-up
Notes	Sample calculation: not stated Ethics approval: yes **Key conclusion of trial authors** • Findings indicate that many pre-adolescents with ADHD exhibit low self-esteem. Despite clinical response to medication, short-term improvement in self-esteem may not occur; however, long-term, multi-modal management that includes medication does appear to improve self-esteem **Comment from review authors** • The data that we used in the review were derived from the cross-over period described Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: CIBA Geigy Pharmaceuticals provided placebos Email correspondence with trial authors: January 2014. Trial authors not able to provide us with further information
Risk of bias	

Kelly 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Child assigned in a double-blind, cross-over format to MPH followed by placebo or placebo followed by MPH
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Because data for a few variables were not obtained for all participants, a procedure for unbalanced analysis of variance was required and was accomplished by using the general linear model (GLM) procedure in the Statistical Analysis System (SAS) Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	Not protocol identified

Kent 1995

Study characteristics	
Methods	Double-blind, cross-over trial with 3 interventions: • MPH 10 mg • MPH 15 mg • placebo Phases: the first 2 doses (7:00 am and noon) were unchanged from the open trial, whereas the 4:00 pm dose was 10 mg of MPH, 15 mg of MPH or placebo. Each of these three 4:00 pm medication conditions was administered in random order during the 12-day period. Each medication condition was administered for a total of 4 days
Participants	Number of participants screened: not stated Number of participants included: 12 (11 boys, 1 girl) Number of participants followed up: not stated (but all 12 seem to appear in the results) Number of withdrawals: not stated Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 9.0 years (SD 2, range 5.5-11.25) IQ: not stated MPH-naive: 60% Ethnicity: not stated

Kent 1995 *(Continued)*

	Country: USA Setting: inpatient ward Comorbidity: ODD (25%), learning disability and ODD (50%), CD (8%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • In addition to fulfilling ADHD diagnostic criteria, patients were considered for the trial only if they showed a beneficial response to an open trial of MPH, as discussed below **Exclusion criteria** • Major depressive disorder • Separation anxiety disorder • Tics or history of tics • Glaucoma • Psychosis or history of psychosis • Known hypersensitivity to MPH
Interventions	Participants were randomly assigned to different possible drug condition orders of 10 mg or 15 mg MPH and placebo Mean MPH dosage: not stated Administration schedule: 7:00 am, noon and 4:00 pm Duration of each medication condition: 4 days Washout before trial initiation: none stated Medication-free period between interventions: none Titration period: open titration of MPH was accomplished within 14 days of the child's admission Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Child Behavior Rating Form, rated by nursing staff: after each day shift and each evening shift **Non-serious AEs** • Sleep latency, sleep adequacy, food intake and weight: recorded by nursing staff
Notes	Ethics approval: informed consent for trial participation was obtained from each child's parent or guardian. All procedures were approved by the trial site's Human Subjects Research Review Committee **Comment from trial authors** • Patient population studied was particularly disturbed, and data were obtained in the context of inpatient treatment **Key conclusions of trial authors** • This trial's findings show that children with ADHD derive substantial symptom reduction from MPH administered in late afternoon, with no untoward effects on sleep. Therefore, 3 times/d should be considered for those children who exhibit ADHD symptoms in the evening • Adverse effects on sleep latency were not apparent in the sample overall

Kent 1995 *(Continued)*

	Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; patients were excluded from consideration for trial participation if they had known hypersensitivity to MPH Any withdrawals due to AEs: none Funding source: this work was supported by the John and Maxine Bendheim Fellowship and by the Leon Lowenstein Foundation Email correspondence with trial authors: March 2014. Sent an email to trial authors to request additional information but have not received a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each of the three 4:00 pm medication conditions was administered in random order during the 12-day double-blind cross-over period
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The identity of each day's 4:00 pm dose was known only to the hospital pharmacist, until the child completed the 12-day protocol
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results are provided for all 12 children Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Kent 1999

Study characteristics

Methods	Cross-over trial with 3 interventions: • MPH 0.3 mg/kg • MPH 0.6 mg/kg • placebo Phases: 3-week, double-blind, 2-way cross-over, long-term (≥ 12 months) follow-up
Participants	Number of participants screened: not stated Number of participants included: 50 (38 boys, 12 girls) Number of participants followed up: 43 Number of withdrawals: 13

Kent 1999 *(Continued)*

	Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean not reported (range 4-14 years) IQ: "overall normal intelligence" MPH-naive: not stated Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: depression (37%), anxiety (37%), learning disability (51%), CD (5%), "psychiatric disorder" (2%), Tourette's disorder (12%), "other" (23%) Comedication: not stated Other sociodemographics: "Fifteen (30%) live in households that have a family income below the Canadian poverty line ($20,000/y)", 26 "rural", 9 "suburban", 14 "urban". 21 live with 1 biological parent, 24 live with both parents, 4 live with adoptive parents or "guardians" **Inclusion criteria** • ADHD diagnosis • 4-14 years of age • English or French speaking • Living with carers with whom they had lived for > 6 months • Presence of a teacher who could evaluate the child in class **Exclusion criteria** • History of significant developmental delay • Previous diagnosis of pervasive developmental disorder • Unwillingness of parents and/or school personnel to meet MPH treatment requirements
Interventions	Participants were randomly assigned to different possible drug condition orders of 0.3 mg/kg MPH and 0.6 mg/kg MPH and placebo Mean MPH dosage: not stated Administration schedule: each new condition started on a Saturday morning (to allow parents' observation/evaluation on weekend) Capsules given at 8:00 am and 12:00 pm. Conners' administered at baseline and on the last day of each week. A 30-min semi-structured follow-up interview was conducted ≥ 12 months after completion of the trial Duration of each medication condition: 1 week Washout before trial initiation: not stated Medication-free period between interventions: 12:00 pm to 8:00 am the following day Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Conners' Parent Questionnaire: baseline and on the last day of each week • Conners' Teacher Questionnaire: baseline and on the last day of each week **Non-serious AEs**

Kent 1999 *(Continued)*

- Weekly reporting of side effects by parents and teachers. No use of standard side-effects questionnaire

Notes	Sample calculation: not stated Ethics approval: yes; the Research Ethics Board of the IWK Grace Health Centre approved the protocol **Comments from trial authors** • "We found the MPT to be helpful, practical, and definitive for families of children with attention-deficit/hyperactivity disorder to making a decision about medication use" • "Regardless of the outcome, it was important for families to complete the MPT to understand, for their own child, the effect of methylphenidate on the child's behaviour and the presence of any side effects" **Key conclusion of trial authors** • "An 'N of 1' MPT was easily performed and permitted families to decide whether to use methylphenidate for long-term treatment of attention-deficit disorder or attention-deficit/hyperactivity disorder. Regardless of methylphenidate use or lack of use, the condition of all of these children was improved at follow-up" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes, "No family found the MPT difficult, but 6 trials were incomplete, usually because of side effects" Funding source: Ms Kent was a summer medical student supported in part by the IWK Grace Research Foundation, Halifax, NovaScotia, and by the Pharmaceutical Manufacturers Association of Canada Studentship, Ottawa, Ontario Email correspondence with trial authors: August 2013. We received additional information from trial authors, but they were not able to provide the additional data that we requested

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Once enrolled in the MPT, the non-blinded hospital pharmacist randomly assigned each child to a particular dosing schedule". "The capsules contained, in random order: placebo of the prescribed dose of MPH (Ritalin) hydrochloride (0.3 mg/kg or 0.6 mg/kg)"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Families (n = 50) with a child eligible for MPT were given 3 bottles of identical capsules". "The family, teacher, and physician were blinded for the order of medication"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"At the end of each trial the code was broken. The physician evaluated this information and made a clinical inference about the degree of response each week"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no

Kent 1999 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol identified

Klorman 1990

Study characteristics	
Methods	Cross-over trial with 2 interventions: • MPH • placebo Phases: 2
Participants	Number of participants screened: not clear Number of participants included: 48. (42 boys, 6 girls) Number of participants followed up: appears to have been 48 Number of withdrawals: not clear Diagnosis of ADHD: DSM-III Age: mean not stated (range 12-18 years) IQ: mean 108.62 MPH-naive: 46/48; 2 had brief trials in childhood Ethnicity: white (46) Country: USA Setting: outpatient clinic Comorbidity: oppositional and CD (24), oppositional not CD (12), anxiety (5), drug or alcohol abuse (2), depression (1) Comedication: no Other sociodemographics: double- or single-parent family, predominantly middle class (mean Hollingshead socioeconomic status score of 48.8 (i.e. social class II)) **Inclusion criteria** • Participants 12-18 years of age without previous stimulant therapy referred for evaluation of response to stimulants from 1984-1988 **Exclusion criteria** • CNS involvement • Childhood autism • Psychosis • Uncorrected visual or auditory problems • IQ < 80
Interventions	Participants were randomly assigned to 3 weeks of MPH and placebo Mean MPH dosage: 35.21 mg (± 5.94 (SD)). Range 15 mg (2 daily doses) to 40 mg (3 daily doses)

Klorman 1990 *(Continued)*

	Administration schedule: doses were gradually increased at the end of the 1st and 2nd weeks Washout before trial initiation: not described Titration period: after randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Abbreviated Conners' Hyperactivity Questionnaire: rated by teacher and parent, weekly • IOWA Inattention/Overactivity and Aggression Scales: rated by teacher and parent, weekly Mean parent- and teacher-reported Conners' hyperactivity and inattention scores were graphed but SD values were not. Also, the paper did not refer to measures of impulsivity or total scores. We could not use these data in our meta-analyses because values were missing and trial authors were not able to provide supplemental data on this outcome **Non-serious AEs** • Side effects reported in Table 3: appetite loss; increased thirst, dry mouth, stomachaches, nausea, headaches, sleep problems, shakiness, crying, anger, unhappiness, sadness
Notes	Sample calculation: not described Ethics approval: not described **Key conclusion of trial authors** • These results support the continued effectiveness of stimulant therapy for attention deficit disorder in adolescence. However, the magnitude of clinical effectiveness reported was smaller than was previously found in younger patients Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to averse events: Unclear, none mentioned Funding source: National Institute of Mental Health (NIMH) grant MH38118 Email correspondence with trial authors: April 2014. We obtained supplemental information/data from trial authors (Magnusson 2014a [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Received information from trial author (Magnusson 2014a [pers comm])
Allocation concealment (selection bias)	Low risk	Received information from trial author (Magnusson 2014a [pers comm])
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Substances were dispensed in capsules of identical appearance" (p 703)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parent and teacher ratings were used and participants were blinded to which capsule they were receiving

Klorman 1990 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Kolko 1999

Study characteristics	
Methods	Randomised, placebo-controlled, cross-over trial with 2 possible drug interventions and placebo, as well as 2 possible psychological interventions: • MPH at 0.3 mg/kg • MPH at 0.6 mg/kg • placebo and • behaviour modification • no behavioural modification
Participants	Number of participants screened: 70 Number of participants included: 22 (all boys) Number of participants followed up: 16 Number of withdrawals: 6 Diagnosis of ADHD: DSM-III-R (subtypes not stated) Age: mean 9.6 years (range 6.9-12.9) IQ: not stated MPH-naive: not stated Ethnicity: African American (75%) Country: USA Setting: "partial hospitalisation" summer treatment programme Comorbidity: CD (44%), ODD (56%), anxiety disorder (18.8%), major depressive disorder (11.5%), dysthymia (6%), intermittent explosive disorder (6%), developmental articulation disorder (6%), asthma (12.5%) Comedication: not stated Other sociodemographics: 3 lived with 1 or both parents, 6 lived with grandparents, 1 lived with an aunt, 4 lived with non-relatives, 2 lived with foster mother. 44% of families received welfare **Inclusion criteria** • Not stated **Exclusion criteria**

Kolko 1999 *(Continued)*

	• Not stated
Interventions	Participants were randomly assigned to different possible drug condition orders of 0.3 mg/kg and 0.6 mg/kg MPH and placebo Mean MPH dosage: not stated Administration schedule: 8:00 am and 11:30 am to 12.00 pm Duration of each medication condition: 1 day. Each medication condition was administered once per week for a total of 6 days during the trial Washout before trial initiation: 2 weeks Medication-free period between interventions: no Titration period: none Treatment compliance: not stated Behavioural intervention: behaviour modification and no behaviour modification were alternated on a weekly basis for a total of 3 weeks per condition
Outcomes	**ADHD symptoms** • Abbreviated IOWA CRS, which includes an Inattentive/Overactive subscale and an Oppositional Defiant subscale **Non-serious AEs** • Barkley Stimulant Side Effects Rating Scale. Adapted by changing the rating scale to include only 4 points rather than 9 points
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusions of trial authors** • MPH and behaviour modification had certain unique, main and incremental effects that extend findings supporting their combination and suggest that integrated studies should evaluate multiple dimensions of functioning in novel settings • Incorporation of other intervention components in combined treatments may be warranted to enhance clinical efficacy **Comments from review authors** • Barkley Stimulant Side Effects Rating Scale was adapted by changing the rating scale to include only 4 points (rather than 9 points) after pilot-testing. Therefore, we cannot be sure whether the scale is still valid • Limitations: the number of participants studied was small, and only 22 of 70 screened met trial eligibility criteria Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes, 2 Funding source: not declared Email correspondence with trial author: January 2014. We were unable to obtain additional data (Nilausen 2014 [pers comm])

Kolko 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each MPH condition was administered once per week for a total of 6 days during the trial, and behaviour modification and no behaviour modification were alternated on a weekly basis, for a total of 3 weeks per condition. Thus, daily MPH conditions were crossed with 2, weekly behavioural intervention conditions
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It is stated: "MPH or placebo was placed in identical opaque capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Not stated Selection bias: exclusion of 2 participants with challenging behaviour
Selective reporting (reporting bias)	Unclear risk	No protocol available

Kollins 2006 (PATS)

Study characteristics

Methods

8-phase, 70-week, multi-centre trial (phase III trial) including:

- phase 1: screening: varying time
- phase 2: uncontrolled parent training: 10 weeks
- phase 3: baseline: 2-4 weeks
- phase 4: open-label, safety lead-in: 1 week
- phase 5: random-sequence, double-blind, placebo-controlled, cross-over titration: 5 weeks. Optional pharmacogenetics trial simultaneously
- phase 6: randomised, optimal dose, double-blind, placebo-controlled, parallel trial: 4 weeks
- phase 7: open-label, uncontrolled maintenance: 10 months
- phase 8: randomised, double-blind, placebo discontinuation: 6 weeks

If parents requested and clinicians agreed that participants were severely symptomatic, children could be moved directly into the medication phase that was concurrent with parent training. If participants did not tolerate the dosing in phase 4, they could enter the open-label maintenance phase if they tolerated lower doses (e.g. 1.25 mg, 2.5 mg). If they tolerated all doses except 7.5 mg, they were eligible to enter phase 5, the cross-over titration, with the planned week on a 7.5-mg dose replaced by an additional 5-mg week. After phase 5, cross-over:

- if the child showed the greatest clinical benefit during 1 of the 5 weeks of the cross-over trial, with no room for improvement, the blind was broken and the child was randomly assigned to that MPH dose or placebo in phase 6

Kollins 2006 (PATS) *(Continued)*

- if the child was a placebo responder, phase 6 was skipped and the child was allowed to enter phase 7 while taking no medication and with monthly monitoring by the treating physician
- if a particular week was deemed best, with ongoing room for improvement, a 2-week double-blind trial of 7.5 mg and 10 mg 3 times/d, each for 1 week, was implemented, and teacher and parent ratings and side effects data were subsequently blindly reviewed to determine the best dose, or
- participants with no clinical benefit any week were not eligible to continue in phase 6 or 7 but were given 1-month follow-up and then were referred for community treatment

Participants	Number of participants screened: 1915 Number of participants included in the trial: 303 (229 boys, 74 girls) Number of participants who completed the last phase of the trial: 8 Number of withdrawals during the trial: 295 Diagnosis of ADHD: DSM-IV (combined (75%), hyperactive-impulsive (25%), inattentive (0%)) Age: mean 4.41 years (range not reported) IQ: > 70 (mean 99.06) MPH-naive: 100% Ethnicity: white (63%), African American (19%), Asian (2%), Hispanic or Latino (16%), American Indian or Alaskan Native (0.7%) Country: USA Setting: outpatient clinic Comorbidity: ODD (52%), communication disorder (22%), elimination disorder (i.e. encopresis, enuresis; 8%), specific phobia (8%), anxiety disorder (8%), developmental co-ordination disorder (3%), CD (2%), pica (2%), adjustment disorder (1%), reactive attachment disorder (1%), OCD (0.7%), sleepwalking disorder (0.3%) Comedication: no Other sociodemographics: double-parent family (76%), single-parent family (18%), mean Hollingshead socioeconomic status 47.20 (SD 9.56) **Phase 4, open-label, safety lead-in** Number of participants included: 183 Number of participants followed up: 169 Number of withdrawals: 12 Number of participants leaving the trial phase and entering maintenance (phase 7): 2 **Phase 5, cross-over** Number of participants included: 165 (122 boys, 43 girls) Number of participants followed up: 147 Number of withdrawals: 14 Number of participants leaving the trial phase and entering maintenance (phase 7): 4 Diagnosis of ADHD: DSM-IV (combined (76%), hyperactive-impulsive (24%), inattentive (0%)) Age: mean 4.74 years (range 3-5.5)

Kollins 2006 (PATS) *(Continued)*

IQ: > 70 (mean 97.93)

MPH-naive: 100%

Ethnicity: white (63%), African American (18%), Asian (1%), Hispanic or Latino (18%), American Indian or Alaskan Native (0.6%)

Country: USA

Comorbidity: ODD (55%), communication disorder (20%), elimination disorder (i.e. encopresis, enuresis; 8%), specific phobia (7%), anxiety disorder (10%), developmental co-ordination disorder (4%), CD (3%), pica (2%), adjustment disorder (0.6%), reactive attachment disorder (2%), OCD (0.6%), sleepwalking disorder (0.6%)

Comedication: no

Sociodemographics: double-parent family (79%), single-parent family (21%), mean Hollingshead socioeconomic status 47.01 (SD 9.58)

Phase 6, parallel

Number of participants included: 114 (85 boys, 29 girls)

Number of participants followed up: 77

Number of withdrawals: 1

Number of participants leaving the trial phase and entering maintenance (phase 7): 36

Diagnosis of ADHD: DSM-IV (combined (75%), hyperactive-impulsive (25%), inattentive (0%))

Age: mean 4.76 years (range not reported)

IQ: > 70 (mean 97.45)

MPH-naive: 100%

Ethnicity: white (65%), African American (17%), Asian (0.9%), Hispanic or Latino (17%), American Indian or Alaskan Native (0.9%)

Country: USA

Comorbidity: ODD (53%), communication disorder (22%), elimination disorder (i.e. encopresis, enuresis; 7%), specific phobia (7%), anxiety disorder (11%), developmental co-ordination disorder (5%), CD (3%), pica (0.9%), adjustment disorder (0.9%), reactive attachment disorder (2%), OCD (0.9%), sleepwalking disorder (0.9%)

Comedication: no

Sociodemographics: double-parent family (80%), single-parent family (19%), mean Hollingshead socioeconomic status 47.61 (SD 9.45)

Phase 7, open-label maintenance

Number of participants included: 140 (104 boys, 36 girls)

Number of participants followed up: 95

Number of withdrawals: 45

Diagnosis of ADHD: DSM-IV (combined (76.4%), hyperactive-impulsive (23.6%), inattentive (0%))

Age: mean 4.4 years

Kollins 2006 (PATS) *(Continued)*

IQ: > 70

MPH-naive: 100%

Ethnicity: white (65.0%), African American (17.1%), Asian (1.4%), Hispanic (15.7%), American Indian (0.7%)

Country: USA

Comorbidity: ODD (52.9%), communication disorder (19.3%), anxiety disorder (11.4%)

Comedication: no

Sociodemographics: double-parent family (81.4%), single-parent family (18.6%), mean Hollingshead socioeconomic status 47.2 (SD 9.5)

Inclusion criteria

- 36-65 months (3-5.5 years)
- DSM-IV criteria for ADHD, hyperactive/impulsive or combined subtype, on Parent DISC-4, and clinical interview by experienced clinician; symptoms were required to be present for a minimum of 9 months
- Age- and sex-adjusted T score ≥ 65 on the Hyperactive-Impulsive subscale of CPRS and CTRS
- Score < 55 on the Children's Global Assessment of Functioning Scale
- IQ > 70 as on the Differential Abilities Scale; children scoring < 70 were considered for inclusion if their composite score from the Vineland Adaptive Behavior Scale was > 70
- Enrolled in some type of day programme: day care, pre-school, nursery school, kindergarten, for ≥ 2 half-days/week. School-type programme, in which class included ≥ 8 same-age peers; if children had been expelled from an eligible programme in the 3 months before screening, they could be considered for enrolment
- Teachers willing to complete rating scale
- Residing with primary carer for ≥ 6 months before screening
- Patients and parents willing to attend all visits required by the trial
- Otherwise generally healthy, and SBP and DBP < 95th percentile for age and sex
- Stimulant-naive

Additional inclusion criteria for phase 4, open-label lead-in

- Not showing substantial ADHD improvement after parent training (phase 2) (continued impairment, operationalised as < 30% reduction on CPRS or CTRS, or a rating of less than "improved" by at least 2 of the 3 raters (parent, teacher, clinician) completing the CGI Scale
- Parental consent to a medication trial

Additional inclusion criteria for phase 5, cross-over

- Tolerating the dosing in phase 4 (i.e. children with moderate to severe AEs at doses < 5 mg in phase 4 were not eligible to continue)

Exclusion criteria

- Children or their parent(s) could not understand or follow instructions given in the trial
- Evidence of moderate to severe AEs or evidence of a much improved response to any dose of MPH or another stimulant
- > 5 weeks of exposure to ≥ 30 mg/d of MPH or equivalent doses of other stimulants
- Use of any other psychotropic medication or an investigational drug in the past 30 days; episodic use of sympathomimetic decongestants for the common cold under the trial physician's supervision was allowed
- History of motor or vocal tics or Tourette's syndrome
- Major medical conditions that would interfere with involvement in a long-term trial or could be affected negatively by MPH

Kollins 2006 (PATS) *(Continued)*

- Current evidence of adjustment disorder, pervasive developmental disorders, autism, psychosis, significant suicidality or other psychiatric disorder, in addition to ADHD that requires treatment with additional medication
- Evidence of current physical, sexual or emotional abuse
- Living with anyone who currently abuses stimulants or cocaine
- History of bipolar disorder in both biological parents

All cases were presented to a cross-site panel of clinicians, and only patients for whom consensus indicated that all inclusion (and no exclusion) criteria were met could be enrolled

Interventions	**Phases 1-3** Enrolment, parent training; baseline: no medical intervention **Phases 4 to 8** Medical intervention (SA-IR-MPH) Phase 4, open-label, safety lead-in Titration: starting dose of 1.25 mg twice daily; increased to 7.5 mg 3 times daily Duration: 1 week Treatment compliance: not stated **Phase 5, cross-over** Randomly assigned sequence of doses of 1.25 mg, 2.5 mg, 5.0 mg or 7.5 mg IR-MPH and placebo administered 3 times daily for a week Medication-free period between interventions: none Mean MPH dose: not stated Duration: 5 weeks **Phase 6, parallel** After a 24-h medication washout, 4 weeks of randomly assigned treatment with a participant's optimal MPH dose as determined in phase 5, or placebo No of participants randomised to each group: MPH 61, placebo 53 Mean MPH dose: 14.22 mg/d, 0.7 mg/kg/d Duration: 4 weeks Treatment compliance: not stated **Phase 7, open-label, maintenance** Maintenance starting doses were based on the best dose decision from cross-over titration. Phase 5 placebo responders were maintained without medication for ≥ 4 weeks, unless their condition deteriorated, in which case open-label treatment could be initiated. For any participant whose condition deteriorated, the MPH dose was gradually titrated for optimal response. The dosing regimen was adjusted to minimise some AEs to 3 times/d (at breakfast, around noon after lunch and at 3:30 pm), 7 days a week Mean MPH dose: increased from 14.04 mg/d (0.71 mg/kg/d) at month 1 to 19.94 mg/d (0.92 mg/kg/d) at month 10 Duration: 10 months Treatment compliance: not stated

Kollins 2006 (PATS) *(Continued)*

Phase 8, discontinuation

Randomised, double-blind, placebo discontinuation trial, in which an abrupt medication replacement consisted of placebo for half of the children, while others continued on their best MPH dose from the end of phase 7. Children returned to active medication if they met relapse criteria, in other words, CPRS or CTRS scores on the Hyperactivity/Impulsivity Index > 1.5 SD above age- and sex-adjusted norms, or a clinician rating of 4 on the CGI-S

Duration: 6 weeks

Treatment compliance: not stated. Those who opted out of the double-blind phases would be allowed to continue on open-label maintenance therapy. This greatly reduced incentive for families to remain in the double-blind phases, especially if there was reason to suspect that a child had been randomly assigned to placebo

Outcomes

ADHD symptoms

- Conners', Loney and Milich Rating Scale, and SKAMP: teacher- and parent-rated weekly in phase 5
- SNAP-IV, average of parent and teacher ratings: at the end of the last week (4th) of phase 6

Serious AEs

- Medication-related serious AEs

General behaviour

- SWAN, Early Childhood Inventory: teacher- and parent-rated at baseline and at the end of phase 6
- CBCL (home functioning)
- Hillside Behaviour Rating Scale (school functioning)

Non-serious AEs

- Height and weight were measured without shoes or heavy clothes at each trial visit. (Growth charts provided by the CDC were used to transform absolute units of measurement into Z-scores.) Laboratory tests were performed at each trial visit
- General clinician inquiry regarding the child's health problems at each trial visit. AEs monitored by telephone, and parent- and teacher-rated in phase 4. Side Effects Rating Scale, parent-rated, weekly in phases 5, 6 and 8; monthly in phase 7. Side Effects Rating Scale, teacher-rated, weekly in phases 5 and 8, and in the last week of phase 6, as well as in first and tenth months of phase 7
- AEs Checklist was based on the Pittsburgh Side Effects Rating Scale. The 4-point (none, mild, moderate or severe) teacher-rated scale included the following: buccal-lingual movements; picking at skin or finger; lip or cheek chewing; other abnormal motor movements; worried, anxious appearance; dull, tired, listless appearance; headaches; stomachaches; crabby, irritable behaviour; tearful, sad, depressed behaviour; appetite loss; prone to crying; and uninterested in others with social withdrawal. The Parent Adverse Events Checklist also included trouble sleeping. Only AEs rated as moderate or severe were counted as reportable in the open lead-in, titration and parallel phases of the trial, whereas AEs rated as mild, moderate or severe were reported from the maintenance phase
- BP and pulse, at each trial visit. Cardiovascular AEs were based on age-adjusted normative values. Tachycardia was defined as 2 measurements of resting heart rate > 120 beats per minute (bpm) at the same visit. Hypertension was defined as 2 BP readings at the same visit that were > 95th percentile for age and sex (SBP or DBP), ranging from 110/72 for 3-year-olds to 115/74 for 6-year-olds. BP was checked again within 7-14 days. If the reading remained above the cut-off limit, an AE for hypertension was reported. Hypertension was rated as mild if < 10 mmHg, moderate if 11 mmHg-20 mmHg and severe if > 20 mmHg above the limit

Notes

Sample calculation: yes. Target sample size stated in the online protocol 165. Sample to be randomly assigned 120

Ethics approval: yes; by institutional review boards at each trial site. The trial was monitored by the Data and Safety Monitoring Board of the NIMH

Comments from trial authors

Kollins 2006 (PATS) *(Continued)*

- Design: the trial included only IR-MPH, not an ER preparation. The trial may have included an order effect in the cross-over phase, particularly for children who were randomly assigned to receive higher doses first. The PATS protocol did not provide a stimulant-untreated clinical control group in non-controlled phases. Comparisons of height and weight before and after treatment were made against population norms (i.e. children without an ADHD diagnosis and MPH-exposure). The follow-up period was not sufficient for evaluation of the critical issue of long-term effects of initial growth suppression observed in the first year of treatment
- Dose: doses used in the PATS were relatively low and homogeneous, and the high end of the proposed dose range was truncated. This may have masked dose-related effects
- Population: the rigorous procedures for diagnosis of ADHD enhanced the validity of the diagnostic process at the expense of excluding some children likely to have met the conventional criteria for AD-HD in other settings. Children who showed substantial ADHD improvement after parent training were not eligible for medication phases. The sample was too small for the medication to be declared safe for this age group. Failure to meet remission criteria may be caused by severity of ADHD symptoms, not by possible ineffectivity of MPH in pre-schoolers with ADHD. A high attrition rate and differential attrition rates in the allocated groups were possibly due to a delayed trial start, repeated consent procedures, an always-available option to skip directly into maintenance and greater nervousness among parents about medication side effects in pre-schoolers. Parents' experience during the titration phase presumably heightened their awareness of behavioural differences associated with active and placebo medication
- Data: missing data in general. AE data entry procedures may have inflated AE rates. Parents were told when double-blind switches between the drug took place. This may have contributed to confounding of negative expectancy and reporting of AEs
- Exploratory moderator analyses of efficacy data from phase 5 (cross-over): no adjustments were made for multiple comparisons. Findings should be considered preliminary. The DISC-4, Parent Version, has not been validated in pre-school children. Sample sizes across different moderator categories/subgroups were relatively small. Data on compliance were missing

Key conclusions of trial authors

- Phase 5 (cross-over): IR-MPH, delivered in 2.5-mg, 5-mg and 7.5-mg doses 3 times/d, produced significant reductions in ADHD symptom scale scores in pre-schoolers compared with placebo, although effect sizes (0.4-0.8) were smaller than those cited for school-aged children taking the same medication
- Pharmacogenetics trial in phase 5 (cross-over): emerging evidence suggests the potential for understanding individual variability of responses to and side effects of ADHD medications through the trial of genetics, although additional research is required before these findings can be proven to have clinical utility
- Exploratory moderator analyses of efficacy data from phase 5 (cross-over): of the 14 variables examined as potential moderators, only 1 (number of concurrent comorbid disorders) served as a moderator of MPH dose response. In pre-schoolers with ADHD, the presence of no or 1 comorbid disorder (primarily ODD) predicted a large treatment response at the same level as has been found in school-aged children, and 2 comorbid disorders predicted moderate treatment response; whereas the presence of ≥ 3 comorbid disorders predicted no treatment response to MPH
- Phase 6 (parallel): medication effects varied by informant and outcome measure. Parent measures and teacher scores on the SWAN did not differentially improve with MPH. Parent-rated depression (P value < 0.02) and dysthymia (P value < 0.001) on the Early Childhood Inventory worsened with MPH, but scores were not in the clinical range. Significant medication effects were found on the clinician CGI-S (P value < 0.0001) and in teacher ratings on the Social Competence Scale (P value < 0.03). Pre-schoolers with ADHD treated with MPH for 4 weeks improve in some aspects of functioning. Additional improvements might require longer treatment, higher doses and/or intensive behavioural treatment in combination with medication
- Phase 7 (maintenance): with careful monitoring and a gradual medication dose increase, most pre-schoolers with ADHD maintained improvement during long-term IR-MPH treatment. Variability in effective and tolerated dosing was substantial
- Entire trial duration
  - AEs during the trial: 11% of pre-schoolers discontinued treatment because of intolerable MPH AEs. Of the serious AEs reported, 1 occurred at baseline, 2 at lead-in, 3 in titration, 1 in parallel and 1 in maintenance. Only 1 was possibly related to MPH

Kollins 2006 (PATS) *(Continued)*

- Growth during the trial: average relative size at baseline was significantly greater than 0 for z height and z weight, indicating greater than expected height (by 2.04 cm) and weight (by 1.78 kg) for participants. During treatment, slopes were significantly less than 0 for z height and z weight, indicating reduction in growth rates. For 95 children who remained on medication, annual growth rates were 20.3% less than expected for height (−1.38 cm/year) and 55.2% less (−1.32 kg/year) for weight. Risks of reduced growth rates should be balanced against expected benefits when pre-school-aged children are treated with stimulant medication

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, participants were selected for specific phases of the trial/interventions depending on response in earlier phases, as described in methods

Withdrawals due to AEs: number of withdrawals due to AEs during medication phases: 21 (i.e. 11%)

Number of participants leaving trial phase and entering maintenance (phase 7): 4

Funding source:

- Phase 5 (cross-over): sponsored by the NIMH, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to J.K.G. Generic MPH was purchased by grant funds
- Phase 6 (parallel-group): sponsored by the NIMH, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to J.K.G. Generic MPH was purchased by grant funds.
- Phase 8 (discontinuation): sponsored by the NIMH, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to J.K.G. Generic MPH was purchased by grant funds

Email correspondence with trial authors: June 2014. We obtained supplemental information/data from the trial authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	• Phase 5 (cross-over): randomisation was done centrally at the co-ordinating site, using a computerised stratified randomisation, a 1:1:1:1 starting dose allocation ratio and a randomised, balanced, cross-over protocol designed to avoid order effects • Phase 6 (parallel-group): a second randomisation to active MPH or to placebo was performed before entry into the parallel-design, placebo-controlled phase • Phase 8 (discontinuation): centralised randomisation used a computer programme; each child was allocated 1:1 to continuing MPH or switching to placebo under double-blind conditions
Allocation concealment (selection bias)	Low risk	• Phase 5 (cross-over): central randomisation using a computer programme • Phase 6 (parallel-group): central randomisation using a computer programme • Phase 8 (discontinuation): central randomisation using a computer programme
Blinding of participants and personnel (performance bias) All outcomes	Low risk	• Phase 5 (cross-over): double-blind. Placebo pills were identical to pills containing active medication capsules • Phase 6 (parallel-group): double-blind. Placebo pills were identical to pills containing active medication capsules

Kollins 2006 (PATS) *(Continued)*

		• Phase 8 (discontinuation): double-blind. Placebo pills were identical to pills containing active medication capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	• Phase 5 (cross-over): double-blind. Except in emergencies, clinicians remained blind to dose sequences. Blinding was maintained for primary dependent measures until after the best dose was determined, or as needed. Parent and teacher dose-response rating scale graphs were prepared and were blindly evaluated by 2 trial clinicians • Phase 6 (parallel-group): double-blind. Except in emergencies, clinicians remained blind to dose sequences. Blinding was maintained for primary dependent measures until after the best dose was determined, or as needed. Parent and teacher dose-response rating scale • Phase 8 (discontinuation): double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	• Phase 5 (cross-over): all analyses were run using the ITT principle (i.e. each observation obtained for the child was used in the analysis, including those from children who entered each of the 2 phases under consideration and did not complete the phase) • Phase 6 (parallel-group): all analyses were run using the ITT principle (i.e. each observation obtained for the child was used in the analysis, including those from children who entered each of the 2 phases under consideration and did not complete the phase) • Phase 8 (discontinuation): ITT Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	• Phase 5 (cross-over): outcome measures reported in accordance with the published protocol • Phase 6 (parallel-group): outcome measures reported in accordance with the published protocol • Phase 8 (discontinuation): not relevant

Kollins 2021

Study characteristics	
Methods	A 1-week parallel-trial with 2 arms: • SerdexMPH/dexMPH (SDX/d-MPH) • placebo
Participants	Number of participants screened: 178 (155 participants included in open-label phase) Number of participants included: 150 randomised (92 male, 58 female) Number of participants followed up: 149 Number of withdrawals: 1 lost to follow-up Diagnosis of ADHD: DSM-5 (percentage of combined (88%), hyperactive-impulsive (0%) and inattentive (12%)) Age: mean 9.6 (range 6-12) IQ: not stated MPH-naive: 89 (59.3%)

Kollins 2021 *(Continued)*

	Ethnicity: 76 white, 56 black/African American, 7 Asian, 10 multiracial, 1 other Country: USA Setting: outpatient clinic, laboratory classroom Comorbidity: some were specified as exclusion criteria Comedication: not stated Additional sociodemographics: none **Inclusion criteria** • Age 6-12 • DSM-5 diagnosis of ADHD • Score of at least 3 (mildly ill) on the clinician administered CGI-S scale and an ADHD-RS-5 total score of at least 28 **Exclusion criteria** • Known non-response to MPH treatment • History of allergic reaction or sensitivity to MPH • History of substance use disorder • Clinically significant medical abnormalities such as cardiovascular abnormalities, and any chronic condition of the CNS • Any of the following: bipolar I or II disorder, major depressive disorder, CD, OCD, any history of psychosis, autism spectrum disorder, disruptive mood dysregulation disorder, intellectual disability, Tourette's syndrome, or confirmed genetic disorder with cognitive and/or behavioral disturbances • Significant suicidal ideation or a history of suicide attempt, as assessed by the C-SSRS
Interventions	Participants were randomly assigned to receive either their optimised dose of SDX/d-MPH (ER) or placebo for 7 days Number randomised to each group: MPH 74, placebo 76 Mean medication dosage: not stated Administration schedule: the appropriate blinded treatment was taken at home, once daily in the morning, on days 22–27 Duration (of (each) medication): 7 days Washout before trial initiation: 2 days Titration period: 3 weeks before randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP assessed by independent investigation at baseline and day 7 **Serious AEs** • Assessed at each trial visit **General behavioral** • Weekly Rating of Evening and Morning Behavior—Revised (WREMB-R) scores (total score, and morning and evening subscores), parent-rated at baseline and day 7 **Non-serious AEs**

Kollins 2021 *(Continued)*

- The occurrence of TEAEs was assessed at each visit, beginning with the 1st dose of the Dose Optimisation Phase and ending with the follow-up or early termination visit

Notes

Sample calculation: yes (126)

Ethics approval: the trial was approved by an Institutional Review Board.

Comments from trial authors

- "The duration of the double-blind Treatment Phase, while consistent with similar studies, was relatively short." (Kollins 2021, p. 606)
- "the eligibility criteria resulted in a fairly homogeneous sample of children without comorbidities, potentially limiting the generalizability of the findings" (Kollins 2021, p. 606)
- "On the morning of the laboratory classroom day, baseline SKAMP-C scores were significantly higher (i.e. more severe symptoms) in subjects treated with SDX/d-MPH compared with placebo" (Kollins 2021, p. 606)
- "These collective findings suggest that after a period of chronic administration, opponent processes that outlast the acute effects of the stimulant may last for several days or more" (Kollins 2021, p. 606)
- "This apparent ''rebound'' phenomenon has implications for understanding the onset and duration, and likely the overall magnitude of observed efficacy in laboratory classroom studies" (Kollins 2021, p. 606)

Key conclusion of trial authors

- "In this dose-optimized, randomized, controlled laboratory classroom study, SDX/d-MPH showed significant improvements in ADHD symptoms compared with placebo in children 6–12 years of age, with a rapid onset and extended duration of effect. SDX/d- MPH was safe and generally well tolerated, with adverse effects comparable with those observed with other stimulant medications." (Kollins 2021, p. 606)
- "SDX/d-MPH is a recently approved ADHD product (Azstarys) containing a molar ratio of 70% SDX, a novel prodrug of d-MPH, and 30% d-MPH. In this study of children (6–12 years of age) with ADHD, SDX/d-MPH was efficacious and generally well tolerated, with a rapid onset and extended duration of effect." (Kollins 2021, 606)

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: no

Funding source: clinical research was funded by KemPharm, Inc. Funding for editorial and writing assistance in the form of proofreading, copyediting, and fact-checking was provided by Corium, Inc

Supplemental information regarding the risk of bias assessment was requested through personal email correspondence with the authors in July 2022 but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about sequence generation available
Allocation concealment (selection bias)	Unclear risk	No information about method of allocation concealment available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomisation was stratified by trial site. Neither the participant, the investigator, nor the sponsor knew a given participant's treatment assignment. The appropriate blinded treatment was taken at home, once daily in the morning, on days 22–27
Blinding of outcome assessment (detection bias)	Low risk	Randomisation was stratified by trial site. Neither the participant, the investigator, nor the sponsor knew a given participant's treatment assignment. The

Kollins 2021 *(Continued)*

All outcomes		appropriate blinded treatment was taken at home, once daily in the morning, on days 22–27
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analyses were conducted in the ITT population Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting, all outcomes are reported

Konrad 2004

Study characteristics	
Methods	Double-blind, placebo-controlled, within-participant trial of cross-over design, lasting 6 days with 2 possible drug interventions and placebo: • MPH 0.25 mg/kg (LD) • MPH 0.5 mg/kg (HD) • placebo The order of drug conditions was randomly assigned, with the restriction that higher doses should never be administered after placebo
Participants	Number of participants screened: not stated Number of participants included: 60 (44 boys, 16 girls) Number of participants followed up: 60 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined 47 (78%), inattentive 13 (22%)) Age: mean 10.8 years (SD 1.6, range 8-12) IQ: mean 97.4 (SD 10.7, range not stated) MPH-naive: 100% Ethnicity: not stated Country: Germany Setting: outpatient clinic and inpatient ward Comorbidity: ODD (n = 6; 10%), CD (n = 18; 30%), anxiety (n = 12; 18%), dyslexia (n = 19; 32%) Comedication: no Other sociodemographics: no significant differences in baseline demographics were noted between the 2 groups **Inclusion criteria** • Only children without a prior history of stimulant treatment were included in the trial protocol **Exclusion criteria** • General IQ < 80 (WISC-III)

Konrad 2004 *(Continued)*

- Any potentially confounding diagnoses such as psychosis, mania, major depression, substance abuse, pervasive developmental disorders, receptive language disorders
- Use of any kind of additional medication (including SSRIs or anticonvulsants)

Interventions	Participants were randomly assigned to "low-dose" MPH (0.25 mg/kg), "high-dose" MPH (0.5 mg/kg) and placebo Number randomised to each group: LD-MPH 60; HD-MPH 60; placebo 60 Mean MPH dosage: 9.2 mg (SD 2.2) for LD group (0.25 mg/kg), 18.4 mg (SD 5.4) for HD group (0.5 mg/kg) Administration schedule: medication was given between 7:00 am and 8:00 am for 6 days. "Cognitive testing began 60 minutes after medication ingestion and lasted 80 minutes". The order of drug conditions was randomly assigned, with the restriction that higher doses should never be administered after placebo. Thus, 11 orders were possible for the 6-day procedure as a whole, and 6 orders were possible for the sequence of the 3 neuropsychological assessments. Children were assigned in equal numbers to the 6 orders Duration of intervention: 6-day intervention, with each child receiving each intervention for 2 random days Titration period: before randomisation, 1 week of 0.3 mg/kg MPH for each participant "to ascertain tolerance" Treatment compliance: not stated

Outcomes	**ADHD symptoms**
	
	• Primary outcomes
	  ◦ German Teacher's and Parental Report on ADHD symptoms (Fremdbeurteilungsbogen für Hyperkinetische Störungen)
	  ◦ Parental questionnaire on ADHD symptoms (Diagnostiksystem für Psychische Störungen im Kindes- und Jugendalter nach ICD-10 und DSM-IV)
	  ◦ CBCL
	• Specific attentional outcome measures
	  ◦ Baseline speed: assessed with a simple reaction time task
	  ◦ Sustained attention: involved the continuous and consecutive presentation of 50 series of 12 different dot patterns (600 signals)
	  ◦ Focused attention: 4 letters were presented simultaneously, and the child was instructed to respond with the 'yes' key to 1 target letter, but only if this occurred in 1 of the relevant diagonal positions
	  ◦ Divided attention: dual task that combined optic and acoustic discrimination tasks
	  ◦ Stop-Signal paradigm: the 'go' task in our stop-signal task was a choice reaction task in which an unidentified flying object (UFO) appeared to the left or right of a fixation cross
	  ◦ Visual set-shifting: task consisted of 3 parts

Notes	Sample calculation: not stated Ethics approval: yes; "the study was approved by the Medical Ethical Committee of the University Hospital of Aachen" **Comments from trial authors** • The present trial investigated effects of day-to-day medication on attentional functions, which might differ from dose-dependent effects in the long run • "Our trial did not include a third methylphenidate dose, which would have allowed additional trial of dose-response curves for higher doses of methylphenidate" **Key conclusions of trial authors**

Konrad 2004 *(Continued)*

- Results indicate that attentional functions are influenced differentially by MPH; intensity-dimension functions are best influenced by higher doses, executive functions by moderate doses and selectivity-dimension functions by variable doses
- Divergent results from behaviour rating scales and from attentional paradigms emphasise that clinicians have to decide what constitutes an appropriate clinical response
- A more comprehensive assessment of attention may help to reveal an individually optimal dose for the treatment of attentional dysfunction

Comment from review authors

- This study focuses on aspects of attention in relation to MPH

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, before testing, all children were given 0.3 mg/kg MPH each day for ≥ 1 week to ascertain tolerance

Any withdrawals due to AEs: not stated

Funding source: German Society for the Advancement of Scientific Research (DFG grant KFO112)

Email correspondence with trial authors: January 2014. We sent an email to the trial author to request additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Within the 6-day protocol, the order of drug conditions was randomly assigned, with the restriction that higher doses should never be administered after placebo
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The active medication and placebo were prepared by a study protocol physician who was not involved in the assessment. All capsules were identical opaque gelatin capsules and were administered in a double-blinded manner. Capsules containing placebo (lactose) or 0.25 mg/kg or 0.5 mg/kg doses of methylphenidate were prepared for each participant"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	"Due to computer problems, data for four children in one task in one condition were missing. As recommended by Tabachnik and Fidell (1996), these data were replaced by the average of the group per condition" Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Konrad 2005

Study characteristics

Konrad 2005 *(Continued)*

Methods	Cross-over trial with 2 interventions: • LD-MPH and HD-MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 44 (37 boys (84%), 7 girls (16%)) Number of participants followed up: 44 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (combined type 100%) Age: mean 10.3 years (SD 1.9, range 8-12) IQ: mean 98.1 MPH-naive: not stated Ethnicity: not stated Country: Germany Setting: inpatient ward Comorbidity: not stated Comedication: no Other sociodemographics: none **Inclusion criteria** • ADHD diagnosis using multiple measures and observation in playroom, etc • Children were included only if they also met criteria for ADHD diagnosis on teachers' rating scale **Exclusion criteria** • General IQ < 80 (WISC-III) • Any pervasive developmental disorders, receptive language disorders, visual impairments • Any kind of additional medication (including SSRIs or anticonvulsants)
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of LD-MPH 0.25 mg/kg or HD-MPH 0.5 mg/kg and placebo Mean MPH dosage: 9.4 mg (SD 2.3) for the 0.25-mg/kg dose; 18.6 mg (SD 5.3) for the 0.50-mg/kg dose Administration schedule: not stated Time points: not stated Duration of each medication condition: 2 days Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: before testing, all children were given 0.30 mg/kg MPH each day for ≥ 1 week to ascertain tolerance Treatment compliance: not stated. Within the 6-day protocol, the order of drug conditions was randomly assigned, with the restriction that the high dose never occurred right after placebo

Konrad 2005 *(Continued)*

Outcomes	**ADHD symptoms** • Primary outcomes ○ German Teachers' Report on ADHD Symptoms (Fremdbeurteilungsbogen für Hyperkinetische Störungen) of the Parental Questionnaire of ADHD symptoms (Diagnostiksystem für Psychische Störungen im Kindes und Jugendalter nach ICD-10 und DSM-IV). Sum scores were calculated separately for both symptom scales (hyperactive-impulsive symptoms and inattentive symptoms)
Notes	Sample calculation: not stated Ethics approval: yes; informed parental consent was obtained for all participants, and the trial was approved by the Medical Ethical Committee of the University **Key conclusions of trial authors** • Trend tests revealed linear effects of MPH dose on Actigraph data in the test session (P = 0.02) and at school (P = 0.001), as well as on sustained attention (P value < 0.001); inhibitory control showed a quadratic dose-response curve (P value < 0.001) • Multi-variate regression analyses revealed that changes in both hyperactive-impulsive symptoms (28%) and inattentive symptoms (23%) could be explained by objective changes in motor activity. Thus, for clinical practice, it should be taken into account that behaviour ratings of ADHD symptoms seemed to be predominantly influenced by changes in motor activity. Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; before testing, all children were given 0.30 mg/kg MPH each day for ≥ 1 week to ascertain tolerance Any withdrawals due to AEs: not stated Funding source: provided through a grant from the German Research Foundation (DFG grant: KFO112–TP5) Email correspondence with trial author: July 2015. Email sent to trial author to ask for additional information, but we have received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Within the 6-day protocol, the order of drug conditions was randomly assigned, with the restriction that the high dose never was given immediately after placebo
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active medication and placebo were prepared by a trial protocol physician who was not involved in the assessment. All capsules were identical opaque gelatin capsules and were administered in a double-blind manner
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no

Konrad 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol identified

Kortekaas-Rijlaarsdam 2017

Study characteristics	
Methods	A 2 -week cross-over trial with 2 arms: • 1 week of ER-MPH (Equasym XL®) • 1 week of placebo Phases: 1
Participants	Number of participants screened: 78 Number of participants included: 65 Number of participants followed-up: 63/61 (43 boys, 20 girls) Number of withdrawals: 4 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 10.49 years (SD 1.24, range 8-13) IQ: 97.68 (SD 13.82) MPH-naive: if participants were MPH-naive, they had to go through a medication titration at their treating physician and be at a stable dose for at least 3 weeks. Ethnicity: not stated Country: the Netherlands Setting: outpatient Comorbidity: not stated Comedication: not stated Additional sociodemographics: socioeconomic status: mean 5.24 (SD 0.86) **Inclusion criteria** • Aged 8-13 years • A clinical diagnosis of ADHD confirmed by the DISC-4, Parent version • A score > 90th percentile on the Inattentive and/or Hyperactive/Impulsive scale of both parent and teacher version of the Disruptive Behavior Disorder Rating Scale • An estimated full-scale IQ of at least 70 • Treatment with MPH or indication for treatment with MPH • At least 1 year of Dutch primary school education to ensure full understanding of test instructions **Exclusion criteria** • Neurological or psychiatric disorder other than ODD, CD, learning disorder, dyslexia, anxiety disorder
Interventions	Participants were randomly assigned to 1 of 2 different medication orders of MPH and placebo Number randomised to each group: 33 received MPH-placebo, 32 received placebo-MPH

Kortekaas-Rijlaarsdam 2017 *(Continued)*

	Mean medication dosage: daily doses varied between 10 and 40 mg, with 27% of the children receiving 10 mg, 44% receiving 20 mg, 24% receiving 30 mg, and 5% receiving 40 mg Administration schedule: not stated Duration of each medication: 1 week Washout before trial initiation: 48 h Medication-free period between interventions: 48 h Titration period: mean treatment before trial initiation: 30.7 months (SD 19.1) Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SWAN, assessed on the last day of each treatment week
Notes	Sample calculation: yes, 63 Ethics approval: the current trial has been carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee. **Key conclusion of trial authors** • "Efficacy of the MPH intervention compared with placebo was confirmed by robust parent- and teacher-rated behavioral improvements with medium to large effect sizes, in line with previous studies." • "For academic accuracy and productivity, effects of MPH were small- to medium-sized and were limited to those academic subjects for which children with ADHD underperformed in comparison to TD [typically developing] children." Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes Any withdrawals due to AEs: 3 (2 not related to intervention) Funding source: unclear, but Shire was a collaborator Email correspondence with the trial authors: August and November 2021. We contacted the trial authors for information regarding risk of bias and first period data through personal email in August and November 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Our academic pharmacist, who was not in contact with any participants, was responsible for randomisation using predefined randomisation blocks to determine medication or placebo sequence"
Allocation concealment (selection bias)	Unclear risk	Nothing stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both active MPH and placebo capsules were inserted in other capsules to ensure visual equality
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers, children, parents, and teachers were blinded to the intervention

Kortekaas-Rijlaarsdam 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT on 63 of 65 participants Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All outcomes from protocol reported

Kritchman 2019

Study characteristics	
Methods	A single-dose cross-over-trial with 2 arms: • IR-MPH 0.3 mg/kg • placebo Phases: 1
Participants	Number of participants screened: no information Number of participants included: 20 (11 male, 9 female) Number of participants followed up: 20 Number of withdrawals: none Diagnosis of ADHD: not stated Age: 10.5 SD 1.99 (8-18) IQ: not measured (based on clinical assessment there was no intellectual disability) MPH-naive: not stated Ethnicity: not stated Country: Israel Setting: outpatient clinic Comorbidity: several comorbidities were exclusion criteria Comedication: not stated Additional sociodemographics: none **Inclusion criteria** • ADHD • Children aged 8-18 years **Exclusion criteria** • Known diagnosis of autistic spectrum disorder (pervasive developmental disorder), schizophrenia, bipolar disorder • Current depressive episode, eating disorder, active anxiety disorder • Current (past 6 months) substance abuse
Interventions	Participants were randomly assigned to 1 of 2 possible orders of 0.3 mg/kg IR-MPH and placebo during 2 medication sessions. Assessments were made 45 min after drug administration.

Kritchman 2019 *(Continued)*

	Number randomised to each group: not stated Mean medication dosage: not stated Administration schedule: single-dose Duration (of (each) medication): single-dose Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: NA Treatment compliance: not stated
Outcomes	**Non-serious AEs** • STAI
Notes	Sample calculation: no Ethics approval: "Study protocol and consent form were approved by both the institutional review board (0009-12-SHA) and the national review board (20120239)" **Comments from trial authors** • There are several limitations of the current trial. First and most importantly, the sample was small, and with considerable age variation **Key conclusion of trial authors** • In the present trial, there was no immediate effect of a single dose of MPH on state anxiety in ADHD paediatric patients. However, there was an incline in baseline anxiety at the second treatment visit in patients who received MPH at the first visit. Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no Any withdrawals due to AEs: no Funding source: Shalvata Mental Health Center Trial authors were contacted for information regarding risk of bias and first-period data through personal email in August and Oktober 2021, but no answer was received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Nothing stated
Allocation concealment (selection bias)	Unclear risk	Nothing stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mention of quadruple blinding, but no mention of method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mention of quadruple blinding, but no mention of method

Kritchman 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	Trial registration mention: “Patient's perspective will be measured by questionnaires assessing treatment adherence issues and patient's view regarding the use of placebo." This is not mentioned in the publication.

Leddy 2009

Study characteristics	
Methods	9-week RCT, cross-over design, with 2 interventions: • MPH • placebo Phases: 1
Participants	Number of participants screened: 154 Number of participants included: 58 (both boys and girls) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (combined (95%), hyperactive-impulsive (2%), inattentive (3%)) Age: mean not stated (range 6-12 years) IQ: > 80 MPH-naive: 19% Ethnicity: not stated Country: USA Setting: outpatient clinic (summer treatment programme) Comorbidity: ODD (52%), CD (10.5%) Comedication: no Other sociodemographics: none **Inclusion criteria** • 6-12 years of age • ADHD (DSM-IV) • IQ ≥80 • Symptoms positive for both Disruptive Behavior Disorders Rating Scale and DISC • Impairment in 2 settings (Impairment Rating Scale) **Exclusion criteria** • Seizures/serious neurological problem • Pervasive developmental disorder, schizophrenia or other psychotic disorder

Leddy 2009 *(Continued)*

	• Necessity of psychotropic medication for treatment of a comorbid disorder
Interventions	Participants were randomly assigned to different possible drug condition orders of 0.15 mg/kg MPH, 0.3 mg/kg MPH, 0.6 mg/kg MPH and placebo Mean MPH dosage: not stated Administration schedule: 3 time points Duration of each medication condition: 12 days for placebo, MPH 0.15 mg and MPH 0.3 mg; 9 days for MPH 0.6 mg Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: not stated Treatment compliance: not stated
Outcomes	**General behaviour** • Disruptive Behavior Disorders Rating Scale **Non-serious AEs** • Pittsburgh Side Effects Rating Scale
Notes	Sample calculation: not stated Ethics approval: yes **Key conclusion of trial authors** • "among children with ADHD, those with DA [dopamine]-related genotypes associated with greater brain DA signalling, DAT SLC6A3 9/9, and DRD2 A2/A2, showed a greater suppression of lunch meal intake as MPH dose increased in comparison to children with DA genotypes associated with lower brain DA signaling" Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: not stated Funding source: not declared Email correspondence with trial author: June 2014. Emailed the trial author to ask for raw data regarding side effects, data from the Disruptive Behavior Disorders Rating Scale and other data. Trial author responded to say he did not have them (Holmskov 2014 [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Drug dose varied daily on a randomized basis and included four conditions (...)"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	Unclear risk	"Double-blind"

Leddy 2009 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): unclear
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Lehmkuhl 2002

Study characteristics	
Methods	4-week, randomised, double-blind, parallel trial with 2 arms: • ER-MPH 20 mg-60 mg • placebo
Participants	Number of participants screened: 102 Number of participants included: 85 (75 boys, 10 girls) Number of participants randomly assigned: MPH 43, placebo 42 Number of participants followed up: MPH 40, placebo 38 Number of withdrawals: MPH 3, placebo 4 Diagnosis of ADHD: DSM-IV (combined (74.1%), hyperactive-impulsive (0%), inattentive (24.7%), unspecified (1.2%)) Age: mean 9.8 years (range 6-15) Mean IQ: MPH 104.8, placebo 102.7 (range 85-146) MPH-naive: 25 (29.4%) Ethnicity: German (82), other (3) Country: Germany Setting: outpatient clinic Comorbidity: ODD (51.8%), CD (9.4%), unspecified CD (3.5%), dysthymia (1.2%) Comedication: no, some of the participants were excluded from the ITT analysis due to comedication Other sociodemographics: the 2 groups were homogeneous in terms of sex distribution, school type, school class and nationality (at baseline, Barkley Side Effect Rating Scale-D ratings for disturbed sleep, nightmares, sadness, weepiness, anxiety, drowsiness and nervous twitching were far more pronounced in group 1 than in group 2. These initial differences – except for sadness – levelled out during the 4-week trial period) Additional CDs are less frequent in the group treated with medication (25 vs 30 participants), but this slight difference is not significant (Fisher's exact test, P value = 0.26)

Lehmkuhl 2002 *(Continued)*

Inclusion criteria

- DSM-IV diagnosis of ADHD, verified against the ADHD Diagnostic Checklist from the Diagnostic System for Mental Disorders in Childhood and Adolescence, as per ICD-10 and DSM-IV
- According to the class teacher, occurrence of considerable ADHD symptoms over the previous 3 school days (provided the mean score on the aggregate Fremdbeurteilungsbogen für Hyper kinetische Störunge rating scale was > 1.0)
- Patients between 6 and 16 years of age
- Attendance at an elementary or secondary school
- IQ > 85
- Body weight > 20 kg

Exclusion criteria

- Diagnosis of depression or anxiety
- Tics or Tourette's syndrome or family occurrence of tic disorder
- Pervasive developmental disorder
- Psychosis
- History of seizures or evidence on the EEG of risk of seizures
- Pre-treatment of patients with MPH or other psychostimulants up to 3 weeks before the trial
- Lack of knowledge of the German language of the patient or legal guardian

Interventions	Participants were randomly assigned to ER-MPH or placebo Mean MPH dosage: not stated Administration schedule: once daily after breakfast Duration of intervention: 4 weeks Titration period: weekly dose titration initiated after randomisation. Initially, 2 5 mg MPH/placebo tablets/d for 2 days, then 20 mg (1 ER-MPH capsule/placebo) dosage increased to 40 mg and 60 mg, depending on weight and course of symptoms. Titration up to 40 mg and 60 mg MR-MPH was possible in the 2nd and 3rd weeks of treatment, respectively (20 kg-30 kg, maximum 20 mg MR-MPH; 31 kg-50 kg, maximum 40 mg MR-MPH; < 50 kg, maximum 60 mg MR-MPH) Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Moderation of ADHD symptoms according to teacher rating on the basis of the Fremdbeurteilungsbogen für Hyperkinetische Störungen (aggregate rating scale), an ADHD response-symptom checklist for observers based on ICD-10 and DSM IV • Fremdbeurteilungsbogen für Hyper kinetische Störungen (aggregate rating scale) rated by observers, parents and teachers: rated each week (teacher rated in the morning, parents in the afternoon) • Conners' abbreviated questionnaire, teacher and parent/guardian rated: rated each week (teacher rated in the morning, parents in the afternoon) **Serious AEs** • 1 serious AE - appendicitis - occurred in the MPH group. A relationship between the AE and the medication product is considered unlikely by the trial authors **Non-serious AEs** • AEs, documented by the investigating physician each week • Vital parameters, assessed each week • Blood analyses, assessed each week • EEG, performed at screening and at the end of the trial - no remarkable changes were found during the trial

Lehmkuhl 2002 *(Continued)*

- Physical and neurological examinations, performed at screening and at the end of the trial - no remarkable changes were found during the trial
- Barkley Side Effect Rating Scale-D, rated by parents and participants, time point not stated
- Neurological psychiatric AEs were classified as follows
  - Neurological disorders (e.g. headaches, disturbed sleep)
  - Psychiatric disorders (e.g. sadness, aggressiveness)

Notes

Sample calculation: yes

Ethics approval: approved by local university ethics committees

Comments from trial authors

- Participant and parent observations differ to some extent from investigating physicians' documentation of AEs. Differences in disturbed sleep, sadness and weepiness between the 2 medication groups during week 1 thus seem more likely to be the result of initial differences and homogeneities before the start of the trial, as they improve over the course of the trial under treatment with MPH
- No clinically relevant changes on laboratory measures before and after the study

Key conclusions of trial authors

- This trial demonstrated clinically relevant and statistically significant benefits of medication over placebo during 4-week therapy
- Lehmkuhl 2002: in both the confirmatory analysis (change in teacher-rated aggregate Fremdbeurteilungsbogen für Hyper kinetische Störungen rating scale) and all secondary hypotheses of efficacy, medication 1 (MPH) always proved far more effective than medication 2 (placebo). This effect is clinically relevant. Under medication 1, however, AEs were considerably more frequent and severe
- Sinzig 2007 (in Lehmkuhl 2002): LA-MPH is effective in the treatment of ODD and aggressive behaviour, especially with milder symptoms. Expected correlation between impulsivity and aggressiveness could be confirmed

Comments from review authors

- Lemkuhl 2002 and Döpfner 2003 (in Lehmkuhl 2002): only one review author, who knew German, has extracted data from these 2 articles. 2 review authors assessed the other 3 articles and extracted data
- No one chose to withdraw, but because of administrative mistakes, comedication, etc., participants were taken out per protocol
- Unpublished data from this study were received from HB Pharma

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: yes; 2 (appendicitis and aggression)

Funding source: Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, D-58638 Iserlohn

Email correspondence with trial authors: April-May 2014. We emailed trial authors twice but received no further information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to MPH or placebo by the following 4 strata: age (6-8 years; 9-11 years; 12-16 years), sex, severity of the problem according to the teachers' evaluation (Fremdbeurteilungsbogen für Hyper kinetische Störungen; sum-score > 40 and < 40) and trial centre attended. Central randomisation was performed

Lehmkuhl 2002 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial drug (or placebo) was dispensed in packages containing a weekly supply that was blinded from medical personnel and parents
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial drug (or placebo) was dispensed in packages containing a weekly supply that was blinded from medical personnel and parents
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Lijffijt 2006

Study characteristics	
Methods	3-week, randomised, double-blind, cross-over, within-participant trial conducted to test MPH/placebo to assess correlations between measures of attention and inhibition with dopamine and norepinephrine blood levels: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 15 (13 boys, 2 girls) Number of participants followed up: 15 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (11), hyperactive-impulsive (2), inattentive (2)) Age: mean 10.74 years (range 7-13) IQ: mean 97.60 MPH-naive: 0% Ethnicity: not stated Country: the Netherlands Setting: outpatient clinic Comorbidity: anxiety (n = 6), ODD (n = 5) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD diagnosis according to DSM-IV

Lijffijt 2006 *(Continued)*

	• Participants familiar with intake of MPH for at least a year **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned to different possible drug condition orders of 0.5 mg/kg or 1.0 mg/kg MPH and placebo Mean MPH dosage: 22.67 mg Administration schedule: not stated Duration of each medication condition: 1 day Washout before trial initiation: 24 h before testing Medication-free period between interventions: no Titration period: none/duration Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS • CTRS **General behaviour** • CBCL; Teachers' Report Form **Non-serious AEs** • Paper mentioned only this: "Although side effects were minimal (a feeling of sleepiness), four participants were too fatigued after placebo or the 1.0 mg/kg dose to continue with the change task after they first completed the stop task"
Notes	Sample calculation: no Ethics approval: yes; "The study was approved by the national medical ethical committee (CCMO)" **Key conclusion of trial authors** • In children with ADHD, MPH could act primarily on inhibitory control and is not influenced by task difficulty Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, see inclusion criteria Any withdrawals due to AEs: yes, "four participants were too fatigued after placebo or the 1.0 mg/kg dose to continue with the change task after they first completed the stop task" Funding source: not declared Email correspondence with trial authors: March 2014: we sent an email to the trial author to request additional information but have received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised

Lijffijt 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts. "All participants were familiar with the intake of MPH for at least 1 year" Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Lin 2014

Study characteristics	
Methods	8-week, multi-centre (31 sites in 5 countries), double-blind, placebo-controlled, comparator (OROS-MPH), parallel trial with 3 interventions: • edivoxetine • OROS-MPH • placebo Phases • Screening • Clinical treatment • Discontinuation
Participants	Number of participants screened: 448 Number of participants included: 340 (70.6% boys, 29.4% girls) Number of participants followed up: 210 Number of withdrawals: 60 Diagnosis of ADHD: DSM-IV-TR (combined (70.9%), hyperactive-impulsive (4.1%), inattentive (25%)) Age: mean 11.6 years (range 6-17) IQ: not stated MPH-naive: all participants treated with MPH were medication-naive. 44% of placebo-treated participants, 47% of edivoxetine-treated participants in the 0.1 mg/kg/d arm and 49% of edivoxetine-treated participants in each of the 0.2 mg/kg/d and 0.3 mg/kg/d arms had used stimulants previously Ethnicity: white (72.6%), African American (not stated), Asian (not stated), Hispanic (not stated), other (not stated) Country: USA, Canada, Taiwan, Mexico and Puerto Rico

Lin 2014 *(Continued)*

	Setting: outpatient clinic Comorbidity: ODD ("less than 20%") Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD DSM-IV-TR diagnosis • > 6 years and < 17 years and 9 months of age at the time of informed consent • Diagnosis confirmed with the K-SADS-PL, and ADHD-RS-IV, score > 1.5 SD above age/sex norms and CGI-S ADHD score > 4 **Exclusion criteria** • Body weight < 18 kg or > 75 kg • History of bipolar I or II disorder, or psychosis, seizure disorder or pervasive developmental disorder; motor tics or a diagnosis of Tourette's syndrome; marked anxiety, tension or agitation sufficient to contraindicate treatment with OROS-MPH • History of EEG abnormalities • Clinically significant abnormal ECG • Serious or unstable medical illness • Any medical condition that would markedly increase sympathetic nervous system activity (e.g. catecholamine-secreting neural tumour) • Requiring daily use of medications with sympathomimetic activity (e.g. albuterol, pseudoephedrine) • Any medical condition that would be exacerbated by an increase in norepinephrine tone • Current or past history of clinically significant hypertension
Interventions	Participants were randomly assigned to 1 of 4 possible drug condition orders of 18 mg, 36 mg or 54 mg OROS-MPH and placebo Mean MPH dosage: not stated Administration schedule: 1/d Duration of each medication condition: 8 weeks Washout before trial initiation: all MPH-naive Medication-free period between interventions: no Titration period: none, initiated after randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV, parent-rated, investigator-administered and -scored: weekly, parent-rated (administered and scored by qualified personnel at the investigative site based on an interview with the parent and the participant) • CGI - ADHD - Improvement Scale • CGI-S ADHD • SNAP, 4th Edition • Conners' Comprehensive Behavior Rating Scales **Non-serious AEs** • AEs, vital signs, clinical laboratory tests (e.g. chemistry, haematology, urinalysis), physical examination and ECGs

Lin 2014 *(Continued)*

- C-SSRS: occurrence, severity and frequency of suicide-related thoughts and behaviours

Notes	Sample calculation: not stated Ethics approval: yes Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes (3 participants) Funding source: Ely Lilly Email correspondence with trial authors: April 2015. We emailed trial authors to ask for supplemental information/data but have received no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Interactive voice response system was used for randomisation and to determine which trial drug should be dispensed
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, exclusion of MPH non-responders (after randomisation)
Selective reporting (reporting bias)	High risk	Clear indication of selective reporting

Lopez 2003

Study characteristics

Methods	Cross-over trial with 3 interventions: • IR-MPH (Ritalin) • ER-MPH (Concerta) • placebo Phases: 4 • Placebo • ER-MPH (Concerta) 18 mg • ER-MPH (Concerta) 38 mg • IR-MPH (Ritalin) 20 mg

Lopez 2003 *(Continued)*

	Evaluated on day 0, randomly assigned to drug condition on days 7, 14, 21 and 28. 1 practice visit for a trial duration of 5 weeks in total
Participants	Number of participants screened: not stated Number of participants included: 36 (29 boys, 7 girls) Number of participants followed up: 36 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9 years (range 6-12) IQ: not stated MPH-naive: no Ethnicity: white (36%), African American (27%), Hispanic or other (36%) Country: USA Setting: outpatient clinic, laboratory classroom setting Co-morbidity: not stated Co-medication: not stated Other sociodemographics: none **Inclusion criteria** • Met ADHD criteria based on DISC • Parents consented to participation **Exclusion criteria** • Concurrent significant medical or psychiatric illness or substance use disorder
Interventions	Participants were randomly assigned to 1 of 24 (4 × 3 × 2 × 1) possible drug condition orders of IR-MPH (Ritalin) 20 mg, ER-MPH 18 mg (Concerta), ER-MPH 36 mg (Concerta) and placebo Mean MPH dosage: not stated Administration schedule: not stated Duration of each medication condition: 1 day Washout before trial initiation: not stated Medication-free period between interventions: on the morning following each trial period, participants resumed their regularly prescribed medication up to Thursday evening before the next trial period day on Saturday Titration period: all participants had been stabilised on an equivalent dose of 10 mg twice daily of MPH before trial entry Treatment compliance: no participants discontinued the trial prematurely
Outcomes	**ADHD symptoms** • SKAMP: observer, during each trial period **Non-serious AEs**

Lopez 2003 *(Continued)*

- Physical exam, vital signs, haematology, blood chemistries, urinalysis - screening
- AEs: self-reported, each trial period
- Vital signs: observer, measured every 2 h at each trial period
- AEs did occur in < 3% of participants exposed to each agent and dose, and 1 participant from each treatment group experienced a single mild AE that included abdominal pain, nausea and dyspnoea

Notes	Sample calculation: yes Ethics approval: yes **Comment from trial authors** • "Although single blinding of raters added to the objectivity of the observations, lack of medication blinding had both negative and positive implications. On the negative side, participants may have noticed the difference in the appearance of agents administered to them, thus producing bias …[...]... another issue to contemplate is that all participants in the study had previously been stabilised on MPH and, irrespective of blinding, may well have been able to identify when they were receiving placebo" **Key conclusion of trial authors** • Although both IR-MPH (Ritalin) and ER-MPH (Concerta) were shown to be effective, the different release profile for each formulation can result in distinct differences between effects on measures of attention and deportment **Comment from review authors** • Not able to use reported data Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, all participants were stabilised previously on MPH Any withdrawals due to AEs: no Funding source: Novartis Email correspondence with trial authors: April 2014. We received supplemental information from trial authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Order of medication assignment was determined by random assignment by a computer programme
Allocation concealment (selection bias)	Unclear risk	Participants were randomly assigned to 4 treatment periods. For purposes of this trial, with the exception of the medicating nurse, all trial personnel were blinded to the medication administered to the child
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind. For purposes of this trial, with the exception of the medicating nurse, all trial personnel were blinded to the medication administered to the child
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported. No participants discontinued the trial prematurely. Selection bias: no

Lopez 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not identified

Lufi 1997

Study characteristics	
Methods	Cross-over trial with 2 interventions: • MPH • placebo Phases: participants randomly assigned to 3 weeks of MPH, 3 weeks of placebo. No washout. Assessment at baseline and by the end of each phase
Participants	Number of participants screened: not stated Number of participants included: 20 (18 boys, 2 girls) Number of participants followed up: 20 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.23 years (± 1.62, range 7.17-12.42) IQ: > 70 MPH-naive: 100% Ethnicity: not stated Country: Israel Setting: outpatient clinic Comorbidity: none Comedication: no Other sociodemographics: none **Inclusion criteria** • IQ > 70 • Treatment-naive **Exclusion criteria** • Implicitly stated: gross physical impairment, intellectual deficits, major disease or serious psychological problems, and not receiving any psychological treatment prior to taking part in the research
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 10 mg MPH and placebo Mean MPH dosage: 10 mg/d Administration schedule: mornings Duration of each medication condition: 3 weeks

Lufi 1997 *(Continued)*

	Washout before trial initiation: all participants were treatment-naive Medication-free period between interventions: none Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CTRS **General behaviour** • Global Teacher Ratings: rating scale from 1-10 constructed specifically for this trial (assessment before ingestion of medication, after 3 weeks of 1st medication period, after 3 weeks of 2nd medication period)
Notes	Sample calculation: not stated Ethics approval: not stated **Comment from trial authors** • Strong placebo effect **Key conclusions of trial authors** • MPH improved classroom behaviour as compared with no treatment • Placebo influence had almost the same effect as medication • Neither of these treatments significantly improved cognitive functioning and personality characteristics of the child with ADHD Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: September 2013. We obtained supplemental information/data from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Everyone involved in the assessment phase ...was blind to the type of medication..." All medications (both placebo and MPH) were given in identical capsules to prevent recognition of the true medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...the parents, the teacher, the child and the psychologist who tested the child did not know what kind of medication the child was taking..."

Lufi 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Lufi 2007

Study characteristics	
Methods	6-week, randomised, double-blind, placebo-controlled, cross-over trial conducted to detect the effects of MPH on co-ordination and handwriting: • MPH • placebo
Participants	Number of participants screened: 19 Number of participants included: 19 (12 boys, 7 girls) Number of participants followed up: 19 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.51 years (range 7.08-13.83) IQ: > 70 MPH-naive: 0% Ethnicity: not stated Country: Israel Setting: outpatient clinic Comorbidity: not stated Comedication: no Other sociodemographics: "Participants were from a medium level social-economic status" **Inclusion criteria** • Not stated **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Mean MPH dosage: 0.4 mg/kg Administration schedule: not stated Duration of each medication condition: 3 weeks

Lufi 2007 *(Continued)*

	Washout before trial initiation: no Medication-free period between interventions: yes Titration period: not stated Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Conners' Abbreviated Symptom Questionnaire (teacher): assessed at baseline, weeks 3 and 6 **General behaviour** • Achenbach's Teacher Report: assessed at baseline, weeks 3 and 6
Notes	Sample calculation: not stated Ethics approval: not stated **Comments from trial authors (limitations)** • Limited group of participants • Use of only 1 dosage level **Key conclusions of trial authors** • Results show that MPH improved some cognitive functions of eye-hand co-ordination slightly better than placebo • Behaviour variables assessed by teachers improved only under the influence of MPH Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: unclear Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: October 2013. We obtained additional information on IQ from the first trial author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized"
Allocation concealment (selection bias)	Unclear risk	"The study was designed as a double-blind, randomized, crossover, placebo-control procedure"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Each participant was given exactly 0.4 mg/kg of MPH in special capsules of MPH and a placebo to avoid recognition of the medication"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	No dropouts

Lufi 2007 *(Continued)*

All outcomes		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Manos 1999

Study characteristics	
Methods	4-week, double-blind titration, placebo-controlled protocol. Cross-over trial with 2 interventions in 4 doses: • MPH 5 mg × 2 daily • MPH 10 mg × 2 daily • MPH 15 mg × 2 daily • placebo × 2 daily Phases • Cross-over trial with MAS (Adderall) and MPH. First phase was not blinded. (The child's paediatrician or family physician determined whether MPH or MAS (Adderall) should be prescribed; criteria were the physician's familiarity with the agent and whether he or she wanted the participant to receive a single dose (MAS) or a twice-daily dose (MPH) of medication treatment for ADHD.) Second phase: a 1-of-3 medication dose sequence was randomly assigned. 15 mg MPH was always given after 10 mg MPH • 42 of the 117 participants receiving MPH were matched, with 42 receiving MAS (Adderall) • Best dose was compared with placebo. Best dose was assigned by consensus of a clinical child psychologist and a board-certified child and adolescent psychiatrist before the medication blind was broken Manos 1999: "7 youths given MPH and 4 given Adderall [MAS] did not receive the 15 mg dose of medication. The decision to forego the 15 mg condition was based on the paediatrician's assessment that the child was too young or underweight for this high dose and our assessment that the best dose had already been achieved at a lower dose"
Participants	Number of participants screened: 195 Number of participants included: 177. (33 boys, 9 girls) Number of participants followed up: 134 Number of withdrawals: 43 Diagnosis of ADHD: DSM-IV (combined (55%), inattentive (45%)) Age: mean 10.1 years (SD not stated, range 5-17) IQ: > 70 MPH-naive: not stated Ethnicity: white (93%), African American (7%), Asian (0%), Hispanic (0%), others (0%) Country: USA Setting: outpatient clinic Comorbidity: no significant comorbid disorders. Although no formal comorbidity data are available, it appears that psychiatric comorbidity was modest in this cohort

Manos 1999 *(Continued)*

Comedication: not stated

Sociodemographics: predominantly well educated

Manos 1999 and Faraone 2002 (secondary reference under Manos 1999): 42 were participants matched to the MAS (Adderall) group in order of diagnostic category, age and sex. Only these 42 of 117 receiving MPH were compared with the MAS (Adderall) group

Findling 2001a (secondary reference under Manos 1999): 195 youths entered the trial. Data for a best dose were provided for 177 participants: 111 in the MPH group, 66 in the MAS group

Diagnosis of ADHD: inattentive (47%), combined (53%). Inattentive subtype is over-represented in the older age group

Age group: 4-8 years (mean 6.35) 69 (57 boys); 8-11 years (mean 9.47) 56 (45 boys); 11-17.59 years (mean 13.64) 52 (41 boys)

Other sociodemographics: no significant differences in baseline demographics were noted between groups

Findling 2001b (secondary reference under Manos 1999):

Number of participants included: 195

Number of participants completed: 137: MPH 82, MAS (Adderall) 55

Diagnosis of ADHD: DSM-IV (combined (57%), inattentive (43%))

Age: mean 10 years (SD not stated, range 4-17)

IQ: > 70

Sex: 66 boys, 16 girls

Ethnicity: white (84%), African American (6%), other (10%)

Country: USA

Comorbidity: without significant comorbid disorders

Comedication: possible, but not recorded

Sociodemographics: predominantly well educated. No differences in sex, ethnicity or ADHD subtype were found between MPH and MAS (Adderall) groups. No participants had a history of hypertension, hypotension or clinically significant cardiovascular disease

Inclusion criteria

- "All children diagnosed with ADHD met full DSM-IV diagnostic criteria for this disorder. The criteria are (1) presence of at least six symptoms for inattention and/or at least six symptoms for hyperactivity/impulsivity; (2) symptoms significantly interfering with functioning at home and at school as noted during structured or semi structured clinical interviews with the Computerized Diagnostic Interview for Children (CDISC); (3) symptom severity on broad-band [i.e. Conners' Abbreviated Symptoms Questionnaire (Conners, 1969)] and narrow-band [e.g. ADHD-RS (DuPaul, 1991)] rating scales at threshold or above (i.e. rated 2 or 3); (4) multiple raters (e.g. parents, teachers) agreed to the presence of the symptoms; and (5) empirical comparison with norms indicating at least a 1/5 SD cutoff on at least rating scale. It should be noted that in identifying the presence of symptoms, behaviours across informants were not pooled observations. Behaviours were considered significant only if two informants agreed to the presence of the symptom on rating scales or in interviews" (Findling 2001a, secondary reference under Manos 1999)

Exclusion criteria

Manos 1999 *(Continued)*

	• No patients were excluded from the trial per se
Interventions	Participants were randomly assigned to different orders of 5 mg, 10 mg or 15 mg MPH and placebo Mean MPH dosage: best dose 9.1 mg-10.4 mg Administration schedule: morning (at 8.00 am) and noon Duration of each medication condition: 1 week Washout before trial initiation: none Titration period: none Treatment compliance: 11 terminated because of AEs
Outcomes	**ADHD symptoms** Findling 2001a (secondary reference under Manos 1999): compared treatment for children and adolescents and weight-adjusted dosing of MPH. Measurement instruments include the following • ADHD-RS • Abbreviated Symptoms Questionnaire (Conners) • Composite Rating and School Situations Questionnaire Revised, parent and teacher. Composite Rating, also observer-rated. Rating every 7th day of each week's dose and baseline. Best dose evaluated and compared with placebo and MAS (Adderall) Best dose based only on Abbreviated Symptoms Questionnaire - Teacher. Does not separate MPH and MAS in tables **Non-serious AEs** • Side Effects Behavior Monitoring Scale by parents every week (symptoms were considered problematic if parents rated them as ≥ 5) • BP and pulse every week Findling 2001b (secondary reference under Manos 1999) • BP and pulse
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusions of trial authors** 1. Manos 1999: both MPH and MAS have been shown to be effective treatments for children with ADHD 2. Faraone 2002 (secondary reference under Manos 1999): the present report extends this prior work by applying drug–placebo response curve methods to the data reported by Manos 1999. Results show that the efficacy of MAS and MPH in improving functioning is seen throughout the full range of improvement scores. Both drugs prevent worsening and, for most patients, lead to improvements that are well into the normal range 3. Findling 2001a (secondary reference under Manos 1999): data suggest that psychostimulants are equally effective in treating children and adolescents with ADHD. Adolescents with ADHD may not necessarily require more medication than younger children to achieve a similar therapeutic response 4. Findling 2001b (secondary reference under Manos 1999): short-term cardiovascular effects of both MAS and MPH were modest. No participants experienced any clinically significant change in these cardiovascular measures during the course of this brief trial Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; 15 youths in the MAS sample had been tried on MPH before enrolment in this medication trial. Because of lack of response or serious side effects, these children discontinued use of

Manos 1999 *(Continued)*

	MPH. A total of 37% of the MAS sample subsequently was composed of children who had unsuccessfully used MPH but successfully responded to MAS Any withdrawals due to AEs: yes; Findling 2001a (11/195) (secondary reference under Manos 1999), due to multiple AEs Funding source: in part by from Shire Pharmaceutical Development Incorporated to Dr. Faraone Email correspondence with trial authors: April 2014. Emailed trial authors twice to request additional data but have received no answer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	First phase not blinded. MPH is a selected group
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Clinician, teacher and parent were blinded only to dose, not to medication
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinician, teacher and parent were blinded only to dose, not to medication
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only best dose compared with placebo. Findling (Abbreviated Symptoms Questionnaire) + 30 participants. Of 43 participants with < 4 weeks of data, 30 had only 3 weeks of data because physicians considered them too young or too small to receive 15 mg before initiating protocol Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Martins 2004

Study characteristics

Methods	4-week, double-blind, randomised, parallel trial with 2 interventions: • MPH group: MPH, 7 days a week • placebo group: MPH Monday through Friday, and placebo on weekends
Participants	Number of participants screened: not stated Number of participants included: 40 (all boys) Number of participants followed up: 38 Number of withdrawals: 2 (receiving MPH) Diagnosis of ADHD: DSM-IV (combined (92.5%))

Martins 2004 *(Continued)*

Age: mean MPH 9 years (SD 2.2, range 6-14), placebo 9.6 years (SD 2.8, range 6-14)

IQ: mean, MPH 97.3, placebo 93.5

MPH-naive: not stated

Ethnicity: European-Brazilian: MPH 16 (76.2%), placebo 15 (78.9%)

Country: Brazil

Setting: outpatient clinic

Comorbidity: yes; conduct or ODD (MPH 57.2%, placebo 57.9%)

Comedication: not stated, no psychiatric medication

Other sociodemographics: monthly family income was calculated according to the following formula: total monthly income received by all members of the family (expressed in number of minimum wages) divided by the number of people in the family. A value lower than 0.7 (approximately USD 68 per family member per month) is usually an indicator of poverty in Brazil. MPH 3.3, placebo 2.4. No significant differences in baseline demographics were noted between the 2 groups

Inclusion criteria

- ADHD diagnosis according to DSM-IV criteria
- Between 6 and 14 years of age
- Male
- Education level between 1st and 8th elementary grades

Exclusion criteria

- Presence of significant neurological or clinical disease
- Presence of bipolar disorder or substance abuse/dependence disorder
- Use of any psychiatric medication in the past 6 months, including MPH
- Estimated IQ < 70

Interventions	Participants were randomly assigned to MPH 7 d/week or to MPH on weekdays and placebo on weekends Number randomised to each group: MPH 21, placebo 19 Mean MPH dosage: initial dose of MPH was 0.3 mg/kg/d the 1st week. Dose was raised to 0.5 mg/kg/d the 2nd week and to 0.70 mg/kg/d the 3rd and 4th weeks Administration schedule: twice/d: breakfast and lunch Duration of intervention: 4 weeks Titration period: none Treatment compliance: only 7 of 160 blister packs were returned with unused pills

Outcomes	**ADHD symptoms**
	
	• 10-item CARS (Conners 1985). Rated every Monday after school by both teachers and parents
	
	Serious AEs
	
	• Barkley Side Effect Rating Scale
	  ○ Number of AEs reported
	  ○ Mean severity of reported AEs
	
	(Completed only by parents for assessment of side effects on weekends)

Martins 2004 *(Continued)*

Notes	Sample calculation: no Ethics approval: approved by the Ethical Committee of the Hospital de Clínicas de Porto Alegre (HCPA) (approved as an International Review Board (IRB) by the Office for Human Research Protections, USA) **Comments from trial authors** • Context established by the home setting on the weekend may have created conditions in which the effects of MPH were minimal or insignificant, because children may have been involved in play activities much of the time • It is reasonable to suggest that during the weekend, when networks related to ADHD neurobiology might be demanded less often, differences between drug and placebo would be more difficult to detect • It is possible that parental tolerance of ADHD symptoms on weekends might be greater than on weekdays. Our findings may not be generalisable to female patients **Key conclusion of trial authors** • "Our findings suggest that weekend holidays during MPH administration reduce the side effects of insomnia and appetite suppression without causing a significant increase in ADHD symptoms, on weekends or on the first day of school after the weekend (Monday)" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: MPH and placebo pills were supplied by Novartis Pharmaceuticals (São Paulo, Brazil) at no cost and without restrictions. No additional funding was requested or received from Novartis or any other commercial entity Email correspondence with trial authors: we have contacted trial authors several times to ask for additional information about data, but we have received no data from this trial that we can use

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, double-blind, parallel-group design was used. Participants were randomly assigned to 1 of 2 groups, according to a computer-derived algorithm (EPIINFO.06)
Allocation concealment (selection bias)	Low risk	Computer-derived algorithm
Blinding of participants and personnel (performance bias) All outcomes	Low risk	MPH and placebo pills were of the same shape and colour
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind. No other information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Measured adherence to protocol by assessing returned, unopened blister packs. None of the findings in the analyses was significantly affected by the 2 participants (they did not follow the protocol as stated by researchers) from the MPH group who did not receive a few doses appropriately on weekends or on Monday. Some teacher ratings (8.5%) were missed because of the child's absence from school on a specific day of evaluation or because of a school holiday

Martins 2004 *(Continued)*

		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of reporting bias

Matthijssen 2019

Study characteristics	
Methods	A 7-week parallel discontinuation trial with 2 arms: • continuation of ER-MPH treatment • gradual withdrawal over 3 weeks to 4 weeks of placebo Phases: 1
Participants	Number of participants screened: 530 Number of participants included: 104 Number of participants followed-up: 94 (73 (77.7%) boys, 21 (22.3%) girls) Number of withdrawals: 25, 10 of whom did not receive allocated intervention Diagnosis of ADHD: no diagnosis by specified diagnostic tool required Age: MPH (continuation): mean 13.8 years (SD 2.2), placebo (discontinuation): mean 13.6 years (SD 2.2, range 8 years-17 years) IQ: IQ < 70 was an exclusion criterion MPH-naive: 0% (discontinuation trial) Ethnicity: European white ethnicity (MPH: n = 47 (100%), placebo: n = 46 (97.9%)) Country: the Netherlands Setting: outpatient Comorbidity: not stated Comedication: both medication and interventions used before trial initiation was allowed during the trial, as long as it did not fall within the exclusion criteria. 35 received comedication; of these: 32 received melatonin, 4 received hay fever medication, 2 received asthma medication, 1 received antipsychotic medication Additional sociodemographics: none **Inclusion criteria** • Children between the age of 8-18, any ethnicity or cultural background • Using MPH as prescribed in clinical practice in any dosage or form for ≥ 2 years. If a child had stopped the medication during, for instance, a weekend or a school holiday, they could still participate if the period of not using MPH had not exceeded 2 continuous months during the past 2 years • During the past 4 weeks, participants should have used ER-MPH at either 36 mg or 54 mg/d. Children who were originally not using 36 or 54 mg/d of ER-MPH could switch to one of these dosages, whichever was the closest to the dosage they were already using, for at least 4 weeks to allow them to participate in the trial. • Children with an IQ > 70 (based on a previous IQ test or attending regular education)

Matthijssen 2019 *(Continued)*

- Parents (or the legal guardian) and children (≥ 12 years) have provided informed consent to participate in the trial

Exclusion criteria

- The intent to start new psychosocial or pharmacological therapies during the trial period
- Inability on the part of the child or the parents to understand or comply with the trial protocol
- Presence of a severe medical or psychiatric condition the treatment of which would have interfered with the trial
- Participants could not start during or 7 weeks before the summer vacation period, to allow for investigating discontinuation effects during regular school attendance.

Interventions	Participants were randomly assigned to 2 different groups, 1 continued either 36 or 54 mg of ER-MPH for 7 weeks, the other discontinued medication by withdrawing gradually over 3 weeks period (week 1: 36 mg/d, week 2: 27 mg/d, week 3: 18 mg/d) followed by 4 weeks of complete placebo Number randomised to each group: discontinuation group (placebo) = 53, continuation group (ER-MPH group) = 51 Mean medication dosage: continuation group at baseline: 0.93 mg/kg/d (SD 0.29) Administration schedule: participants used the same schedule for taking their medication as they did before the trial (e.g. daily or with weekend stops). Duration (of (each) medication): placebo group: 36 mg/d during week 1, 27 mg/d during week 2, 18 mg/d during week 3, and placebo for weeks 4 through 7. MPH group: 7 weeks of MPH Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS • CTRS-R:S **Serious AEs** • Spontaneous reporting to investigator by child or parents **General behaviour** • Strength and Difficulties Questionnaire • Retrospective Modified Overt Aggression Scale (R-MOAS) **Quality of life** • The parent- and child-rated Revised questionnaire for Children and adolescents to record health-related quality of life (KINDL-R) **Non-serious AEs** • Spontaneous reporting to investigator by child or parents
Notes	Sample calculation: yes, 120 (60 in each arm); “With this sample size, it is possible to detect an effect size (Cohen’sd) of 0.251 with a power of 0.80 and alpha of 0.05, as calculated with the program G*Power, version 3.1.” Sample size calculation was not met Ethics approval: the trial was approved by national and local institutional review board committees. **Comments from trial authors** • “We cannot exclude the possibility that the differential impact of discontinuation on inattention and hyperactivity impulsivity symptoms according to investigator and teacher ratings were due to limited statistical power"

Matthijssen 2019 *(Continued)*

- "Those who declined to participate may have felt more confident that the medication was helpful and may therefore have been unwilling to risk being assigned to the placebo condition"
- "we lack evaluations of participants prior to the discontinuation trial"
- "The apparent absence of ongoing effectiveness in older youths may partially be explained by the lessened sensitivity of investigator or teacher ratings of ADHD symptoms, as older youths are less likely than younger children to display overt hyperactivity"

Key conclusion of trial authors

- "[…]Our study suggests that methylphenidate is still an effective treatment after 2 years of use, even if the treatment effect size appeared rather small."
- "[…]the fact that most participants in our study did not experience significant worsening after discontinuation of methylphenidate supports guideline recommendations to periodically assess whether there is a continued need for methylphenidate treatment[…]"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: only children and adolescents who had used MPH for ≥ 2 years were included

Any withdrawals due to AEs: yes, 1

Funding source: The Netherlands Organization for Health Research and development (ZonMw, grant 836011014)

Email correspondence with trial authors: August and October 2021. We received information regarding risk of bias through personal email correspondence with the trial authors in August and October 2021 (Storm 2021d [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial pharmacy dispensed trial medication for either continued active medication or discontinuation according to 2 separate computer-generated randomisation lists, for each dosage. A block-randomisation of 6 was used to ensure even groups.
Allocation concealment (selection bias)	Low risk	Placebo capsules matched to medication. Dispensed by trial pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial medication consisted of an over-encapsulation of MPH in an osmotic-controlled release oral delivery system (18 mg, 27 mg, 36 mg, and 54 mg). The over-encapsulation was backfilled with lactose monohydrate for blinding purposes. Matching placebo capsules contained only the filler.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not told the randomly determined treatment allocation of the trial participants. To ensure blinding the outcome assessors did not rate AEs and families were instructed not to discuss AEs with the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Analyses were conducted on the full data set, which included all participants who received at least 1 dose of the trial drug. In those who had withdrawn from the trial, we used ratings that were obtained at the time of trial termination." "A chi-square test was used to analyse whether there was a difference between the two groups in the number of participants prematurely withdrawing from the trial." Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no

Matthijssen 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	No indication of selective reporting. The following outcomes will be part of separate reports: Barkley Side Effect Rating scale (BSERS), Family atmosphere questions, Parental Frustrations Questionnaire (PFQ), Child Depression Inventory (CDI)

McBride 1988a

Study characteristics	
Methods	Individual, double-blind, cross-over trial for 4 weeks with 2 interventions: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 73 Number of participants followed up: 70 (53 boys, 17 girls) Number of withdrawals: 3 Diagnosis of ADHD: DSM-III (77% met the criteria for ADD-H) Mean age: MPH responders 8.5 (SD not stated), MPH non-responders 9.5 (SD not stated). Range 6-17 years Mean IQ: MPH responders 102 (SD 21), MPH non-responders 89 (SD 23) MPH-naive: 71 (97%) Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: carbamazepine or phenytoin or valproic acid or mephobarbital (6.4 receiving a combination of these drugs). Clonidine (n = 1) Sociodemographics: no information **Inclusion criteria** • Referred because the child's academic performance was below that expected on the basis of his abilities, as documented by psychological testing, or because his behavioural dysfunction was interfering with self-image and socialisation, or for both reasons • 6-17 years of age • No child was excluded from the trial on the basis of low intelligence, history of seizures or concurrent medication **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg MPH and placebo. MPH was rounded to the nearest 1.25 mg Mean MPH dosage: no information, but mean dose during follow-up was 0.36 mg/kg/dose

McBride 1988a *(Continued)*

Administration schedule: morning and 4 h later

Duration of each medication condition: 2 weeks

Washout before trial initiation: none

Medication-free period between interventions: none

Titration period: none

Treatment compliance: no information

Outcomes

ADHD symptoms

- Abbreviated Conners' Teacher and Parent Questionnaire
- Parent Questionnaires was rated at the end of each weekend and at the end of each school week. Teacher Questionnaires were filled out at the end of the week

Serious AEs

- No serious side effects during the trial

Non-serious AEs

- No information about how data on side effects were obtained

None of the parents of responders who had experienced side effects during the trial thought the effects were significant enough that they should not treat their child with MPH, and no side effects other than appetite suppression continued during regular therapy after the trial

Follow-up 6 months after: n = 33. 15 had no change in weight curves. 1 gained 7 kg beyond his original percentile

Notes

Sample calculation: no information

Ethics approval: no information

Comments from trial authors

- Participants in this study were not a randomly selected group of children with ADD but, rather, a referral population already screened by their school psychologists and primary care physicians
- Individual children with differing absorption, metabolism or underlying neurochemical abnormality may have different response thresholds, and potential responders may have been overlooked because they did not consistently try a higher dose
- 15% of children with ADD in this study were adopted
- The finding that non-responders were older may reflect the development of secondary characteristics such as decreased motivation and poor study habits in long-term ADD -symptoms not easily reversed during a short trial
- A problem inherent in this trial, as in an open trial, is dependence on the observations of teachers and parents who have variable observational skills, variable tolerance for symptoms of ADD and different perspectives on medication
- Lower Conners' scores may be explained by the fact that many characteristics rated on Conners' questionnaires reflect hyperactivity, and some of these children were more inattentive than hyperactive

Key conclusions of trial authors

- 51 (of 70) children showed improvement during 1 of the 2-week periods, and that period corresponded with MPH therapy in 48
- 6 of the 22 who did not respond to MPH experienced worsening of function while taking the drug. No serious side effects were reported during the trial

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

McBride 1988a *(Continued)*

	Any withdrawals due to AEs: no Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The pharmacist labelled the 2 sets of capsules as “Medicine A” and “Medicine B” in either order by coin flip for the first 22 trials, and then by using a random numbers table
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The manner of labelling was sealed by the pharmacist in an envelope that was not opened until the trial had ended and findings had been discussed with the parents
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Objectivity was lessened for a few parents because the decreased appetite associated with MPH led them to suspect which capsules contained the drug
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the few trials for which 1-3 of 10 items on Conners' questionnaire had not been scores, the score was prorated based on 30 points maximum Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

McCracken 2016

Study characteristics

Methods	An 8-week parallel-trial with 3 arms: • weeks 1-4: placebo; weeks 5-8: placebo + ER-D-MPH • weeks 1-4: IR-guanfacine; weeks 5-8: IR-guanfacine + placebo • weeks 1-4: IR-guanfacine; weeks 5-8: IR-guanfacine + ER-d-MPH Phases: 2
Participants	Number of participants screened: 323 Number of participants included: 212; 5 withdrew, before receiving trial drug, leaving 207 participants (142 (68%) boys, 65, (32%) girls) Number of participants followed-up: 182 (ER-d-MPH = 61, IR-guanfacine = 60, IR-guanfacine+ER-d-MPH = 61) Number of withdrawals: 30 (including 5 before receiving trial drug) (ER-d-MPH = 9, IR-guanfacine = 11, IR-guanfacine+ER-d-MPH = 10) Diagnosis of ADHD: DSM-IV (information available for 202 participants: 105 (51%) combined, 5 (2%) hyperactive/impulsive, 92 (44%) inattentive)

McCracken 2016 *(Continued)*

	Age: mean 10.0 years (SD2.1, range 7-14) IQ: mean 102.4 (SD 13.5) MPH-naive: not stated Ethnicity: Hispanic (n = 44, 21.3%). Race reported: white (n = 143, 69%), African American (n = 36, 17%), Asian, Pacific Islander (n = 16, 8%), other (n = 12, 6%) Country: USA Setting: not stated Comorbidity: ODD 68 (33%) Comedication: CNS medication not allowed Additional Sociodemographics: none **Inclusion criteria** • 7-14 years • Diagnosis of DSM-IV ADHD by K-SADS-PL and confirmed by clinical interview • CGI-S score of at least 4 for ADHD • Resided with primary carer for at least 6 months prior to trial entry **Exclusion criteria** • History of autism, pervasive developmental disorder, chronic tic disorder, psychosis, or bipolar disorder • Current major depression or panic disorder • SBP or DBP at screening > 95th percentile or < 5th percentile for age and BMI • Any medical condition that might make stimulant or alpha agonist therapy medically inadvisable • Need for chronic use of other medications with CNS effects • Pregnant, breastfeeding, or beyond menarche and has a positive urine pregnancy test • History of structural heart defects, syncope, or fainting while exercising • Clinically significant cardiac abnormality as determined by ECG at trial entry • Intellectual disability as determined by clinical functional assessment and an IQ estimate of < 70 based on Wechsler Adult Intelligence Scale (WAIS) subtests
Interventions	Participants were randomly assigned to 3 different treatment sequences covering the periods baseline, weeks 1-4, and weeks 5-8 as follows: • sequence 1: placebo (weeks 1-4) - placebo + ER-d-MPH (weeks 5-8) • sequence 2: IR-guanfacine (weeks 1-4) - IR-guanfacine + placebo (weeks 5-8) • sequence 3: IR-guanfacine (weeks 1-4) - IR-guanfacine + ER-d-MPH (weeks 5-8) ER-d-MPH (sequence 1 and 3) was given to participants < 25 kg at 5 mg on week 5, 10 mg to participants > 25 kg with an increase of 5 mg/week until week 7 IR-guanfacine (sequence 2 and 3) was initiated at 0.5 mg then increased to 1 mg and increased by 0.5 mg each week until week 3. If Clinical-Global Impression—Improvement ratings were either 1 or 2, no dose increases were made Placebo was mirrored Number randomised to each group: 70 ER-d-MPH, 71 IR-guanfacine, 71 IR-guanfacine + ER-d-MPH Mean medication dosage: mean final (week 8) daily doses of: • ER-d-MPH: 16.0 mg (± 3.9) • IR-guanfacine: 2.2 mg (± 0.7)

McCracken 2016 *(Continued)*

- IR-guanfacine + ER-d-MPH: IR-guanfacine 2.4 mg (± 0.6), ER-d-MPH 15.1 mg (± 4.8)

Mean mg/kg daily doses of guanfacine were 0.06 (± 0.03) mg/kg/d for both guanfacine groups

Administration schedule: twice daily

- ER-d-MPH: once daily for placebo, once daily for ER-d-MPH
- IR-guanfacine: twice daily for IR-guanfacine, once daily for placebo
- IR-guanfacine + ER-d-MPH: twice daily for IR-guanfacine, once for ER-d-MPH
- IR-guanfacine and IR-guanfacine placebo; twice daily, ER-d-MPH and ER-d-MPH placebo; once daily

Duration (of (each) medication): IR-guanfacine 8 weeks, ER-d-MPH 4 weeks, placebo (sequence 2) 4 weeks, placebo (sequence 1) 8 weeks

Washout before trial initiation: not stated

Medication-free period between interventions: no

Treatment compliance: not stated

Outcomes

ADHD symptoms

- ADHD-RS-IV

Serious AE**s**

- Spontaneous reporting

Non-serious AEs

- Assessed by a modification of the Physical Symptoms Checklist 48
- Open-ended clinician inquiry
- Vital signs
- ECG
- AE recordings

Notes

Sample calculation: not stated

Ethics approval: yes; “All study procedures were approved by the University of California, Los Angeles (UCLA) institutional review board and were overseen by a data safety and monitoring board."

Comments from trial authors

- “[…] We note that this differs by degree from a traditional 3-arm longitudinal design with each arm receiving a specific treatment over the entire study period, but this is a hybrid sequential within-/between subjects design. This design arose from the clinical and ethical need to keep trial length and placebo-only exposure to a minimum. However, the within-subject component also increases statistical power.”
- “Larger group sizes would have enabled more conclusive tests of treatment differences.”
- “Our study design began with guanfacine first, with the addition of a stimulant second, which may yield differences in comparison to those study designs adding guanfacine to ongoing stimulants, and, like any sequential design, may blur the timing of individual treatment effects when combined.”

Key conclusion of trial authors

- “ The clinical implications of our results suggest that combination of DMPH and GUAN over 8 weeks is associated with substantial clinical benefits on ADHD symptoms in the short term, and is more successful at approaching contemporary goals for ADHD treatment.”
- “Our results also support the acceptable safety profile of COMB treatment.”

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no

Any withdrawals due to AEs: yes, IR-guanfacine =1, Er-d-MPH 1, IR-guanfacine + ER-d-MPH = 2

McCracken 2016 *(Continued)*

Funding source: NIMH Research Center grant P50MH077248, “Translational Research to Enhance Cognitive Control” (JTM)

Email correspondence with trial authors: September 2021. We received supplemental information regarding risk of bias assessment through personal email correspondence with the trial authors in September 2021 (Storm 2021e [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised based on a computer-generated program to yield a 1:1:1 allocation to the 3 different treatment sequences
Allocation concealment (selection bias)	Low risk	Dosing clinicians were blinded to group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	At the time of submission of a participant found to be eligible into the centralised database, the program generated the treatment sequence assignment, which was then sent electronically to the Research Pharmacist only and was not shared with any trial staff. All staff involved in clinical assignments remained blinded, as were participants. Participants were blinded by use of uniform over-encapsulation of drug or placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A blinded clinician without knowledge of AEs completed the CGI-S and ADHD-RS-IV at baseline and at the end of each within-participant condition or last visit based on parent, participant and other available data.
Incomplete outcome data (attrition bias) All outcomes	High risk	Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, exclusion of 1 non-responder
Selective reporting (reporting bias)	Low risk	No indication of selective reporting. The secondary outcome Tests of Academic Performance is set in the second phase of the trial. Analysis has not yet been completed or published.

McGough 2006

Study characteristics

Methods	Phase II, randomised, double-blind, placebo-controlled, laboratory-classroom, cross-over trial with a lead-in open-label dose-optimisation phase: • MPH transdermal system • placebo
Participants	Number of participants screened: 93 entered the open-label dose-optimisation phase Number of participants included: 80 (from ITT: 57 boys (72%), 22 girls (28%)) Number of participants followed up: 79 Number of withdrawals: 1 participant discontinued because of "protocol violation" Diagnosis of ADHD: DSM-IV-R (combined 62 (79%), hyperactive-impulsive 4 (5%), inattentive 13 (17%)) Age: mean 9.1 years (SD 1.7, range 6-12)

McGough 2006 *(Continued)*

	IQ: > 70 MPH-naive: 37% Ethnicity: white 55 (70%), African American 8 (10%), Asian 2 (3%), other 14 (18%) Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: no Other sociodemographics: none **Inclusion criteria** • 6 to-12 years of age inclusive • ADHD DSM-IV diagnosis using Kiddie Schedule for Affective Disorders and Schizophrenia and psychiatric assessment • ADHD-RS score ≥ 26 at baseline/unmedicated • Normal laboratory parameters and vital signs including ECG • Either known to be responsive to stimulants or-naive to stimulant treatment **Exclusion criteria** • Comorbid psychiatric diagnosis (apart from ODD) • History of seizures • History of tic disorders • Intellectual disability • Any illness or skin disorder that might jeopardise safety or compromise trial assessments • No clonidine, atomoxetine, antidepressants, investigational medications, hepatic P450 enzyme-altering agents, medications with CNS effects, sedatives, anxiolytics or antipsychotics within the 30 days before screening
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Number randomised to each group: cross-over, 42 MPH/placebo, 38 placebo/MPH Mean MPH dosage: "At the end of the dose optimization phase of the study, the majority of patients (78%) were optimized to either the 16 mg or 20 mg dosage strengths" Administration schedule: once daily Duration of each medication condition: 1 week Washout before trial initiation: "up to 28 days" Medication-free period between interventions: 4:00 pm to 7:00 am the next day (15 h) Titration period: 5-week dose-optimisation phase before randomisation Treatment compliance: "During the laboratory classroom period, 97% and 96% of participants were compliant with [methylphenidate transdermal system] MTS and placebo treatments respectively"

Outcomes	**ADHD symptoms**
	
	• Primary outcome
	  ◦ SKAMP at multiple time points: pre-dose and 2, 3, 4, 5, 6, 7.5, 9. 10.5 and 12 h post-dose
	  ◦ ADHD-RS-IV (administered at each visit)

McGough 2006 *(Continued)*

- CPRS-R-S (Conners 1997a). Completed at 11:00 am and 3:00 pm on the Sunday before the first visit and subsequently, before each visit to the centre

"The mean values of the CPRS-R over the 11:00 am and 3:00 pm time points were used in the analysis"

Non-serious adverse outcomes

- Vital signs, BP, pulse, oral temperature, respiratory rate, height, weight, laboratory measures, physical examination, dermal evaluation

Notes	Sample calculation: yes Ethics approval: yes **Key conclusions of trial authors** • Treatment with MPH transdermal system resulted in statistically significant improvement in all efficacy measures • Time course and therapeutic effects of MPH transdermal system suggest that this novel MPH delivery system provides efficacious once-daily treatment for ADHD Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; "Participants were either known to be responsive to stimulants or-naive to stimulant treatment". Participants were only randomised after the open-label phase if they reached acceptable efficacy without unacceptable AEs. Any withdrawals due to AEs: no Funding source: Shire US Inc Email correspondence with trial authors: June 2014. We obtained supplemental information regarding risk of bias. Additional data were not available (Ramstad 2013a [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomized into either 1 week of [methylphenidate transdermal system] MTS or 1 week of [placebo transdermal system] PTS (in their individually optimized dose) and were crossed over to the opposite treatment the following week" From correspondence: "Participants were randomized centrally for each of the study conditions. Randomization codes were not available to site study staffs, but were provided to research pharmacies at each site which corresponded to a particular dose pack" (Ramstad 2014 [pers comm])
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Phase-II randomized, double-blind, placebo-controlled laboratory classroom, crossover study with a lead-in open-label dose optimization phase" From correspondence: "Active and inactive patches were identical in appearance" (Ramstad 2014 [pers comm])
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias)	Low risk	Only 1 participant excluded due to protocol violation

McGough 2006 *(Continued)*

All outcomes		Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Trial protocol identified (NCT00466791), all outcomes reported

McInnes 2007

Study characteristics	
Methods	Cross-over trial with 2 interventions: • MPH at low, medium and high doses • placebo Phases: 4
Participants	Number of participants screened: 17 Number of participants included: 16 (12 boys, 4 girls) Number of participants followed up: 16 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (combined (63%), hyperactive-impulsive (6%), inattentive (31%)) Age: mean 9.2 years (range 7-12) IQ: mean 107.7 (range not reported) MPH-naive: ~ 80% Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: ODD (19%), CD (25%), generalised anxiety disorder (31%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Children 7-12 years of age with ADHD referred to an outpatient neuropsychiatry clinic for evaluation of response to MPH **Exclusion criteria** • Children with low cognitive performance (IQ < 80)
Interventions	Participants were randomly assigned to 1 of 12 possible drug condition orders of low, medium and high MPH and placebo Mean MPH dosage: LD (mean 0.21 mg/kg to 0.33 mg/kg, SD 0.07 to 0.02); MD (mean 0.31 mg/kg to 0.43 mg/kg, SD 0.09 to 0.03); and HD (mean 0.42 mg/kg to 0.65 mg/kg, SD 0.13 to 0.15) MPH Administration schedule: 1/d at 9:00 am Duration of each medication condition: 1 day

McInnes 2007 *(Continued)*

	Washout before trial initiation: 48 h before trial Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Inattention/overactivity symptoms based on 5/10 items from the IOWA Conners' Rating Scale, rated by observer 90 to 120 minutes after ingestion of capsule
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • "With respect to the medication protocol, we cannot predict that similar results would hold with longer-term treatment with MPH, given that these findings were obtained under a single acute drug challenge" • "Our findings for a predominantly male group of children with ADHD may not be generalisable to other groups of children with ADHD, for example, community samples that involve more girls and different rates of occurrence of comorbid conditions" • "Small sample size places limitations on conclusions that can be drawn from our findings" **Key conclusions of trial authors** • Findings provide preliminary evidence that MPH affects higher-level language comprehension skills, which require sustained attention and mental effort • If generalisable to classroom listening skills, these findings have implications for clinicians and teachers involved with children with ADHD Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: The Psychiatric Endowment Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Multiple blind procedures", capsules identically packaged by pharmacists
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Examiner, who was kept blind to child's medication status"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU Selection bias (e.g. titration after randomisation → exclusion): no

McInnes 2007 *(Continued)*

Selective reporting (reporting bias)	High risk	Symptom data not reported

Merrill 2021

Study characteristics	
Methods	A 6-week cross-over trial with 3 arms: • placebo • LD-MPH • HD-MPH
Participants	Number of participants screened: not stated Number of participants included: 21 (all boys) Number of participants followed up: 21 Number of withdrawals: 0 Diagnosis of ADHD: not stated Age: mean 9.32 years, no range stated IQ: mean 105.52 MPH-naive: not stated Ethnicity: not stated Country: USA Setting: summer treatment programme Comorbidity: not stated Comedication: not stated Additional sociodemographics: none **Inclusion criteria** • None stated **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned to different drug condition orders of 0.3 mg/kg MPH, 0.6 mg/kg MPH and placebo twice daily Number randomised to each group: 21 Mean medication dosage: fixed-dose trial with a period of 0.3 mg/kg twice/d (LD) and 0.6 mg/kg twice/d (HD) Administration schedule: not stated Duration (of (each) medication): not stated, but full duration of the trial was 6 weeks Washout before trial initiation: not stated

Merrill 2021 *(Continued)*

	Medication-free period between interventions: not stated Titration period: none Treatment compliance: not stated
Outcomes	**General Behavior** • Disruptive behaviours recorded by trained observers
Notes	Sample calculation: no Ethics approval: not stated **Comments from trial authors** • "Although the sample size (*n* = 21 children with ADHD) used in the current study was relatively small and may have precluded our ability to detect significant mediation effects, our use of a repeated-measures mediation procedure combined with bootstrapping has been implemented in similarly sized samples" (Merrill 2021, p. 441) • "This study utilized measures of sensitivity and bias to evaluate CPT [continuous performance tasks] performance, and, although these have been used extensively throughout the literature, more sophisticated measures using diffusion modeling may have provided different results. Unfortunately, the current sample was too small to allow for such analyses, and access to the raw trial-by-trial performance data was not available for this task." (Merrill 2021, p. 441) • "naturalistic measures of behavior were collected during the STP [Summer treatment camp] where behavioral treatment was in place, and this may have affected results by attenuating variability in child behavior. However, there was sufficient variability to detect robust medication effects" (Merrill 2021, p. 441) **Key conclusion of trial authors** • "The novel CPT utilized herein successfully taxed sustained attention as evidenced by the significant decline in performance over time on the measure of sensitivity and the significant medication-induced improvement in overall CPT performance." (Merrill 2021, p. 441) • "Though psychostimulants improved cognitive task performance and naturalistic behavior, preliminary analyses indicated that improvements in naturalistic behavior were not significantly mediated by proximal improvements in cognitive task performance" (Merrill 2021, p. 441) • "Overall, psychostimulants improve both behavior and cognitive performance, but cognitive task performance, specifically on tasks involving attention and/or sustained attention, does not appear to be an appropriate metric for psychostimulant efficacy as it has not been shown to consistently relate to observed improvements in presenting problem behaviors that are typically the focus of treatment." (Merrill 2021, p. 441) Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: not stated Any withdrawals due to AEs: no Funding source: not stated Supplemental information regarding trial design was requested through personal email correspondence with the authors in July 2022 but no answer was received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not stated

Merrill 2021 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blind but there is no information about the method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No trial protocol identified

Moshe 2012

Study characteristics	
Methods	2-week, randomised, double-blind, cross-over trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: 78 Number of participants included: 57 (all boys) Number of participants followed up: 57 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined and hyperactive-impulsive (53%), inattentive (47%)) Age: mean 9.5 years (range 7-12) IQ: normal MPH-naive: 100% Ethnicity: not stated Country: Israel Setting: outpatient clinic Comorbidity: no Comedication: no Other sociodemographics: representing all socioeconomic strata **Inclusion criteria** • Male

Moshe 2012 *(Continued)*

- 7-12 years
- ADHD, DSM-IV
- Drug-naive and with no other intervention
- Suitable candidate for MPH treatment
- Attention disorder was associated with a significant effect on daily life, and scores on 1 of the Attention subscales of both parent and teacher questionnaires were 1.5 SD or above the mean as suggested in clinical guidelines

Exclusion criteria

- Chronic psychiatric and neurological disorders, for example, OCD
- Tourette's syndrome
- Seizure disorder
- Severe learning disability (defined by special education enrolment)
- Definitive primary diagnosis of an anxiety disorder (DSM-IV) or sensory impairment

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg IR-MPH and placebo MPH dose range: 6 mg-12 mg Administration schedule: once daily Duration of each medication condition: 1 week Washout before trial initiation: no (drug-naive) Titration period: no Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CTRS, revised: weekly (after each intervention period)
Notes	Sample calculation: yes Ethics approval: yes **Comments from trial authors** • Results of the present study should be interpreted with caution • As only boys were included, the results might not be valid for girls • Children were clinic referrals and therefore might not be representative of the population of children with ADHD at large Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: none Email correspondence with trial authors: April-October 2013. We received supplemental data from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement

Moshe 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomly assigned with a table of random numbers
Allocation concealment (selection bias)	Low risk	Placebo (prepared as look-alike capsules by the hospital pharmacy)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting. According to trial authors, all planned outcomes were assessed and analysed

Muniz 2008

Study characteristics	
Methods	Randomised, multi-centre, double-blind, 5-period, cross-over trial in a laboratory classroom setting with 3 interventions: 1. ER-d-MPH 2. ER-d,l-MPH 3. placebo Phases: ER-d-MPH 20 mg/d, ER-d-MPH 30 mg/d, ER-d,l-MPH 36 mg/d, ER-d,l-MPH 54 mg/d and placebo
Participants	Number of participants screened: 84 Number of participants included: 84 (55 boys, 29 girls) Number of participants followed up: 81 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV (combined (89.3%), inattentive (10.7%)) Age: mean 9.5 years (SD 1.7, range 6-12) IQ: not stated MPH-naive: 0% Ethnicity: white (42.9%), African American (27.4%), Hispanic (28.6%), other (1.2%) Country: USA Setting: outpatient clinic Comorbidity: no

Muniz 2008 *(Continued)*

Comedication: no

Other sociodemographics: none

Inclusion criteria

- DSM-IV diagnosis of ADHD using DISC
- On stabilised total daily dose or nearest equivalent dose of 40 mg-60 mg of ER-d,l-MPH or 20 mg-30 mg ER-d-MPH for ≥ 2 weeks before screening visit

Exclusion criteria

- Tic disorder or Tourette's syndrome
- History of a seizure disorder
- Psychiatric illness
- Substance abuse disorder
- Taking prohibited concomitant medications or ADHD medication other than MPH
- Taking antidepressant or psychotropic medications
- Had begun psychotherapy within 3 months before randomisation
- Home-schooled children
- Girls of child-bearing potential with positive urine pregnancy test before enrolment (or, if sexually active, not using adequate and reliable contraception)

Interventions	Participants were randomly assigned to 1 of 5 possible drug condition orders of ER-d-MPH 20 mg/d, 30 mg/d, 36 mg/d, 54 mg/d and placebo Mean MPH dosage: not stated Administration schedule: once daily. Morning dosing as 2 capsules Sunday to Saturday. 6 doses were administered at home (Sunday to Friday), and the Saturday dose was administered by research staff. This was repeated until all 5 treatments had been administered. Mean duration of exposure to trial medication was 7 days for all 5 treatments Washout before trial initiation: 6 days medication-free Titration period: "On stabilized total daily dose or the nearest equivalent dose of 40 to 60 mg of d,l-MPH or 20 to 30 mg d-MPH for at least 2 weeks prior to the screening visit" initiated before randomisation Treatment compliance: not stated

Outcomes	**ADHD symptoms**
	
	• Primary efficacy variable
	  ○ Change from pre-dose SKAMP-Combined score at 2 h post-dose with ER-d-MPH 20 mg/d compared with ER-d,l-MPH 36 mg. This change was calculated by subtracting the pre-dose value (hour 0 score) from the post-dose value
	• Secondary outcome measures
	  ○ Change from pre-dose (0 hour) on Combined, Attention and Deportment subscores of the SKAMP, at specified intervals post-dose (0.5, 1, 2, 3, 4, 6, 8, 10, 11 and 12 h), and area under the score vs time curve (AUC) of the change from pre-dose in Combined score from hour 0 to hour 4 (AUC 0 to 4), and from hour 0 to hour 12 (AUC 0 to 12)
	
	Serious AE**s**
	
	• Safety assessments consisted of monitoring and recording of all AEs
	
	General behaviour
	
	• "The Conners' Parent Rating Scale (CPRS), a 27-item questionnaire designed to evaluate children's behaviour (Conners 1998a), was completed by parents on the Practice Day to assess behaviour with-

Muniz 2008 *(Continued)*

out medication and at each subsequent assessment day to rate the child's behaviour during the previous week"

Non-serious AEs

- Safety assessments consisted of monitoring and recording all AEs and recording vital signs and body weight at each visit
- Laboratory parameters (including haematology, blood chemistry and urinalysis), ECGs and results of physical examinations were assessed for abnormalities at screening and final visits (no final visit assessments were carried out for ECGs and physical examinations)

Notes	Sample calculation: yes; "It was determined that approximately 90 patients were required to detect a 0.05-level treatment difference at 84% power assuming a difference and standard deviation of 3.5 and 11 for SKAMP-Combined score, at 2 h post-dose using a paired t-test" Ethics approval: no information

Key conclusions of trial authors

- "The results of this study demonstrated that all active treatments generally provided significant improvement in ADHD symptoms over placebo over 11 to 12 hours post-dose in children 6–12 years old"
- "The primary efficacy variable, adjusted mean change in SKAMP-Combined score from pre-dose to 2 hours post-dose, was significantly greater during treatment with d-MPH-ER 20 mg/d than d,l-MPH-ER 36 mg/d (adjusted mean change 10.65 and 5.94, respectively; p 0.001). Similar results at 2 hours post-dose were noted for the secondary measure of SKAMP-Combined score comparing d-MPH-ER 30 mg/d with d,l-MPH-ER 54 mg/d (adjusted mean change 11.17 and 7.52, respectively; p0.001)."

Comment from review authors

- We did not include the Swanson pencil and paper math test of "academic productivity" among ADHD outcome measures. This may be seen as an ADHD outcome measure, but it does not specifically measure the 3 key ADHD core signs of inattention, hyperactivity and impulsivity.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; "Children recruited for this study had been stabilized on a total daily dose or the nearest equivalent dose of 40 to 60 mg of d,l-MPH or 20 to 30 mg d-MPH for at least 2 weeks prior to the screening visit" - so presumably non-responders to MPH and those experiencing intolerable AEs while taking MPH were not included

Any withdrawals due to AEs: no

Funding source: "This study was funded by Novartis Pharmaceuticals Corporation and reports the following involvement: design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, and approval of the manuscript"

Email correspondence with trial authors: July 2014. Emailed trial authors to ask for additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A total of 84 subjects were randomized to receive treatment and were included in the efficacy and safety analyses"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"After the Practice Day, the first assigned treatment was dispensed to the parents as blinded capsules according to their child's randomized sequence. To maintain blinding, all treatments were over-encapsulated and the same number of capsules were given once daily for each sequence"

Muniz 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The ratings were based on the frequency and quality of behaviours as observed by three independent, blinded raters in each class. To maintain consistency throughout the study, the blinded observers were responsible for observing and rating the same 6 children at specified intervals throughout the 12-hour testing period at each center"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The intent-to-treat population included all randomized patients who took at least 1 dose of study medication and had at least 1 post-dose efficacy measurement" Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No selective outcome reporting

Murray 2011

Study characteristics	

Methods	Double-blind, randomised, cross-over, analogue classroom trial with 2 interventions:
	• OROS-MPH
	• placebo
	
	Phases
	• Screening/washout phase: up to 28 days
	• Titration: up to 6 weeks
	• Double-blind assessment period, with the following subperiods
	  ○ open-label OROS-MPH
	  ○ school day 1: OROS-MPH or placebo
	  ○ open-label OROS-MPH: ≥ 7 days
	  ○ school day 2: OROS-MPH or placebo

Participants	Number of participants screened: 89 were included in the open-label phase Number of participants included: 68 (45 boys, 23 girls) Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV-TR (combined (59%), hyperactive-impulsive (4%), inattentive (37%)) Age: mean 10.75 years (range 5-15) IQ: > 80 MPH-naive: 65% Ethnicity: white (62%), African American (28%), Asian (not stated), Hispanic (not stated), other (10%) Country: USA Setting: outpatient clinic Comorbidity: anxiety (9%), depressive disorders (1%), learning disability (38%) Comedication: not stated

Murray 2011 *(Continued)*

	Other sociodemographics: none
	
	Inclusion criteria
	
	• 9-12 years of age
	• DSM-IV-TR diagnosis of ADHD
	• Parent-completed ADHD-RS-IV total or subscale scores ≥ 90th percentile for their age and sex
	• Attendance at a public or private school
	• Ability to read and understand English
	• Patients currently receiving ADHD medication must be inadequately managed on their current stimulant dose
	• To be eligible for the double-blind, randomised assessment period, participants had to reach their individualised OROS-MPH dose, defined as
	  ○ ADHD-RS-IV (as scored by parent or guardian): ≤ 75th percentile for age and sex
	  ○ ADHD-RSs-IV (as scored by parent or guardian): between 75th and 85th percentiles for age and sex after either (1) a dose decrease for tolerability (1 dose decrease by 18 mg to a minimum of 18 mg/d was allowed), or (2) having reached a dosage of 54 mg/d
	
	Exclusion criteria
	
	• Estimated full-scale IQ score ≤ 80, as determined by the 4-subtest version of the WASI
	• Severe learning disability, defined as ≥ 2 SD below the mean score for their age on Gray Oral Reading Test, Test of Phonological Processing or Wechsler Individual Achievement Test, Second Edition
	• History or current diagnosis of a neurological or psychiatric disorder that might compromise the participant's welfare or ability to comply with trial requirements
	• Inability to take or tolerate OROS-MPH
	• History of or current primary diagnosis of severe anxiety disorder, CD, psychotic disorders, pervasive developmental disorder, eating disorder, OCD, sleep disorder, major depressive disorder, bipolar disorder, substance use disorder, chronic tic disorder, personal or family history of Tourette's syndrome
	• Weight < 3rd percentile for age
	• History of hospitalisation for treatment of a mood, anxiety or psychotic disorder
	• History of failed response to MPH

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of OROS-MPH and placebo Mean OROS-MPH daily dosage: 47.6 mg Administration schedule: once daily, morning Average duration of OROS-MPH treatment: not stated, but the medication was given under double-blind condition on 1 day Duration of placebo intervention: 1 day Washout before trial initiation: up to 28 days Medication-free period between interventions: no Titration period: before randomisation, up to 6 weeks Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP, observer-rated: 4 h post-dose (at the 2 laboratory days) **Serious AEs** • Serious adverse effects assessed at the 2 laboratory days and during open-label periods

Murray 2011 *(Continued)*

	Non-serious AEs • Adverse effects, vital signs and body weight, at the 2 laboratory days • Adverse effects were collected during the open-label phase
Notes	Sample calculation: yes Ethics approval: yes **Key conclusion of trial authors** • OROS-MPH improves performance on measures of attention and vigilance, behaviour and working memory in a laboratory school setting in 9- to 12-year-olds with ADHD. Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; a history of failed response to MPH was an exclusion criterion. During the open-label phase before randomisation, 21 participants withdrew. Any withdrawals due to AEs: 2 Funding source: supported by Ortho-McNeil Janssen Scientific Affairs, LLC Email correspondence with trial authors: June 2013-June 2014. We have attempted to obtain supplemental efficacy data (SKAMP) and safety data from trial authors. We are awaiting data from the Yale Open Data Access Project

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Placebo and OROS-MPH were matched in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants received OROS-MPH on both laboratory school days in error; therefore, only data for their 1st laboratory school assessment were included in the analyses Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	Outcomes reported according to protocol

Musten 1997

Study characteristics

Musten 1997 *(Continued)*

Methods	Double-blind, randomised, placebo-controlled, cross-over trial with 3 interventions: • LD-MPH • HD-MPH • placebo
Participants	Number of participants screened: 109 Number of participants included: 54 met inclusion criteria; of these, the parents of 13 children refused MPH treatment. In the final sample, 41 children (26 boys, 5 girls) were included. Number of participants followed up: 31 Number of withdrawals: 10 Diagnosis of ADHD: DSM-III-R (subtype not stated) Regarding participants completing the trial Age: mean 58.07 months (approximately 4.8 years) (range 48-70) IQ: mean 99.26 MPH-naive: 93.5% Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: ODD (84%), CD (19%), mood disorder (0%), OCD (0%), overanxious disorder (0%), somatisation disorder (0%), psychotic symptoms (0%) Comedication: not stated Other sociodemographics: combined parental income CAD 42,000: 2-parent home (74%), single-parent home (26%). Significant differences were observed between the treatment-refused group (n = 13) and the treatment-completed group (n = 31) on baseline symptoms assessed by Diagnostic Interview for Children and Adults-Parents; SNAP; and Conners' hyperactivity ratings **Inclusion criteria** • 4-6 years of age • DSM-III-R diagnosis of ADHD (assessed by parent reports in the Diagnostic Interview for Children and Adults-Parents and a score > 1 of 8 on the 14 DSM-III-R items on the parent-rated SNAP) • Standard score 80 on the Peabody Picture Vocabulary Test if unilingual English, 72 if bilingual • Mean score 1.5 SD above age and sex means on the Hyperkinesis Index of CPRS-Revised, as completed by the parent. Reports from day care providers or pre-schools were also required to indicate problem behaviours • Attention score < 88 seconds on the parent-supervised attention task. This criterion is 1.5 SD above the mean for attention on the task as performed by normal pre-school children • Parents and children fluent in English **Exclusion criteria** • Attending or entering 1st grade at the time of assessment or for the duration of the trial • Sensory or physical handicaps, developmental disorders (e.g. autism), neurological disease or obvious CNS dysfunction as assessed by a paediatrician • Had been receiving MPH > 6 months, or daily dose was above dose specified in the research protocol

Musten 1997 *(Continued)*

Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of LD (0.3 mg/kg) and HD (0.5 mg/kg) MPH and placebo Administration schedule: twice/d, morning and lunch Duration of each medication condition: 7 to 10 days Washout before trial initiation: 48 h before screening assessment Titration period: none Treatment compliance: treatment compliance was determined by counting the number of pills returned to the researcher at the end of each assessment week Data on compliance: not stated
Outcomes	**ADHD symptoms** • CPRS - Revised **Non-serious AEs** • Side Effects Rating Scale (Barkley 1990) rated by parent at the end of each treatment period
Notes	Sample calculation: no Ethics approval: no information **Comment from trial authors** • Data on side effects are limited because of the age group of the population under investigation (4 to 6 years) - pre-schoolers cannot always articulate medication-related sensations, and this may have interfered with parents' ability to detect medication side effects **Key conclusions of trial authors** • Musten 1997: "results suggest that MPH can be used to improve the functioning of pre-school-aged children with ADHD, in a manner similar to their school-age counterparts" • Firestone 1998 (Musten 1997): "The results indicate that MPH has relatively low toxicity in pre-school children (over the first 7-10 days), that some behavioural changes that might be viewed as side effects of MPH are actually normal behaviours or ADHD behaviours in pre-school children (e.g. sociability), that these "side-effect" behaviours are more common in pre-school than school-aged children, that some "side effects" of MPH are associated with improvements in behaviour and that pre-school and school-aged children may experience different side effects of MPH (e.g. mood changes, anxiety)" Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: unclear, reasons for withdrawals not stated Funding source: Health Canada grant Email correspondence with trial authors: June 2013. Personal email correspondence with trial author did not provide supplemental data and information as requested because of author's retirement, and because he has no access to the data because the trial took place 15 years ago.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was presented in a fully randomised order as prepared by the hospital's pharmacy department

Musten 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	MPH and placebo were placed in orange gelatin capsules to disguise taste differences
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants, research personnel and medical personnel were unaware of the order of medication conditions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants, research personnel and medical personnel were unaware of the order of medication conditions
Incomplete outcome data (attrition bias) All outcomes	High risk	Only data for children completing the entire trial were analysed. Resons for withdrawals not stated Selection bias (e.g. titration after randomisation → exclusion): not stated
Selective reporting (reporting bias)	Unclear risk	Not possible to get a copy of the protocol

NCT00409708

Study characteristics	
Methods	A 12-week parallel trial with 2 arms: • behavior therapy • ER-MPH and behavior therapy Phases: 1 or 2 (there is mention of a washout, but it appears to happen after the trial)
Participants	Number of participants screened: 142 Number of participants included: 109 randomised, baseline characteristics from 104 (66 boys, 38 girls) Number of participants followed-up: 77 Number of withdrawals: 32 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 8.4 years (SD 1.83, range 6-12) IQ: not stated MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient Comorbidity: some were exclusion criteria Comedication: not stated Additional sociodemographics: not stated **Inclusion criteria**

NCT00409708 *(Continued)*

- Children of both genders, 6-12 years old
- Written informed consent by the parent and the patient (over 7 years old)
- Diagnosis of ADHD
- Age-appropriate cognitive functioning
- All patients who had at least one post-baseline cytogenetic assessment in the core trial can enter the observation phase

Exclusion criteria

- History of malignant neoplasm
- History of seizures (except childhood febrile seizures)
- Hyperthyroidism
- Concurrent medical condition which may interfere with trial

Interventions	Participants were randomly assigned to: receive either behavior therapy alone or with MPH. Number randomised to each group: 56 randomised to behavior therapy, 53 randomised to behavior therapy and MPH Mean medication dosage: not stated. Participants received between 10-60 mg/d Administration schedule: not stated Duration of each medication: 12 weeks Washout before trial initiation: there is mention of a washout, but it appears to happen after the trial. Titration period: not stated Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Conners' ADHD/DSM-IV Scale for Parents (CADS-P) assessed at baseline to end of treatment (Week 12) **Serious AEs** • Spontaneous reporting **Non-serious AEs** • Spontaneous reporting
Notes	Sample calculation: no Ethics approval: not stated Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: not stated Any withdrawals due to AEs: no Funding source: Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated

NCT00409708 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Almost a third of participants withdrew. Reasons for withdrawals are not stated. Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): unclear
Selective reporting (reporting bias)	Low risk	Since no cytogenetic effects were observed, blood samples were not analysed for pharmacokinetics/pharmacodynamics, otherwise all outcomes reported

NCT02039908

Study characteristics	
Methods	A 4-week cross-over trial with 2 arms: • 2 weeks of MPH • 2 weeks of placebo Phases: 3 phases (titration phase, double-blind cross-over phase, and 10-month medication-holiday-trial)
Participants	Number of participants screened: not stated Number of participants included: 267 (213 boys, 54 girls) Number of participants followed-up: 248 Number of withdrawals: 19 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean not reported (range 6-12 years) IQ: > 80 MPH-naive: not stated Ethnicity: Hispanic or Latino (n = 224, 83.9%), not Hispanic or Latino (n = 43, 16.1%). Race: Asian (n = 2, 0.7%), black or African American (n = 22, 8.2%), white (n = 237, 88.8), mixed race (n = 6, 2.2%) Country: USA Setting: outpatient, summer treatment programme Comorbidity: some were exclusion criteria; ODD, CD or a mood or anxiety disorder not requiring psychotropic medication were allowed Comedication: no psychotropic comedication allowed

NCT02039908 *(Continued)*

Additional sociodemographics: none

Inclusion criteria

- Aged 6-12 years old
- Diagnosis of ADHD according to DSM-IV-TR
- Full scale IQ > 80

Exclusion criteria

- Psychotropic medications for conditions other than ADHD
- Active medical or psychiatric conditions that could be worsened by stimulants
- Diagnosis of Autism or Asperger's Disorder
- Documented intolerance for MPH or failed trial of OROS-MPH

Interventions	Participants were randomly assigned to receive either 13 days of optimal-dose MPH then a 2-day medication/placebo probe followed by 13 days of placebo, or 13 days of placebo then a 2-day medication/placebo probe followed by 13 days of optimal-dose MPH Number randomised to each group: 129 medication first, 138 placebo first Mean medication dosage: not stated Administration schedule: not stated Duration of each medication: 13 days plus probe Washout before trial initiation: not stated Medication-free period between interventions: yes, 2 days Titration period: 9 days during the first 2 weeks of the summer treatment camp, placebo-controlled assessments of up to 4 different OROS-MPH doses (18 mg, 27 mg, 36 mg, 54 mg; max dose not to exceed 2 mg/kg/d) will be conducted to establish each child's optimal dose Treatment compliance: not stated
Outcomes	**Serious AEs** • Mortality (none), assessed by spontaneous reporting • Hospitalisation, assessed by spontaneous reporting **Non-serious AEs** • Pittsburgh Side Effect Rating Scale. Assesed "daily for the first 2 weeks of the summer and weekly for the final 6 weeks of the summer. During Phase 2, side-effects ratings were completed by parents monthly at medication dispensing visits. daily for the first 2 weeks of the summer and weekly for the final 6 weeks of the summer. During Phase 2, side-effects ratings were completed by parents monthly at medication dispensing visits." (NCT02039908)
Notes	Sample calculation: not stated Ethics approval: not stated No comments or conclusions Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes, titration phase before randomisation Any withdrawals due to AEs: not stated Funding source: Florida International University

NCT02039908 *(Continued)*

	Email correspondence with trial authors: August and October 2021. We contacted the trial authors for information regarding risk of bias and data through personal email in August and October 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Nothing stated
Allocation concealment (selection bias)	Unclear risk	Nothing stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mention of blinding, but no mention of method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mention of blinding, but no mention of method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	19 withdrawals, nothing further stated Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All protocol outcomes reported

NCT02293655

Study characteristics

Methods	A 4-week parallel discontinuation trial with 2 arms: • MPH discontinuation (placebo) • MPH at optimised dosage
Participants	Number of participants screened: 204 Number of participants included: 109 (72 boys, 37 girls) Number of participants followed up: 100 Number of withdrawals: 9 (no reason given) Diagnosis of ADHD: DSM-5 (type not stated) Age: range 7-11 IQ: < 80 MPH-naive: not stated Ethnicity: Hispanic or Latino (n = 9), not Hispanic or Latino (n = 100). Race: white (n = 88), more than one race (n = 10), black or African American (n = 8), Asian (n = 3)

NCT02293655 *(Continued)*

Country: USA

Setting: outpatient

Comorbidity: not stated

Comedication: all psychiatric medications were exclusion criteria

Additional sociodemographics: none

Inclusion criteria

- ADHD diagnostic status: meets DSM-5 criteria for ADHD, with CGI rating corresponding to at least "moderately ill."
- Cognitive and academic functioning: IQ of > 80 as estimated by Vocabulary and Block design subtests of the WISC-IV and scaled scores > 80 on the Wechsler Individual Achievement Test-2nd Edition Reading and Math subtests
- Physical health: physical exam and ECG findings are judged to be normal for age and sex by trial physician and/or medical consultant, and there is no co-existing condition for which MPH is contraindicated
- School: enrolled in a school setting rather than a home-school program. This ensures that they can obtain parent and teacher ratings from separate individuals for diagnosis and outcome assessment

Exclusion criteria

- Psychiatric medications: current or prior use of any medication for psychological/psychiatric problems
- Behavioral interventions: current active participation in ADHD-related behavioral interventions, given that improvements due to these interventions may confound our group comparisons
- Psychiatric or neurobehavioral conditions: children with mania/hypomania, schizophrenia, or severe depressive disorder, as determined by the K-SADS, will be excluded since ADHD medications may not be an appropriate first line of treatment for children with these comorbid disorders
- Organic brain injury: history of head trauma, neurological disorder (including epilepsy), or other disorder affecting brain function due to potential differences in neurophysiology of ADHD phenotype
- Cardiovascular risk factors: children with a personal history or family history of cardiovascular risk factors will be excluded, or given the option of participating in the trial after obtaining an ECG and verification from a paediatric cardiologist regarding the safety of their participation in a trial of MPH. In this case, families will be responsible for the costs of ECG and any necessary cardiologist evaluation
- Pregnancy: the safety of MPH use during pregnancy has not been established

Interventions

Participants were randomly assigned to either discontinue MPH (and receive placebo) or remain on optimal dose of MPH (OROS-MPH) for 4 weeks.

Number randomised to each group: MPH = 17, placebo = 92

Mean medication dosage: not stated

Administration schedule: once daily

Duration (of (each) medication): 4 weeks

Washout before trial initiation: none

Medication-free period between interventions: none

Titration period: 4-week placebo controlled MPH titration trial before randomisation (followed by a 4 weeks of maintenance phase at optimal dosage)

Treatment compliance: not stated, but according to the protocol compliance will be elaborated at each visit

Outcomes

ADHD symptoms

- Parent Vanderbilt ADHD-RS Total Symptom Score

NCT02293655 *(Continued)*

Serious AEs

- C-SSRS

General behavior

- Behavior Rating Inventory of Executive Function (BRIEF) scales

Non-serious AEs

- Pittsburg Side Effect RatingScale
- CSHQ

All outcomes assessed at baseline, during the maintenance period and 3 times during the discontinuation trial on/around day 1, 14 and 28

Only the Parent Vanderbilt ADHD-RS Total Symptom Score and prevalence of side effect data were available for the review

Notes	Sample calculation: not stated Ethics approval: not stated Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes; participants were only randomised if they completed the dose titration and maintenance phases Any withdrawals due to AEs: not stated Funding source: Children's Hospital Medical Center, Cincinnati

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method of sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"With blinded randomisation during MPH titration Trial and Discontinuation Phase (through use of over-encapsulated medication and identical placebos), the entire trial will be triple-blind (i.e., participant families, trial staff, and teachers will be blinded to medication and dose)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"With blinded randomisation during MPH Titration Trial and Discontinuation Phase (through use of over-encapsulated medication and identical placebos), the entire trial will be triple-blind (i.e., participant families, trial staff, and teachers will be blinded to medication and dose)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information regarding reason for withdrawals and method of analysis Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): not stated
Selective reporting (reporting bias)	High risk	All outcomes have not been published yet

NCT02536105

Study characteristics	
Methods	A 4-week cross-over trial with 4 arms: • ER-MPH tablets 1 • Placebo • ER-MPH tablets 2 • ER-MPH for suspension Phases: 3 (screening and wash-out, open-label titration phase, and double-blind trial)
Participants	Number of participants screened: 88, of which 80 were included in the open-label phase Number of participants included: 76 randomised in double-blind trial (59 boys, 21 girls) Number of participants followed-up: 67 in MPH tablet 1 group, 72 in placebo group, 66 in MPH tablet 2 group, 68 in oral suspension group Number of withdrawals: unclear Diagnosis of ADHD: DSM-5 (subtype not stated) Age: mean 9.45 (SD 1.86, range 6-12) IQ: not stated MPH-naive: not stated Ethnicity: Asian (n = 2), black or African American (n = 14), white (n = 45), mixed race (n = 16), race unknown or not reported (n = 3) Country: USA Setting: outpatient Comorbidity: specific phobia, motor skills disorders, ODD, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders are allowed Comedication: no Additional sociodemographics: none **Inclusion criteria** • Male and female outpatients • Aged 6-12 years at time of screening • Judged by the investigator to be physically healthy and suitable for participation in the trial • Diagnosis of DSM-5: ADHD combined, predominantly inattentive or hyperactive/impulsive presentation, per clinical evaluation and confirmed by the MINI-KID • CGI-S ≥ 3 • ≥ 90th percentile normative value for gender and age on the ADHD RS-IV total score at screening or baseline • Trial participant has a parent/legal guardian who is willing and able to give written informed consent for him/her to participate in the trial • Trial participant must be able to give assent to participate in the trial • Trial participant and legal guardian must be able to speak and understand English • Able to tolerate multiple finger pricks • Willing to comply with all trial procedure**s** **Exclusion criteria**

NCT02536105 *(Continued)*

- Current (last month) psychiatric diagnosis other than specific phobia, motor skills disorders, ODD, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders. Participants with school phobia or separation anxiety will not be eligible
- Cognitively impaired, in the investigator's opinion
- Any clinically significant chronic medical condition that, in the judgment of the investigator, may interfere with the participant's ability to participate in the trial
- Seizure disorder excluding a history of febrile seizures
- Thyroid disease
- Tourette's disorder or chronic tic disorder (mild medication-induced tics are allowed)
- Serious cardiac condition including cardiomyopathy, serious arrhythmias, structural cardiac disorders, or severe hypertension
- Glaucoma
- Current or recent (within the past 6 months) DSM-5 drug dependence or substance abuse (excluding nicotine and caffeine)
- Pregnant or nursing female participants. Female participants must have a negative urine pregnancy test at screening as well as 4 additional visits and must be abstinent or use adequate and reliable contraception throughout the trial
- Currently treated and satisfied with ADHD medication
- Current psychotropic medications other than sedative hypnotics for sleep
- Use of atomoxetine, clonidine, guanfacine or a MAOI within 28 days of the baseline visit
- Participation in another investigational medication trial within 30 days prior to screening
- Clinically significant abnormal laboratory result, ECG result, physical examination, or vital signs at screening that the investigator considers to be inappropriate to allow participation in the trial
- Planned use of prohibited drugs from the baseline visit through the end of the trial
- History of allergic reaction or a known or suspected sensitivity to any substance that is contained in the trial drugs
- Food allergies that are determined by the PI as too severe to be easily accommodated for during the trial
- Inability to swallow trial medication

Interventions	Participants were randomly assigned to 1 of 24 different medication orders of 1 week of 3 different types of MPH at optimised dosage (between 18-72 mg) or placebo Number randomised to each group: not stated Mean medication dosage: not stated Administration schedule: not stated Duration of each medication: 1 week Washout before trial initiation: 3-7 days (with the exception of atomoxetine, clonidine, guanfacine or a MAOI, which require a 28-day washout) Medication-free period between interventions: none Titration period: appears to be 8 weeks (until visit 8 in trial protocol) Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP (SKAMP-Attention, SKAMP-Deportment, SKAMP-Quality of Work, and SKAMP-Compliance) assessed at 0.5, 1.5, 2.5, 4, 5, 6, 8, 10 and 12 h post-dose on each classroom day **Serious AEs** • C-SSRS: no information on timing of outcome assessment available **Non-serious AEs**

NCT02536105 *(Continued)*

- Spontaneously reported

Notes	Sample calculation: yes, 150 Ethics approval: yes Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes, during the dose-optimisation phase Any withdrawals due to AEs: not stated Funding source: Massachusetts General Hospital Email correspondence with trial authors: August 2021. We contacted the trial authors for information regarding risk of bias and first-period data through personal email in August 2021; however, as the contact investigator has retired, we were unable to receive any answers.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The order of assignment will be generated by a statistician who is not involved in any of the trial procedures"
Allocation concealment (selection bias)	Low risk	Blinding ensured at external facility
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The external facility will ensure the packaging for the placebo and active are identical"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only one staff member unblinded at all times for emergencies
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The missing data will not be imputed and the incomplete individual observations will be included in the analyses as the non-linear mixed effect modeling approach used to conduct the PK and the PK/PD [Pharmacokinetic-Pharmacodynamic] analyses does not require complete data sets" Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	ADHD-RS-IV and CGI-S not reported

Newcorn 2008

Study characteristics

Methods	20-site, randomised, placebo-controlled, double-blind, 6-week, parallel trial with 3 arms: • ER-MPH • placebo • atomoxetine (not used in this review)
Participants	Number of participants screened: 635

Newcorn 2008 *(Continued)*

	Number of participants included: 294 (211 boys, 83 girls) randomised to the arms used in this review (516 including the atomoxetine arm, not used in this review) Number of participants followed-up: 237 (MPH 180, placebo 57) Number of withdrawals: 57 (MPH 40, placebo 17) DSM-IV diagnosis of ADHD (combined (67%), hyperactive-impulsive (1%), inattentive (32%)) Age: MPH mean 10.2, placebo mean 10.1 (range 6-16) IQ: not stated MPH-naive: 41%/121 Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: ODD (36%) Comedication: not stated Other sociodemographics: no significant differences in baseline demographics were noted between the 2 groups **Inclusion criteria** • Children 6-16 years of age • Meeting DSM-IV criteria for ADHD, any subtype • Symptom severity at entry was required to be ≥ 1.5 SD above USA age and sex norms, as assessed by the ADHD-RS-IV - Parent Version • ADHD as the primary diagnosis **Exclusion criteria** • Seizures, bipolar disorder, psychotic illness or pervasive developmental disorder • Taking concomitant psychoactive medications • Anxiety or tic disorders or both • Previously treated with an adequate trial of MPH or amphetamine and either did not experience at least some improvement in ADHD signs and symptoms (non-responders) or did experience intolerable AEs
Interventions	Participants were randomly assigned to OROS-MPH or placebo Number of participants randomised: MPH 220, placebo 74 Mean MPH dosage: 39.9 mg/d (SD 14.6) or 1.26 mg/kg/d (SD 0.55) Administration schedule: single morning dose Duration of intervention: 6 weeks Titration period: none Treatment compliance: not stated. Participants were required to discontinue any psychoactive medication for ≥ 5 days before entering the trial
Outcomes	**ADHD symptoms** • ADHD-RS: observer-rated at baseline and at weeks 1, 3 and 6 • CPRS, ADHD Index: rated at baseline and at weeks 1, 3 and 6

Newcorn 2008 *(Continued)*

- General behaviour

Quality of life

- Child Health Questionnaire: parent/teacher/observer-rated at baseline and at weeks 3 and 6
- Serious AEs

Non-serious AEs

- Open-ended questioning for AEs and vital signs: observer-rated at baseline and at weeks 1, 3 and 6
- No differences were observed in mean change in SBP between placebo and MPH
- Weight loss was significantly greater with MPH than with placebo

Notes

Sample calculation: no

Ethics approval: yes; approved by each site's ethical review board

Comments from trial authors

- It is likely that the MPH dose was suboptimal for some adolescent participants
- Restricting the dose of MPH to 54 mg could also have limited response in some younger participants, as OROS-MPH sometimes is prescribed at doses higher than the FDA-recommended maximum for children

Key conclusion of trial authors

- Both treatments produced robust improvement, with a statistically significant difference in response favouring OROS-MPH

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes

Any withdrawals due to AEs: yes. 12 in assessment 1, and 3 in assessment 2

Funding source: Eli Lilly and Company

Email correspondence with trial authors: November 2013 and January 2014. We requested additional data from trial authors but never received them

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial drugs were administered according to a double-dummy design. Identically appearing capsules were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial drugs were administered according to a double-dummy design. Identically appearing capsules were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	NNTB was calculated for each treatment in relation to placebo and for atomoxetine in relation to MPH. The number of participants was chosen to have 90% power to declare non-inferiority on the basis of a comparison of response rates, with a non-inferiority margin of 15%

Newcorn 2008 *(Continued)*

		Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Newcorn 2017a (flexible dose)

Study characteristics	
Methods	A 8-week parallel trial with 3 arms: • MPH • LDX • placebo Phases: 4 (up to 4 weeks screening and washout, 5-week dose optimisation, 3 weeks maintenance dosage, 1 week follow-up)
Participants	Number of participants screened: 628 Number of participants included: 464 randomised (278 included to relevant interventions MPH and placebo) 459 included in analysis (305 (66.4%) boys, 154 (33.6%) girls) Number of participants followed-up: 380 Number of withdrawals: 84 (5 of them, after randomisation, were not included in the analysis; reason for withdrawal not stated) Diagnosis of ADHD: DSM-IV-TR (260 combined, 5 hyperactive-impulsive and 194 inattentive) Age: 14.7 years (SD 1.37, range 13-17 years) IQ: not stated MPH-naive: not stated Ethnicity: Hispanic/Latino (n = 93), not Hispanic/Latino (n = 366). Race: white (n = 345), black/African American (n = 73), Native Hawaiian/Pacific Islander (n = 2), Asian (n = 7), American Indian or Alaska native (n = 2), other (n = 1), multiple (n = 29) Country: USA Setting: outpatient clinic Comorbidity: only ODD and mild stable asthma was not an exclusionary criterion Comedication: stable use of bronchodilator inhalers is not exclusionary Additional sociodemographics: none **Inclusion criteria** • 13-17 years of age at the time of consent • Weight > 79.5 lb (approx 36 kg) • The parent/legal representative must be available at approximately 7:00 am (± 2 h) • Female participants must have a negative serum beta-HCG pregnancy test and a negative pregnancy test and agree to comply with any applicable contraceptive requirements of the protocol • Participant has an ADHD-RS-IV total score ≥ 28 • Participant is able to swallow a capsule • Participant does not have hypertension and has a resting sitting BP ≤ 135/85 mmHg

Newcorn 2017a (flexible dose) *(Continued)*

Exclusion criteria

- Participant has a current, controlled (with medications prohibited in this trial) or uncontrolled, comorbid psychiatric diagnosis with significant symptoms such as any significant comorbid Axis II disorder or significant Axis I disorder (such as post-traumatic stress disorder, psychosis, bipolar illness, pervasive developmental disorder, severe OCD, depressive or anxiety disorder
- Diagnosis of CD. ODD is not exclusionary
- Participant is considered a suicide risk, has previously made a suicide attempt, or is currently demonstrating active suicidal ideation. Participants with intermittent passive suicidal ideation are not necessarily excluded
- Participant is underweight or overweight
- Participant has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition. Mild, stable asthma is not exclusionary
- Participant has a history of seizures (other than infantile febrile seizures), a chronic or current tic disorder, or a current diagnosis and/or a known family history of Tourette's Disorder
- Participant has a known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place him/her at increased vulnerability to the sympathomimetic effects of a stimulant medication
- Participant has a known family history of sudden cardiac death or ventricular arrhythmia
- Participant has any clinically significant ECG or clinically significant laboratory abnormality
- Participant has current abnormal thyroid function, defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4). Treatment with a stable dose of thyroid medication for at least 3 months is permitted
- Participant has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product
- Participant has a documented allergy, hypersensitivity, or intolerance to MPH or to any excipients in the reference product
- Participant has failed to fully respond to an adequate course(s) (dose and duration) of MPH or amphetamine therapy
- Participant has a history of suspected substance abuse or dependence disorder (excluding nicotine). Participants with a lifetime history of amphetamine, cocaine, or other stimulant abuse and/or dependence will be excluded.
- Participant has a positive urine drug result
- Participant has previously participated in this trial or another clinical trial involving SPD489/NRP104
- Participant has glaucoma
- Participant is required to take or anticipates the need to take medications that have CNS effects or affect performance, such as sedating antihistamines and decongestant sympathomimetics, or are MAOI. Stable use of bronchodilator inhalers is not exclusionary
- Participant is female and is pregnant or lactating
- Participant is well controlled on his/her current ADHD medication
- Participant has a pre-existing, severe gastrointestinal tract narrowing

Interventions	Participants were randomly assigned to 3 different groups: LDX, MPH or placebo. Number randomised to each group: placebo 93, LDX 186, OROS-MPH 185 Mean medication dosage: LDX 50.15 ± 12.501 mg/d, OROS-MPH 44.47 ± 12.754 mg/d Administration schedule: not stated Duration (of (each) medication): 8 weeks Washout before trial initiation: 4-week screening/washout period, specific length of washout not stated Titration period: during the first 5 weeks dosage was increased or decreased according to clinical assessment. LDX started at 30 mg/d and OROS-MPH started at 18 mg/d

Newcorn 2017a (flexible dose) *(Continued)*

	Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV total scale **Serious AEs** • C-SSRS • Spontaneous reporting **Non-serious AEs** • Vital signs • TEAEs were assessed at each visit
Notes	Sample calculation: no Ethics approval: yes. Trial protocols and related information were approved by either a central review board or institution-specific review boards and appropriate regulatory agencies (US FDA, Therapeutic Product Directorate of Canada, Medical Products Agency of Sweden, Medical Research Council of Hungary, The Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte] of Germany) before trial initiation. **Key conclusion of trial authors** • LDX dimesylate was superior to OROS-MPH for improving ADHD symptoms in a forced-dose study but not in a flexible-dose study. • Both LDX and OROS-MPH are highly efficacious in treating adolescents with ADHD and are generally well tolerated, demonstrating that either stimulant class can be used with confidence. This may be important in cases of inadequate response or poor tolerability to one of the stimulant classes (as has previously been reported), although the sequencing of treatment was not assessed in these studies. • The overall safety and tolerability profiles of LDX and OROS-MPH were consistent with previous reports. • LDX may have a somewhat higher effect size than OROS-MPH at US FDA-approved doses, though with perhaps slightly numerically higher rates of AEs. Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes Any withdrawals due to AEs: yes, 20 Funding source: Shire Email correspondence with trial authors: September and October 2021. We contacted the trial authors for information regarding risk of bias through personal email in September and October 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised (2:2:1) using an interactive web-response system (IWRS) to once-daily LDX, OROS-MPH, or placebo, respectively.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain blinding, treatments were identical in appearance; participants were also instructed to take 1 capsule from 2 separate bottles

Newcorn 2017a (flexible dose) *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	No imputation for ADHD-RS-IV, LOCF for CGI-S Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, participants excluded due to lack of efficacy
Selective reporting (reporting bias)	Low risk	All outcomes reported according to protocol

Newcorn 2017b (forced dose)

Study characteristics	
Methods	A 6-week parallel trial with 3 arms: • LDX • OROS-MPH • Placebo Phases: 4 (4-week screening/washout, 4 weeks forced titration, 2-week maintenance dosage, 1-week follow-up phone-call)
Participants	Number of participants screened: 778 Number of participants included: 549 (330 to relevant interventions). 547 started treatment (361 boys, 186 girls) Number of participants followed-up: 464 Number of withdrawals: 85 (of which 2 were before treatment start) Diagnosis of ADHD: DSM-IV-TR (358 combined, 8 hyperactive-impulsive and 181 inattentive) Age: 14.7 (SD 1.4, range 13-17) IQ: not stated MPH-naive: not stated Ethnicity: Hispanic/Latino (n = 101), not Hispanic/Latino (n = 446). Race: white (n = 401), black/African American (n = 110), native Hawaiian/Pacific Islander (n = 2), Asian (n = 8), American Indian or Alaska native (n = 3), other (n = 3), multiple (n = 20) Country: USA Setting: outpatient clinic Comorbidity: only ODD and mild stable asthma were not exclusionary criteria Comedication: stable use of bronchodilator inhalers is not exclusionary Additional sociodemographics: none **Inclusion criteria** • 13-17 years of age at the time of consent

Newcorn 2017b (forced dose) *(Continued)*

- Weight > 79.5 lb (approx 36 kg)
- The parent/legal representative must be available at approximately 7:00 am (± 2 h)
- Female participants must have a negative serum beta-HCG pregnancy test and a negative pregnancy test and agree to comply with any applicable contraceptive requirements of the protocol
- Participant has an ADHD-RS-IV total score ≥ 28
- Participant is able to swallow a capsule
- Participant does not have hypertension and has a resting sitting BP ≤ 135/85 mmHg

Exclusion criteria

- Participant has a current, controlled (with medications prohibited in this trial) or uncontrolled, comorbid psychiatric diagnosis with significant symptoms such as any significant comorbid Axis II disorder or significant Axis I disorder (such as PTSD, psychosis, bipolar illness, pervasive developmental disorder, severe OCD, depressive or anxiety disorder
- Diagnosis of CD. ODD is not exclusionary
- Participant is considered a suicide risk, has previously made a suicide attempt, or is currently demonstrating active suicidal ideation. Participants with intermittent passive suicidal ideation are not necessarily excluded
- Participant is underweight or overweight
- Participant has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition. Mild, stable asthma is not exclusionary
- Participant has a history of seizures (other than infantile febrile seizures), a chronic or current tic disorder, or a current diagnosis and/or a known family history of Tourette's Disorder
- Participant has a known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place him/her at increased vulnerability to the sympathomimetic effects of a stimulant medication
- Participant has a known family history of sudden cardiac death or ventricular arrhythmia
- Participant has any clinically significant ECG or clinically significant laboratory abnormality
- Participant has current abnormal thyroid function, defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4). Treatment with a stable dose of thyroid medication for at least 3 months is permitted
- Participant has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product
- Participant has a documented allergy, hypersensitivity, or intolerance to MPH or to any excipients in the reference product
- Participant has failed to fully respond to an adequate course(s) (dose and duration) of MPH or amphetamine therapy
- Participant has a history of suspected substance abuse or dependence disorder (excluding nicotine). Participants with a lifetime history of amphetamine, cocaine, or other stimulant abuse and/or dependence will be excluded.
- Participant has a positive urine drug result
- Participant has previously participated in this trial or another clinical trial involving SPD489/NRP104
- Participant has glaucoma
- Participant is required to take or anticipates the need to take medications that have CNS effects or affect performance, such as sedating antihistamines and decongestant sympathomimetics, or are MAOIs. Stable use of bronchodilator inhalers is not exclusionary
- Participant is female and is pregnant or lactating
- Participant is well controlled on his/her current ADHD medication
- Participant has a pre-existing severe gastrointestinal tract narrowing

Interventions	Participants were randomly assigned to 3 different groups of LDX, MPH or placebo Number randomised to each group: placebo 110, LDX 219, OROS-MPH 220

Newcorn 2017b (forced dose) *(Continued)*

Mean medication dosage: forced dosage: LDX week 1, 30 mg/d; week 2, 40 mg/d; week 3, 50 mg/d) and then in a 20-mg increment (week 4) to a maximum of 70 mg/d; initial OROS-MPH dose (18 mg/d) was increased weekly in 18-mg increments to a maximum of 72 mg/d during weeks 2 through 4

Dosage could only be increased or be kept as it was

Administration schedule: not stated

Duration (of (each) medication): 6 weeks

Washout before trial initiation: 4 weeks of screening/washout

Titration period: 4 weeks

Treatment compliance: not stated

Outcomes

ADHD symptoms

- ADHD-RS-IV total scale

Serious AEs

- C-SSRS
- Spontaneous reporting

Non-serious AEs

- Vital signs
- TEAEs were assessed at each visit

Notes

Sample calculation: no

Ethics approval: yes. Trial protocols and related information were approved by either a central review board or institution-specific review boards and appropriate regulatory agencies (US FDA, Therapeutic Product Directorate of Canada, Medical Products Agency of Sweden, Medical Research Council of Hungary, The Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte] of Germany) before trial initiation.

Key conclusion of trial authors

- LDX dimesylate was superior to OROS-MPH for improving ADHD symptoms in a forced-dose trial but not in a flexible-dose trial.
- Both LDX and OROS-MPH are highly efficacious in treating adolescents with ADHD and are generally well tolerated, demonstrating that either stimulant class can be used with confidence. This may be important in cases of inadequate response or poor tolerability to one of the stimulant classes (as has previously been reported), although the sequencing of treatment was not assessed in these studies.
- The overall safety and tolerability profiles of LDX and OROS-MPH were consistent with previous reports.
- LDX may have a somewhat higher effect size than OROS-MPH at US FDA-approved doses, though with perhaps slightly numerically higher rates of AEs.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: yes, 30 (15 in LDX group)

Funding source: Shire

Email correspondence with trial authors: September and October 2021. We contacted the trial authors for information regarding risk of bias through personal email in September and October 2021, but no answer was received.

Risk of bias

Newcorn 2017b (forced dose) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised (2:2:1) using an interactive web-response system to once-daily LDX, OROS-MPH, or placebo, respectively
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To maintain blinding, treatments were identical in appearance; participants were also instructed to take one capsule from 2 separate bottles
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	No imputation for ADHD-RS-IV, LOCF for CGI-S. Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, participants excluded due to lack of efficacy
Selective reporting (reporting bias)	Low risk	Reported according to protocol

Nikles 2006

Study characteristics	
Methods	Cross-over trial with 2 interventions 1. SA-MPH and SA-dexamphetamine) 2. Placebo Phases: each trial included 3 pairs of treatment periods (n-of-1). Each pair contained the stimulant and the comparator stimulant or placebo. The child's doctor individualised the dosing, and the order of drugs was randomly assigned within each pair. 2 treatment periods were included in a school week, and 2 days per treatment period (not including Wednesdays and weekends)
Participants	Number of participants screened: 108 (85 boys, 21 girls). 2 boys repeated n-of-1 trials; 22 (20%) trials were not completed Number of participants included: 86. (66 boys, 18 girls) Number of participants followed up: 86 Number of withdrawals: 10 (12%) trials were not completed Diagnosis of ADHD: DSM-IV (subgroups not stated) Age: median 10 years (range 5-16) IQ: not stated MPH-naive: 36 were taking MPH, 47 dexamphetamine, 3 unknown pre-trial medication Ethnicity: all were white (Nikles 2007 in Nikles 2006) Country: Australia

Nikles 2006 *(Continued)*

	Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: caregiver's occupation: full-time work 21%, part-time or casual work 33%, unemployed or retired 5%, unpaid homemakers 25%, other 10%, unknown 5% **Inclusion criteria** • Clinical diagnosis of ADHD according to DSM-IV criteria • Stable on an apparently optimal dose of stimulant • Informed consent from parent and school teacher (children 12 years of age provided assent) • 5-16 years of age • Uncertainty about treatment effectiveness **Exclusion criteria** • No teachers available and willing to provide observations
Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of individual doses of MPH, dexamphetamine and placebo Mean MPH dosage: not stated Administration schedule and time points: different for different individuals, as this is a series of n-of-1 trials Duration of each medication condition: 2 days each of MPH and placebo/week Washout before trial initiation: 40 h (from 4:00 pm Tuesday to 8:00 am Thursday) and 64 h (4:00 pm Friday to 8:00 am Monday) Titration period: not stated, but all were stabilised on an "optimal" dose of stimulant, initiated before randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** First 41 participants used at the end of each treatment period • Conners' Teacher and Parent Self Reported - Revised, short form • Conners-Wells Adolescent Rating Scales From 42nd participant onwards used at the end of each treatment period • Changed to ADHD du Paul Rating Scale IV parent and teacher questionnaires, "because they were less expensive but adequately reliable and valid for monitoring response to treatment" • Conners-Wells Adolescent Rating Scales **Non-serious AEs** • Assessment of AEs by parent and teacher during and at the end of each treatment period
Notes	Sample calculation: irrelevant Ethics approval: yes **Key conclusion of trial authors** • ADHD n-of-1 trials can be implemented successfully by mail and telephone communication. This type of trial can be valuable in clarifying treatment effect when it is uncertain, and in this series, treatments had a noticeable impact on short-term management

Nikles 2006 *(Continued)*

Comments from review authors

- This study was more about the use of n-of-1 trials in determining optimal drug treatment in cases for which this was uncertain
- Nikles 2007 (in Nikles 2006) does not add any relevant outcome data

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: yes (n = 1, insomnia and depression)

Funding source: The General Practice Evaluation Program, the Department of Health and Aged Care, Queensland Medical Laboratory, and the Royal Australian College of General Practitioners

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The order of drugs was randomly assigned within each pair"; "There were three pairs of treatment periods, with the order of drugs randomly assigned by a computer-generated randomisation schedule within each"
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, parents, doctors, and the research assistant were all blinded to medication order"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A hospital pharmacy encapsulated the medication (crushing of tablets and production of identical capsules containing either medication or placebo)"; "Active medication was encapsulated and identical placebo capsules were produced by a hospital pharmacy"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	All outcomes are reported

Oesterheld 1998

Study characteristics

Methods	Cross-over trial with 3 interventions: • MPH • lactose placebo • vitamin C placebo Phases: 5-day trial lasting for 3 consecutive weeks, with 2 medication-free days between phases
Participants	Number of participants screened: 30 Number of participants included: 4

Oesterheld 1998 *(Continued)*

	Number followed up: 4 (2 boys, 2 girls) Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (66.7%), hyperactive-impulsive (0%), inattentive (33.3%)) Age: mean 8.25 years (range 5-11) IQ: mean 72.5 (range 63-79) MPH-naive: 100% Ethnicity: Native American (100%) Country: USA Setting: outpatient clinic (residential school, laboratory classroom) Comorbidity: not stated Comedication: no Other sociodemographics: not living with family **Inclusion criteria** • Native Americans • 5-12 years of age • Residing at the residential school for 6 months • DSM-IV ADHD diagnosis • Diagnosis of foetal alcohol syndrome, partial foetal alcohol syndrome or alcohol-related birth defects according to criteria from the Fetal Alcohol Study Group of the Research Society of Alcoholism (1989) **Exclusion criteria** • Pregnancy • Lactose intolerance • Prior psychotropic medication use • Bipolar disorder • Acute and chronic medical or neurological disorders • Current history of seizures • Lead levels > 9 mcg/dL • Height and weight ≤ 3rd percentile • IQ < 60
Interventions	Participants were randomly assigned to different possible drug condition orders of MPH (0.6 mg/kg), lactose placebo and vitamin C placebo Mean MPH dosage: not stated (range 10 mg/d to 17.5 mg/d) Administration schedule: 7:30 am, 11:00 am and 2:00 pm Duration of each medication condition: 5 days for 3 consecutive weeks Washout before trial initiation: not stated Medication-free period between interventions: 2 days Titration period: none. Fixed dose Treatment compliance: medication given by nurse (directly observed treatment)
Outcomes	**ADHD symptoms**

Oesterheld 1998 *(Continued)*

- CPRS (48 items) and CTRS (39 items): both completed daily in each trial period by carers and teachers, respectively

Non-serious AEs

- Barkley Side Effects Questionnaire was completed by both teacher and carer before treatment

Notes

Sample calculation: no

Ethics approval: yes; Human Subjects Committee of the University of South Dakota's School of Medicine and the Research Committee of the Black Hills Children's Home Society

Key conclusion of trial authors

- When foetal alcohol syndrome and ADHD co-exist, ADHD symptoms of native children may respond to standard treatment with MPH without major side effects

Comment from review authors

- MPH was prepared to the nearest 2.5 mg using regular 5 mg and 10 mg MPH tablets that had been crushed and placed within gelatin capsules, which may result in uncertainty of actual dose administered

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: a University of South Dakota/USF-Mini Grant

Email correspondence with trial authors: not able to find email addresses for trial authors because information is missing from the paper. Not possible to find on the Internet, etc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The order of the trials was randomly determined
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	School carers, nurses, teachers and researchers were blinded as to whether treatment consisted of placebo or active agent. All agents were placed in identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	On each day of each trial, a teacher, blinded to evaluation data, rated the child's behaviour in school using CTRS (39 items). The caregiver, blinded to evaluation data, completed CPRS (48 items) on a daily basis. School carers, nurses, teachers and researchers were blinded as to whether treatment consisted of placebo or active agent. All agents were placed in identical capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Overtoom 2003

Study characteristics	
Methods	Double-blind, randomised, cross-over trial with 4 interventions: • MPH • desipramine • L-dopa • placebo
Participants	Number of participants screened: not stated Number of participants included: 16 Number of participants followed up: 16 (all boys) Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (combined (100%)) Age: mean 10.4 years (range 7-12) IQ: 95.4 MPH-naive: 0 (0%) Ethnicity: not stated Country: the Netherlands Setting: outpatient clinic Comorbidity: ODD (n = 6), comorbid anxiety disorder (n = 1), specific developmental disorders (n = 3) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Diagnosis of ADHD according to DSM-III-R criteria • Scored in the clinical range on both the CBCL Inattention factor (t scores > 70, i.e. 98th percentile) and CTRS Hyperactivity factor (mean factor score > 2.2) **Exclusion criteria** • Diagnosis of tic disorder or pervasive developmental disorder • Abnormal values (1 week before medication trial) of ECG and blood measures that contraindicate desipramine medication • Family history of severe heart problems
Interventions	Participants were randomly assigned to 1 of 2 of the possible drug condition orders of MPH, desipramine, L-dopa and placebo Mean MPH dosage: 15 mg Administration schedule: once, in the afternoon Duration of each medication condition: 1 day Washout before trial initiation: 3 days before for MPH users

Overtoom 2003 *(Continued)*

	Medication-free period between interventions: not stated Titration period: none Treatment compliance: 100%
Outcomes	**Non-serious AEs** • Sleepiness reported by 1 participant
Notes	Sample calculation: no Ethics approval: yes **Key conclusions of trial authors** • Inhibition of performance improved under desipramine but not under MPH or L-dopa. Response time to the stop signal was marginally shortened after intake of desipramine • MPH decreases omission and choice errors and causes faster reaction times in trials without the stop tone • No effects of L-dopa whatsoever were noted Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; all participants were already stable on MPH Any withdrawals due to AEs: no Funding source: Netherlands Organisation for Scientific Research (NWO) Grant 575-63-082

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"A double-blind randomised design was used"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Palumbo 2008

Study characteristics

Palumbo 2008 *(Continued)*

Methods	Multi-centre, randomised, double-blind, 16-week, parallel trial with 2 × 2 factorial design: • MPH alone • MPH and clonidine • clonidine alone • placebo 2 successive 4-week titration periods followed by an 8-week maintenance period
Participants	Number of participants screened: 205 Number of participants included: 122 (98 boys, 24 girls) Number followed up: 93 (MPH 18, placebo 10, MPH + clonidine 24, clonidine 31) Number of withdrawals: 44 (MPH 11, placebo 20, MPH + clonidine 8, clonidine 5) DSM-IV diagnosis of ADHD (combined (76%), hyperactive-impulsive (4%), inattentive (20%)) Age: mean 9.5 (range not reported) IQ: > 70 MPH-naive: 57 (46.7%) Ethnicity: white (77.9%), African American (10.7%), Hispanic (6.6%), other (4.9%) Country: USA Setting: outpatient clinic Co-morbidity: ODD (47%), CD (9%) Co-medication: not allowed, but all participants received protocol-based behavioural interventions Other sociodemographics: participant groups were similar except for a higher percentage of white children in the clonidine group and some minor differences with regard to family history of ADHD and tics **Inclusion criteria** • Children 7-12 years of age in school • DSM-IV ADHD, any subtype: indication of a sufficient number of ADHD symptoms on the Disruptive Behavior Disorders Rating Scale as rated by a teacher • Rating of ADHD symptoms above specified cut-off scores (boys: grades 2-3 = 10; grades ≥ 4 = 9; girls: grades 2-3 = 7, grades ≥ 4 = 6) on the IOWA-CTRS • Indication of the presence of sufficient ADHD symptoms at home on the IOWA-CPRS • Investigators rating of global functioning on the CGAS ≤ 70, with difficulty evident in ≥ 2 areas, such as school and home • ADHD must be viewed as worthy of treatment with medications, as judged by the parent and the site investigator • Informed consent/assent signed • Designated school for each participant agrees to participate in the trial by completing all required questionnaires and following all specified procedures • Child must be able to swallow the tablets and capsules used in this trial **Exclusion criteria** • Evidence of a tic disorder • Major depression • Pervasive developmental disorder • Autism

Palumbo 2008 *(Continued)*

	• Psychosis • Mental disability • Anorexia nervosa • Bulimia • Serious cardiovascular (e.g. significant hypotension, congenital heart disease) or other medical disorder that would preclude safe use of MPH or clonidine • Impaired renal function or pregnancy • Family history of long QT syndrome, cardiomyopathy or premature (age 45 years) sudden death • Prolonged QTc interval (> 440 milliseconds), high-grade ventricular ectopy, atrioventricular block beyond first degree, bundle branch block, intraventricular conduction block (> 100 milliseconds), pacemaker rhythm or HR < 60 bpm on the ECG, significant hypotension, cardiomyopathy, congenital heart disease, aortic or pulmonary stenosis, history of syncope • BP ≥ 2 SD above or below the age- and sex-adjusted mean • Stimulants had to be discontinued ≥ 2 weeks before enrolment • Any other psychotropic medications, anxiolytics or hypnotics had to be discontinued ≥ 6 weeks before enrolment Previous use of MPH or clonidine was permitted
Interventions	Participants were randomly assigned to IR-MPH or placebo Number randomised to each group: MPH 29, placebo 30, MPH + clonidine 32, clonidine 31 Mean MPH dosage: 0.76 ± 0.54 mg/kg/d (30.2 ± 18.9 mg/d (MPH-only group) and 25.4 ± 18.2 mg/d (MPH + clonidine)) Administration schedule: 1-3 times daily (morning, noon and afternoon) Duration of intervention: 12-16 weeks Washout before trial initiation: 2 weeks Titration period: 8-week flexible-dose titration period (4 weeks for clonidine, then 4 weeks for MPH) initiated after randomisation Maintenance period of optimal dose: 8 weeks Treatment compliance: monitored using pill counts (results of monitoring not stated)
Outcomes	**ADHD symptoms** • ADHD-RS (ADHD RS-IV, 18-item): child psychiatrist-rated at baseline and at 16 weeks • ASQ-teacher: rated at baseline and at 4, 8, 12 and 16 weeks • ASQ-parent: rated at baseline and at 4, 8, 12 and 16 weeks • IOWA Conners' Rating Scale: teacher-rated at baseline and at 4, 8, 12 and 16 weeks **Quality of life** • CGAS: rated at baseline and at 4, 8, 12 and 16 weeks **Non-serious AEs** • Pittsburgh Side Effects Rating Scale (20 items, modified from the original 13 items to include potential clonidine side effects): parent- and teacher-rated at baseline and at 4, 8, 12 and 16 weeks. • Spontaneous self-reports of AEs: parent- and participant-rated at baseline and at 4, 8, 12 and 16 weeks, or by telephone calls conducted between visits • Weight, ECG, supine and standing BPs and pulse at visits 4, 8, 12 and 16
Notes	Sample calculation: yes; sample size of 140 participants (35 per treatment group) was determined to provide between 80% and 90% power to detect a group difference (effects of clonidine) Ethics approval: yes; approved by the institutional review board at each site

Palumbo 2008 *(Continued)*

Comments from trial authors

- Overall, findings should be viewed cautiously in the light of the relatively small sample size and differential rates of attrition across groups
- Findings are limited by the exclusion of children with certain co-morbid disorders such as mood and anxiety disorders, known cardiac problems or abnormal ECGs
- Also, given that all participants received psychoeducational and behavioural interventions as part of the protocol, these results may be limited to settings in which such behavioural interventions are applied
- Trial relied largely on parent and teacher questionnaires to identify possible side effects of medications. However, such rating scales may overestimate rates of medication side effects because sometimes such complaints reflect other factors, such as underlying conditions or co-morbid psychopathology

Key conclusions of trial authors

- Based on Conners' Teachers Abbreviated Symptom Questionnaire; MPH offers best combination of efficacy and tolerability for ADHD
- Clonidine, used alone or with MPH, appears safe and well tolerated in childhood ADHD
- Trial provides evidence that measures of quality of life for the family are sensitive to pharmacological treatment for ADHD

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: moderate to severe AEs were cited as a reason for withdrawal in 8 participants: MPH + clonidine 5, clonidine 2, MPH 1

- MPH + clonidine: irritability (n = 1), tearfulness and irritability (n = 1), headaches (n = 1), itching (n = 1), asymptomatic ECG abnormalities (prolonged QTc) (n = 1)
- MPH: tachycardia and palpitations (n = 1)

Funding source: NIH and National Institute of Neurological Disorders and Stroke

Email correspondence with trial authors: March 2014 to June 2014. We attempted to obtain supplemental efficacy data from the trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation plan included stratification by centre (investigator) and by sexual maturity status (Prepubertal: Tanner I-II, Pubertal: Tanner III-V)
Allocation concealment (selection bias)	Low risk	Only the programmer in the Biostatistics Centre and the pharmacist knew the allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	MPH (or matching placebo) powder packaged in gelatin capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators, trial co-ordinators, teachers, parents and children were blinded to treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Statistical analyses were performed according to the ITT principle, and last available observations were carried forward and imputed when needed for

Palumbo 2008 *(Continued)*

		both efficacy and safety measures. However, only data from the ADHD-RS for children who completed the titration period were analysed Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Pearson 2013

Study characteristics	
Methods	4-week, cross-over trial with 2 interventions: • MPH • placebo Phases • 1-week placebo • 1-week LD-MPH • 1-week MD-MPH • 1-week HD-MPH
Participants	Number of participants screened: 94 Number of participants included: 24 (19 boys, 5 girls) Number of participants followed up: 24 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined 19, inattentive 5) Age: mean 8.8 years (range 7.1-12.7) IQ: mean 85 (range 46-112) MPH-naive: 13 Ethnicity: white (n = 13), African American (n = 4), Asian (n = 1), Hispanic (n = 5), other (n = 1) Country: USA Setting: outpatient clinic Comorbidity: ODD (n = 5), OCD (n = 2), separation anxiety disorder (n = 1) Comedication: yes Other sociodemographics: Hollingshead 4 Factor Social Class 1.7 (0.9); Hollingshead 4 Factor socioeconomic status score 52.3 (10.8) Mean parental education level: mothers 15.8 years (SD = 2.3), fathers 17.2 years (SD = 3.1) **Inclusion criteria** • Age between 7-12 • DSM-IV diagnosis of autistic disorder, as per the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) • Child manifests current symptoms of ADHD

Pearson 2013 *(Continued)*

- Confirmation of ADHD-diagnosis by Diagnostic Interview for Children and Adolescents-IV

Exclusion criteria

- Sensory or motor deficits sufficient to interfere with testing (e.g. blindness, severe cerebral palsy)
- Serious neurological disorders (e.g. epilepsy, stroke)
- Down syndrome, fragile X syndrome, Tourette syndrome, or foetal alcohol syndrome
- Bipolar disorder or a family history of bipolar disorder in a first-degree relative
- Other serious psychopathology that resulted in psychiatric hospitalisation (e.g. for psychotic episode). The investigators will screen for this using the Diagnostic Interview for Children and Adolescents-IV, and getting a complete developmental/medical history
- Serious physical handicaps that would interfere with performance on laboratory tasks
- IQ < 50 and > 130
- Verbal mental age (VMA) < 36 months (to exclude participants unable to understand simple task instructions)
- History of intolerance to MPH
- Weight < 20 kg or > 59 kg (< 44 pounds or > 130 pounds)
- Concomitant use of dextroamphetamine preparations (Dexedrine, Dextrostat), MAS (Adderall XR), other MPH preparations (e.g. Concerta, Metadate); venlafaxine, bupropion, atomoxetine, guanfacine, modafinil
- Concomitant use of any herbal preparations
- Medical condition for which stimulants are contraindicated (e.g. high BP)
- Past treatment failure on a MPH trial

Interventions	Participants were randomly assigned to 1 of 8 possible drug condition orders of 3 doses of MPH (low, moderate and high) and placebo Mean MPH dosage: low = 0.21 mg/kg; moderate = 0.35 mg/kg; high = 0.48 mg/kg Administration schedule: twice daily Duration of each medication condition: 1 week Washout before trial initiation: yes Medication-free period between interventions: not stated Titration period: 1 week before randomisation Treatment compliance: "Parents completed a medication administration form, were asked about missing or late doses at weekly interviews and teachers were asked as well. Forms were verified by number of pills in returned vials. Families were asked again in case of discrepancy. Parents and teachers were also asked about unanswered items on questionnaires" 5 children discontinued the afternoon IR-MPH dose due to behaviour concerns
Outcomes	**ADHD symptoms** • CPRS - Revised • CTRS - Revised • SNAP, 4th Edition • ACTeRS Parent and Teacher Forms **Non-serious AEs** • 9 of 24 parents (38%) reported insomnia at the high dose, compared with 5 (21%) while taking placebo • 9 parents reported loss of appetite at the high dose, compared with only 1 during placebo
Notes	Sample calculation: no

Pearson 2013 *(Continued)*

Ethics approval: yes

Key conclusions of trial authors

- It is ideal for clinicians to assess behavioural response in both home and school settings when titrating MPH treatment for children with Autism spectrum disorder and significant ADHD symptoms
- It is important to monitor each child for side effects (e.g. increases in stereotypies or irritability)
- MPH formulations are efficacious and well tolerated in children with Autism spectrum disorder and significant ADHD symptoms

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, past treatment failure on a MPH trial was an exclusion criteria

Any withdrawals due to AEs: no

Funding source: grant number MH072263 from NIMH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We used the Digram balanced randomisation method that Dr. David Lane (a professor of both psychology and statistics at nearby Rice University) used to create the 8 balanced drug dose orders to which our 24 participants were assigned"
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	One-week, single-blind, "lead-in-dosing"; all trial personnel with participant contact were blind with respect to dosages given during the drug trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The study medication was prepared by the University of Texas Psychiatry Research Pharmacy: the Ritalin LA beads were mixed with (inert) placebo beads and placed in two opaque gelatin capsules, and the white generic IR-MPH was crushed and mixed with cornstarch and placed in two size 1 gelatin capsules"
Incomplete outcome data (attrition bias) All outcomes	High risk	Blank was left for missing data Selection bias: yes; exclusion of placebo responder during single-blind placebo washout week
Selective reporting (reporting bias)	Low risk	All outcomes are reported

Pelham 1989

Study characteristics

Methods

Cross-over trial with 2 interventions:

- MPH
- placebo

Phases

Pelham 1989 *(Continued)*

	• No clear method description: "The procedure was double-blind placebo-controlled in which each child received, in random order with condition varied daily, placebo twice/d and 0.3 mg MPH/kg twice/d." - "5 to 9 days of data were gathered"
Participants	Number of participants screened: not stated Number of participants included: 24 (12 boys, 12 girls) Number followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-III (combined (not stated), hyperactive-impulsive (19/24), inattentive (2/24)) Age: mean not reported (range: boys 5 years 6 months-11 years; girls 5 years 8 months-11 years 3 months) IQ: boys 100.8 (SD 14.23), girls 104.0 (SD 16.52) MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic (summer treatment programme) Comorbidity: attention deficit disorder (1/24), CD (5/24), ODD (15/24), learning disability (6/25) Comedication: yes; other doses of stimulants reported but not on trial days Other sociodemographics: none **Inclusion criteria** • None stated **Exclusion criteria** • Children with an intellectual disability and those who had gross neurological disorders were not included in the trial
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg methylphenidate and placebo. "Each child received, in random order with condition varied daily, placebo twice a day and 0.3 mg MPH/kg twice a day." Mean MPH dosage: boys 9.8 mg (range 5.3-16.9), girls 9.5 mg (range 5.2-13.1) Administration schedule: twice daily at breakfast and at lunchtime Duration of each medication condition: not stated Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Abbreviated CTRS: 1-3 times per condition • Revised Behaviour Problem Checklist: counsellor-rated, 1-3 times per condition

Pelham 1989 *(Continued)*

- IOWA CTRS (IOWA CTRS)

General behaviour

- Daily frequencies (following rules, non-compliance, positive peer behaviours, conduct problems, negative verbalisations, numbers of time-outs per day): daily
- Time-out: daily
- Classroom measures, teacher recorded: daily
- Daily report card
- Observed peer interaction using modification of RECESS code: daily

Notes

Sample calculation: no
Ethics approval: not stated

Comment from trial authors

- Trial involved only 12 boys and 12 girls; 1 dose of MPH in the context of a highly structured summer programme: results must be considered preliminary

Key conclusions of trial authors

- Results revealed equivalent and beneficial effects of MPH for both boys and girls
- MPH therefore would appear to be a treatment that is as useful for girls with ADD as for boys with ADD

Comments from review authors

- Data reported from this trial cannot be considered robust
- No information on ethics committee approval, on randomisation, on primary endpoint (multiple endpoints), on sample size calculation, on safety, etc. Concomitant behavioural treatment was provided, but no details are given in the Methods section

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: not stated

Any withdrawals due to AEs: not stated

Funding source: not declared

Email correspondence with trial authors: October 2014. We received no supplemental information/data from trial authors. We asked authors whether this article was part of the Johnston 1988 trial but received no response, so we extracted the data as from 2 separate studies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each child received, in random order with condition varied daily, placebo and MPH
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active medication and placebo were disguised in gelatin capsules and were pre-packaged in individual, dated envelopes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Pelham 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion): unclear
Selective reporting (reporting bias)	Unclear risk	No protocol found

Pelham 1990a

Study characteristics	
Methods	Double-blind, placebo-controlled, cross-over trial: • IR-MPH • ER-MPH • ER-dextroamphetamine • pemoline • placebo
Participants	Number of participants screened: not stated Number of participants included: 22 (all boys) Number of participants followed up: 22 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 10.39 years (range 8.08-13.17) IQ: mean 105.68 Methlyphenidate-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic (summer treatment programme) Comorbidity: oppositional/defiant disorder (n = 9), CD (n = 4), "suggesting the presence of a learning disability", but IQ > 80 (n = 13) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Participating in the Summer Treatment Program of the 1988 Western Psychiatric Institute and Clinic Attention Deficit Disorder Program **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned different possible drug condition orders of MPH (10 mg twice/d, ER-MPH 20 mg every morning) and placebo

Pelham 1990a *(Continued)*

	Mean MPH dosage: IR-MPH 10 mg = 0.29 mg/kg Administration schedule: twice daily: IR-MPH twice daily: morning and lunchtime; ER-MPH once daily: morning Duration of each medication condition: 1 day, but in total 3-6 days Washout before trial initiation: none Medication-free period between interventions: not stated Titration period: no Treatment compliance: none All completed trial: not stated
Outcomes	**ADHD symptoms** • Teacher ratings on the Abbreviated CTRS: 2-4 times in each medication condition • Counsellor ratings on the Abbreviated CTRS: 2-4 times in each medication condition **Non-serious AEs** • Parent, teacher and counsellor side effect checklist: at least once per condition
Notes	Sample calculation: no Ethics approval: not stated **Comments from trial authors** • "It should be noted that the results we have presented apply to the short-term effects of these medications" • "Results of this trial might not predict long-term response to the initial dose" **Key conclusions of trial authors** • The 3 long-acting stimulants and IR-MPH were superior to placebo • All 4 had similar time courses with effects from 1-9 h after ingestion • Individual differences in drug responsivity were noted **Comments from review authors** • The article states that comorbidity is diagnosed according to DSM-III-R, but trial authors do not mention whether the ADHD diagnosis is based on DSM-III-R • We have chosen in our data extraction to assume that this is so Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: January 2014. No contact made through author correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement

Pelham 1990a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active medication and placebo were disguised in gelatin capsules and were pre-packaged in individual daily pill reminders
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Pelham 1993a

Study characteristics	
Methods	Cross-over trial with 2 interventions: • MPH 0.3 mg/kg and 0.6 mg/kg • placebo Phases: 3
Participants	Number of participants screened: not stated Number of participants included: 31. Number of participants followed up: 31 (all boys) Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (therefore no subtype) Age: mean 98.8 months (approximately 8.2 years; range 5.42-9.92) IQ: mean 110.7 (range not stated) MPH-naive: not stated Ethnicity: white (93.5%), African American (6.5%) Country: USA Setting: hospital (Summer Treatment Program) Comorbidity: ODD (32%), CD (48%) Comedication: not stated

Pelham 1993a *(Continued)*

	Other sociodemographics: none **Inclusion criteria** • Boys with ADHD attending a Psychiatric Institute and Clinic Summer Treatment Program **Exclusion criteria** • None described
Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of 0.3 mg/kg and 0.6 mg/kg MPH and placebo Mean MPH dosage (SD): low 8.1 mg (range 5-15); high 16.0 mg (range 10-22.5) Administration schedule: twice/d morning and midday; conditions were changed daily over 6 weeks Duration of each medication condition: 2 weeks overall (individual treatment condition 1 day) Washout before trial initiation: not described Titration period: none Treatment compliance: not reported
Outcomes	**ADHD symptoms** • Teachers rated inattention/overactivity daily with the IOWA CTRS
Notes	Sample calculation: no Ethics approval: not stated **Key conclusion of trial authors** • Relatively small incremental value was gained by the higher dose of medication or by the addition of behaviour modification compared with the effects of the low dose of MPH Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial author: June 2014. Emailed trial author to ask for additional information but have received no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Referred to as a randomised trial but sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules were identically packaged

Pelham 1993a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Referred to as double-blind but not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be 100% follow-up Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	Protocol not identified

Pelham 1999

Study characteristics	
Methods	6-week, within-participant, double-blind, placebo-controlled, cross-over design with 5 arms: • IR-MPH (10 mg) (Ritalin) • IR-MPH (17.5 mg) (Ritalin) • MAS (7.5 mg) (Adderall) • MAS (12.5 mg) (Adderall) • placebo
Participants	Number of participants screened: 26 Number of participants included: 25 (21 boys, 4 girls) Number of participants followed up: 23 Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.6 years (range 5.8-12.7) IQ: average intelligence MPH-naive: not stated Ethnicity: white (88%) Country: USA Setting: outpatient clinic Comorbidity: ODD (n = 13), CD (n = 8) Comedication: not stated Other sociodemographics: "Median family income was US $40 000, with incomes ranging widely (from US $10 000 per year to US $100 000 per year)" **Inclusion criteria** • Not stated **Exclusion criteria** • Not stated

Pelham 1999 *(Continued)*

Interventions	Participants were randomly assigned to receive 5 different interventions changing on a daily basis. The 5 interventions were 10 mg and 17.5 mg of IR-MPH (Ritalin), 7.5 and 12.5 mg of MAS (Adderall) and placebo Administration schedule: 2 time points Duration of each medication condition: 5-day period Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: none initiated before/after randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • IOWA CPRS • IOWA CTRS **Non-serious AEs** • Tics
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusions of trial authors** • "Both drugs were routinely superior to placebo and produced dramatic improvements in rates of negative behaviour, academic productivity, and staff/parent ratings of behaviour" • MAS produced greater improvement than MPH. Doses of MAS used were more potent than those of MPH • Both drugs produced low levels of side effects. 25% of trial participants were judged by the clinical team to be non-responders Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes; 1 (exacerbation of tic disorder) Funding source: grants from the Shire Richwood Pharmaceutical Company and NIMH (Grants MH53554, MH45576 and MH50467) Email correspondence with trial authors: April 2014. We requested additional information from trial authors but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	Unclear risk	"The clinical team was not blind to medication condition when making their recommendations. Therefore, as a reliability check of the clinical team's recommendations, one of the authors (J.W.) who was not involved in the clinical

Pelham 1999 *(Continued)*

All outcomes		team meetings made independent recommendations based on the same data given to the clinical team. This rater was blind to drug condition except placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The clinical team was not blind to medication condition when making their recommendations. Therefore, as a reliability check of the clinical team's recommendations, one of the authors (J.W.) who was not involved in the clinical team meetings made independent recommendations based on the same data given to the clinical team. This rater was blind to drug condition except placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion): Unclear, not stated
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Pelham 2001a

Study characteristics	
Methods	Cross-over trial with 3 interventions: • ER-MPH (Concerta) • IR-MPH • placebo Phases: 3
Participants	Number of participants screened: 70 Number of participants included: 68. (89% boys, 11% girls) Number of participants followed up: 68 (66 for ADHD symptoms) Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.1 years (range 6-12) IQ: mean 104.8 MPH-naive: 0% Ethnicity: white (94%), other (6%) Country: USA Setting: outpatient clinic (Summer Treatment Program) Comorbidity: ODD (43%), CD (37%) Comedication: no Other sociodemographics: none **Inclusion criteria**

Pelham 2001a *(Continued)*

- Children 6-12 years of age with ADHD were recruited via several sources, including advertisement; physician, agency and school referral; and parent referral
- All participants were required to be medicated with MPH and to receive a stable dose for ≥ 4 weeks before the start of the trial

Exclusion criteria

- Medical condition that would contraindicate the use of stimulants
- Physical condition or severe learning difficulty that would interfere with participation in trial, including IQ < 80
- Receiving additional medication for ADHD
- Any medication with CNS effects, anticonvulsants or investigational medications
- Reached menarche
- BP ≥ 95th age and height percentile

Interventions	Participants were randomly assigned to different possible drug condition orders of IR-MPH 3 times/d, Concerta MPH once/d, and placebo Mean MPH dosage: 0.75 mg/kg (SD 0.34) (3 dosing levels were used: • 5 mg IR-MPH 3 times/d or 18 mg ER-MPH (Concerta) daily • 10 mg IR-MPH 3 times/d or 36 mg ER-MPH (Concerta) once/d • 15 mg IR-MPH 3 times/d or 54 mg ER-MPH (Concerta) once/d The dose level used for each child was based on that child's MPH dosing before the start of the trial Administration schedule: IR-MPH 3 times/d or ER-MPH (Concerta) once daily Duration of each medication condition: 7 days Washout before trial initiation: not described Titration period: none Treatment compliance: "virtually 100%"
Outcomes	**ADHD symptoms** • Teachers and parents completed weekly symptom ratings using the IOWA CRS • Teachers and parents rated oppositional defiant behaviour weekly using the Abbreviated CRS • Teacher ratings on the SKAMP, daily **Non-serious AEs** • Reports of AEs were collected via spontaneous reports over the course of the trial. Additionally, each week, parents provided responses to questions on AEs, sleep quality, appetite and tics
Notes	Sample calculation: no Ethics approval: yes **Comment from trial authors** • All participants also received a behavioural intervention **Key conclusion of trial authors** • "This investigation clearly supports the efficacy of the Concerta long-acting formulation of MPH for parents who wish to have medication benefits for their child throughout the day and early evening" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; all participants were required to be medicated with MPH and were receiving a stable dose for ≥ 4 weeks before the start of the trial

Pelham 2001a *(Continued)*

	Any withdrawals due to AEs: no Funding source: ALZA Corporation, the manufacturers of Concerta Email correspondence with trial author: June 2014. Emailed trial author to ask for additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Referred to as double-blind; capsules were identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Referred to as double-blind; capsules were identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported for 66/70 for ADHD and behaviour Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Pelham 2002

Study characteristics

Methods	Cross-over trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 136 (all boys) Number of participants followed up: 136 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (therefore no subtype) Age: mean 9.7 years (range 7.6-12.7) IQ: mean 104.5 MPH-naive: not stated Ethnicity: white (81%), African American (15%)

Pelham 2002 *(Continued)*

	Country: USA Setting: Summer Treatment Program Comorbidity: ODD (53%), CD (24%) Comedication: not stated Other sociodemographics: median family income: USD 25,000, (range USD 10,000 to > USD 100,000) **Inclusion criteria** • Boys attending a psychiatric institute and clinic intensive Summer Treatment Program over 8 weeks **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg MPH and placebo Mean MPH dosage: 10 mg (SD 2.7) Administration schedule: twice daily at 7:45 am and 11:45 am Duration of each medication condition programme: 12 days (order randomly assigned daily over 6 weeks, doses administered over week days, except on Fridays); follow-up: 30 days Washout before trial initiation: 2 weeks medication-free baseline in programme, unclear for follow-up Titration period: none Treatment compliance: not reported
Outcomes	**ADHD symptoms** • Daily ratings of inattention/hyperactivity using IOWA CRS completed by counsellor • Daily ratings of inattention/hyperactivity using IOWA CRS completed by teacher **General behaviour** • Daily ratings of oppositional defiant behaviour using IOWA CRS completed by counsellor • Daily ratings of oppositional defiant behaviour using IOWA CRS, completed by teacher
Notes	Sample calculation: no Ethics approval: yes **Comment from trial authors** • Boys were told 50% of the time whether they were receiving placebo or medication and incorrectly 50% of the time; all boys received behavioural interventions over the course of the programme **Key conclusion of trial authors** • Expectancy (of treatment effectiveness) did not improve behaviour; only active medication improved behaviour Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: NIMH (Grant MH48157)

Pelham 2002 *(Continued)*

	Email correspondence with trial authors: June 2014. Emailed trial authors to ask for additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules were identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Raters were blinded to medication condition
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All of the outcomes used for this review are reported for 133 of the 136 boys. The reason for the missing data is not stated. Selection bias (e.g. titration after randomisation → exclusion): Unclear
Selective reporting (reporting bias)	Unclear risk	Although measures were rated daily, how data were aggregated/reported as a single result per phase is not clear.

Pelham 2005

Study characteristics

Methods	8-day, multi-centre, double-blind, randomised, dose-ranging, cross-over trial with 2 interventions: • MPH transdermal system • placebo From a Summer Treatment Program
Participants	Number of participants screened: 36 Number of participants included: 36 (33 boys, 3 girls) Number of participants followed up: 36 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.6 years (range 6-13) IQ: mean 105.3 (SD 18) MPH-naive: 15 (42%) Ethnicity: white (75%), African American (19%), Hispanic (3%), mixed African American/white (3%)

Pelham 2005 *(Continued)*

Country: USA

Setting: outpatient clinic (summer treatment programme)

Comorbidity: not stated

Comedication: no; antidepressants were withdrawn from 2 participants before trial enrolment

Other sociodemographics: parents were manual workers (6%), clerical/sales workers (32%), technicians/semi-professionals (23%) and executives/major professionals (32%)

Inclusion criteria

- Not stated

Exclusion criteria

- Medical history prohibiting patients from taking stimulants or participating
- Involvement in Summer Treatment Program activities
- Skin problems or allergies to ingredients in the patches

Interventions	Participants were randomly assigned to 1 of 8 possible drug conditions of MPH transdermal system and placebo MPH transdermal system dosage: 6.25 cm^2 (0.45 mg/h), 12.5 cm^2 (0.9 mg/h), 25 cm^2 (1.8 mg/h) Administration schedule: once/d (at 6:00 am and 7:00 am). Application sites were alternated each day between left and right hips Duration of each medication condition (crossed with time of application): 1-day; patch worn for ≥ 12 h/d Duration of trial: 8 days Washout before trial initiation: no Medication-free period between interventions: no Titration period: none Treatment compliance: 100%. Parents returned patches and dosing records to the trial site
Outcomes	**ADHD symptoms** • IOWA CRS and Abbreviated CRS were rated daily by parents, counsellors and teachers **Non-serious AEs** • Pittsburgh Side Effects Rating Scale completed daily by parents, counsellors and teachers • Any other AEs that the child experienced were recorded • Skin irritation at application sites rated each day by parents for skin reactions or irritations before application, before removal and the following morning. Presence of erythema: none (0), very slight (1), well defined (2), moderate (3) or severe (4). Presence of discomfort: none (0), mild (1), moderate but tolerable (2) or severe (3)
Notes	Sample calculation: yes (36-48) Ethics approval: yes; institutional review board at each site approved the trial **Comments from trial authors** • No children experienced a skin reaction severe enough that the study physician recommended discontinuing the patch • Limitations: short study duration, no controlled time-course evaluation

Pelham 2005 *(Continued)*

Key conclusions of trial authors

- MPH transdermal system produced significant effects that were similar to those previously reported with comparable MPH doses
- Substantial effect of application time on total daily functioning not apparent in this setting; additional controlled time-course studies will be necessary to fully evaluate the question of morning onset
- Further study will be necessary to establish long-term efficacy and safety of the MPH transdermal system

Comment from review authors

- Families received monetary compensation to participate

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: Noven Pharmaceuticals. Furthermore, Dr. Pelham was supported by grants from National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse; NIMH and National institute of Neurological Disorders and Stroke

Email correspondence with trial authors: February-March 2014. We attempted to obtain supplemental information regarding randomisation, allocation concealment, washout period and efficacy and safety data from trial authors but without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial sponsor produced random orders and prepared medication kits in numbered containers for each participant
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment sequences were concealed until completion of the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment sequences were concealed until completion of the trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Evaluable participant data were analysed. As the result of record-keeping difficulties at 1 site, efficacy data were excluded for 5 participants Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol found

Pelham 2011

Study characteristics

Pelham 2011 *(Continued)*

Methods	3-week, randomised, double-blind, double-dummy, cross-over trial with 3 interventions: • IR-MPH • MPH transdermal system • placebo Parents and children spent Friday evening to Sunday morning in a laboratory setting, where data collection took place
Participants	Number of participants screened: not stated Number of participants included: 10 (all boys) Number of participants followed up: 9 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (combined (80%), hyperactive-impulsive (0%), inattentive (20%)) Age: mean 8.6 years (range 6.4-9.7) IQ: mean 95.3 (range 83-109) MPH-naive: none; all receiving a stable dose of IR-MPH before enrolment Ethnicity: white (50%), African American (20%), Asian (0%), Hispanic (0%), Native American (10%), other (20%) Country: USA Setting: outpatient clinic Comorbidity: ODD/CD (80%) Comedication: no other psychotropics Other sociodemographics: none **Inclusion criteria** • ADHD diagnosis according to DSM-IV • IQ > 80 **Exclusion criteria** • Skin sensitivity or any significant dermatological disease • Atypical ECG results or hypertension • Atypical blood and urine test results or evidence of other medical condition that could be worsened by stimulant usage • Participants taking other psychotropics besides MPH • Participants with psychopathology other than ADHD or ODD or CD severe enough to merit additional treatment
Interventions	Participants were randomly assigned to different drug orders of IR-MPH, MPH transdermal system, and placebo **IR-MPH** • Mean dosage: 30 mg/24 h • Administration schedule: 10 mg 3 times/d: morning, lunch, afternoon **MPH transdermal system**

Pelham 2011 *(Continued)*

- Mean dosage: 33 mg/24 h
- Administration schedule: 2 10 cm^2 MPH transdermal system patches worn for 24 h at the buttock, with sides alternated daily
- Time point: applied in the morning

Duration of each medication condition: 1 week

Washout before trial initiation: 48 h before trial (no washout between treatment periods)

Titration period: none

Treatment compliance: dosing and adhesion records were collected each week, but no data were available in the article

Outcomes

ADHD symptoms

- IOWA CRS, rated by the laboratory classroom teacher at each treatment condition

Non-serious AEs

- Vital signs (temperature, weight, BP, pulse) were measured Friday night by staff. Furthermore, vital signs were taken at 0, 4, 8 and 24 h after the first dose on Saturdays
- AEs were measured Friday night by staff and during weekdays by parents, and were reported spontaneously on Saturday evening and Sunday morning
- Skin was examined Friday night by staff. Furthermore, nurses assessed each MPH transdermal system application for skin irritation during the laboratory day before application and at 0.5, 12 and 24 h after removal
- Sleep: parents rated the child's sleep during week days. On Friday and Saturday nights in the laboratory setting, nursing staff monitored children hourly between 9:00 pm and midnight and recorded sleep onset
- Appetite: parents rated this during weekdays

Notes

Sample calculation: no

Ethics approval: yes

Key conclusion of trial authors

- MPH transdermal system demonstrates efficacy and tolerability comparable with IR-MPH 3 times/d

Comments from trial authors

- All participants had been receiving MPH previously, and this may explain the small number of side effects
- Furthermore, tolerability findings cannot be generalised to stimulant-naive children

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; however, all participants had been receiving MPH previously, and this may explain the small number of side effects

Any withdrawals due to AEs: yes; 1 receiving placebo

Funding source: grant from Noven Pharmaceuticals (manufacturer of the MPH transdermal system)

Email correspondence with trial authors: July 2014. Emailed trial authors to request additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement

Pelham 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Random assignment; no information about how
Allocation concealment (selection bias)	Low risk	Double-dummy procedure: all children received patches and capsules each day, with applicable placebos
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant discontinued the trial during the first week because of worsening behaviour while taking placebo and was not included in the analyses: all other participants completed the trial AEs: all participants receiving ≥ 1 dose of medication were included in the safety analysis Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	Not possible to find the protocol

Pelham 2014

Study characteristics	
Methods	3-week, randomised, controlled, cross-over trial with 2 factors - medication and behavioural intervention - with daily medication changes: • MPH • placebo • behavioural treatment
Participants	Number of participants screened: not stated Number of participants included: 48 (44 boys, 4 girls) Number of participants followed up: 47 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (subtypes not stated) Age: mean 9.35 years (range 5-12) IQ: mean 106.33 (SD 14.61; range not stated) MPH-naive: not stated Ethnicity: white (79%), African American (12.5%) Country: USA

Pelham 2014 *(Continued)*

	Setting: outpatient, Summer Treatment Program Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-IV ADHD • IQ ≥ 80 • No documented adverse response to, or medical conditions that would contraindicate use of, MPH **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of 0.15 mg/kg/dose MPH 3 times/d; 0.3 mg/kg/dose MPH 3 times/d; 0.6 mg/kg/dose MPH 3 times/d and placebo Mean MPH dosage: not clearly stated: "average doses were 5.4 mg (range 2.5-10), 11 mg (range 6.25-20), and 21 mg (range 11.25-30), respectively" Administration schedule: 3 time points Duration of each medication condition: 0.15 mg dose for 4 days, 0.30 mg dose for 4 days and 0.6 mg dose for 3 days, switched daily Washout before trial initiation: not stated Medication-free period between interventions: not stated Titration period: not stated Treatment compliance: "One child's parents withdrew from the study after 2 days because of their concerns about possible side effects of the medication"
Outcomes	**ADHD symptoms** • IOWA CRS: rated by counsellors, daily **General behaviour** • IOWA CRS O/D: rated by counsellors, daily **Non-serious AEs** • Counsellors completed the Pittsburgh Side Effects Rating Scale, daily • Trial staff monitored ratings for clinically significant AEs, daily
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • "The prototypic child with ADHD could be treated with the equivalent of 0.15 mg/kg MPH (5 mg per dose in the current sample) twice daily—a dose lower than that used in studies of stimulant treatment in the past 30 years—if he or she is receiving moderate- to high-intensity behavioural treatment" • "Our data show that stimulant doses can be reduced dramatically if a child is treated with behaviour modification" **Key conclusion of trial authors**

Pelham 2014 *(Continued)*

- "Results illustrate the importance of taking dosage/intensity into account when evaluating combined treatments; there were no benefits of combined treatments when the dosage of either treatment was high but combination of the low-dose treatments produced substantial incremental improvement over unimodal treatment"

Comment from review authors

- Very difficult to understand the real effect of medication because of daily oscillation of the dose

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; only participants not having any documented adverse response to MPH were included

Any withdrawals due to AEs: yes (n = 1)

Funding source: grant from the NIMH (MH62946). Dr. Pelham was funded by grants from the NIH (MH62946, MH69614, MH53554, MH69434, MH65899, MH78051, MH062946, NS39087, AA11873, DA12414, HD42080) and the Institute of Education Sciences (L03000665A). Dr. Fabiano was supported in part by a Ruth S. Kirschstein National Research Service Award Predoctoral Fellowship (1F31MH064243-01A1) and by the Department of Education, Institute of Education Sciences (R324J06024, R324B06045)

Email correspondence with trial authors: April 2015. We emailed trial authors to request supplemental information but have not received a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The children, their parents, and clinical staff members were uninformed of medication condition and only the research coordinator, pharmacist and medical director had access to the medication order. The medical director could reveal medication conditions in cases of severe side-effect reports"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Observers were independent staff members who were not involved in the children's treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one participant withdrew from the trial. Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No access to protocol. No description in clinicaltrials.gov

Perez-Alvarez 2009

Study characteristics

Methods	12-month, randomised, controlled, parallel trial with 2 different treatment strategies.

Perez-Alvarez 2009 *(Continued)*

- A) Participants with a score ≥ 2.5/1.8 on the SNAP, 4th Edition (teacher/parents), were randomly assigned to
  - OROS-MPH (Concerta)
  - Humanistic psychology
  - OROS-MPH (Concerta) + psychology
- B) Participants with score < 2.5/1.8 on the SNAP, 4th Edition, were randomly assigned to
  - Humanistic psychology
  - OROS-MPH (Concerta) + psychology

Participants	Number of participants screened: not stated Number of participants included: 118 to the arms used for this review 150 in all 3 arms (boy:girl 4:1 for those with combined type; 1:3 for those with inattentive type) Number followed up: OROS-MPH (Concerta) + psychology 59, humanistic psychology 59 Number of withdrawals: OROS-MPH (Concerta) + psychology 0, humanistic psychology 0 Diagnosis of ADHD: DSM-IV-TR (combined (67%), hyperactive-impulsive (0%), inattentive 33%)) Age: mean 10 years (range 7-14) MPH-naive: 100% Ethnicity: not stated Country: Spain Setting: outpatient clinic Comorbidity: no Comedication: no IQ: > 70 Other sociodemographics: none **Inclusion criteria** • ADHD DSM-IV-TR, combined or inattentive type • 7-15 years • IQ > 70 **Exclusion criteria** • Previous medication or therapy • Comorbidity
Interventions	Participants were randomly assigned to OROS-MPH (Concerta) + psychology or humanistic psychology Number assigned to each group: 59 to humanistic psychology, 59 to OROS-MPH (Concerta) + psychology OROS-MPH dose: not stated Administration schedule: not stated Duration of intervention: 12 months Titration period: not stated Treatment compliance: not stated

Perez-Alvarez 2009 *(Continued)*

Outcomes	**ADHD symptoms** 1. SNAP, 4th Edition (18-item): rated at baseline, 6 months and 12 months by teachers and parents
Notes	Sample calculation: no Ethics approval: yes **Key conclusion of trial authors** • "In summary, while further confirmation is awaited, the cognitive PASS [planning, attention, successive, and simultaneous processes] assessment may be a useful tool for better diagnostic and prognostic classification in comparison with behavioural phenotyping" **Comment from review authors** • In trial methods and data extraction, all participants receiving OROS-MPH (Concerta) + psychology (3A + 2B) were analysed together, as were all participants receiving humanistic psychology (2A + 1B) Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding: none. Research was part of the work day, participants were voluntary and no funding was needed to implement the trial Email correspondence with trial authors: June 2014. We received supplemental information regarding funding, ethics approval and protocol from the trial authors, although they were not able to send data from the SNAP, 4th Edition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned, but no information was given to explain how assignment was done
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting, all planned analyses are described in the paper

Pliszka 1990

Study characteristics	
Methods	4-week, double-blind, cross-over trial, in which children were randomly assigned to the following: • 2 doses of MPH (low: 0.25 mg/kg-0.40 mg/kg; and high: 0.45 mg/kg-0.70 mg/kg) • placebo
Participants	Number of participants screened: 79 (74 boys, 5 girls) Number of participants included: 46 Number of participants followed up: 43 (30 without anxiety, 13 with anxiety) Number of withdrawals: 3 Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 9 years (range not reported) IQ: > 70 MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: anxiety (30%), ODD (56.0%), CD (23.3%) (Participants who expressed transient anxiety or depression about consequences of punishment for misbehaviour were considered to not meet the criteria for an overanxious disorder) Comedication: no Other sociodemographics: none **Inclusion criteria** • DSM-III-R criteria for ADHD • Candidate for a stimulant trial **Exclusion criteria** • None stated No patients met the criteria for any psychotic or depressive disorder. Participants were free of medication, as well as any other medical disorder.
Interventions	A total of 4 weeks of medication. First week always placebo; remaining 3 weeks, participants were randomly assigned to different orders of placebo and low- (0.25 mg/kg to 0.40 mg/kg) and high-dose (0.45 mg/kg to 0.70 mg/kg) MPH. Doses were as follows: 5 mg and 10 mg for weight < 25 kg; for those overweight, the 2 dose conditions were 10 mg and 20 mg Administration schedule: twice/d, 7:00 am and 12 noon. Saturday, the dose was adjusted so that it was given 90 min before measurements were taken Duration of each medication condition: 1 week Washout before trial initiation: not relevant; did not take MPH before Medication-free period between interventions: 17 h Titration period: none

Pliszka 1990 *(Continued)*

	Treatment compliance: not stated
Outcomes	**ADHD symptoms** • IOWA CTRS (both Inattention/Overactivity and Aggressive subscales): rated weekly by teachers at the end of each week
Notes	Sample calculation: no information Ethics approval: no information **Comments from trial authors** • Data strongly suggest that children who met criteria for ADHD and anxiety are not children who simply have become "demoralised" by frequent conflicts with parents and teachers. They represent a distinct subgroup • It is unclear from these data whether children with comorbid ADHD and anxiety form a separate subtype of ADHD, similar to the DSM-III diagnosis of ADD without hyperactivity, or whether this is a group of children with primary anxiety that may lead to oppositional behaviour and temper tantrums, and the presence of these symptoms may lead parents and teachers to report inattention and overactivity when the symptoms may not be objectively present • This study strongly suggests that it is important to control for the presence of anxiety disorders in research on ADHD • Analyses were made on the basis of whether anxiety was present with ADHD. To meet criteria for anxiety, children had to report the symptoms themselves **Key conclusions of trial authors** • A total of 43 participants completed a double-blind trial of MPH; participants with comorbid anxiety had a significantly poorer response • Results suggest that ADHD with comorbid anxiety may characterise children with primary anxiety who develop secondary inattentiveness, or may represent a different subtype of ADHD, perhaps similar to the condition of attention deficit disorder without hyperactivity, as under DSM-III • ADHD participants with anxiety were rated significantly lower on the IOWA CTRS, Inattention/Overactivity subscale, than those without anxiety, although the mean score for both groups was well into the disturbed range Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: not stated Funding source: NIMH Email correspondence with trial authors: November 2013. We received from the trial authors supplemental information regarding participants' intellectual function and funding and additional data. The raw data no longer exist; therefore we cannot analyse data from different periods in the cross-over trial, only endpoint data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned to placebo and LD- and HD-MPH
Allocation concealment (selection bias)	Unclear risk	Randomly assigned to placebo and LD- and HD-MPH. Not stated how investigators allocated participants to the intervention

Pliszka 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The child, his or her parents, teachers and research assistants were all blinded to drug status
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The child, his or her parents, teachers and research assistants were all blinded to drug status
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 3 dropouts. All other participants were included in the final analysis Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): unclear, no reason for dropouts stated
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Pliszka 2000

Study characteristics	
Methods	3-week, randomised, double-blind, placebo-controlled, parallel trial with 3 arms: 1. MAS (Adderall) 2. MPH 3. placebo
Participants	Number of participants screened: 73 Number of participants included: 58 Number randomly assigned: MPH 20, placebo 18 Number followed up: MPH 19, placebo 16 Number of withdrawals: MPH 1, placebo 2 Diagnosis of ADHD: DSM-IV. DISC diagnosis of ADHD (subtype not stated) Age: mean 9 years (range not reported) IQ: > 75 MPH-naive: MPH 5 (25%), placebo 1 (6%) Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: ODD (MPH 14%, placebo 10%), CD (MPH 1%, placebo 2%), anxiety disorder (MPH 20%, placebo 5%) Comedication: not stated Other sociodemographics: no significant difference in baseline demographics were noted between the 2 groups **Inclusion criteria**

Pliszka 2000 *(Continued)*

- Children in grades 1-5
- ADHD according to DISC
- IQ > 75
- ≥ 1.5 SD above the mean for his/her age and sex on the IOWA CTRS, Inattention/Overactivity factor

Exclusion criteria

- Other medical illness
- Meeting DISC criteria for major depression episode, manic episode or tic disorder
- History of psychosis or signs of psychosis or significantly depressed mood on the mental status examination
- Current treatment consists of non-stimulant psychotropic medication

Interventions	Participants were randomly assigned to IR-MPH or placebo Mean MPH dosage: total dose 25.2 mg/d Administration schedule: 17 (85%) received ≥ 2 doses Time points: 1-3 times/d: morning, after school and additional noon if needed Duration of intervention: 3 weeks Titration period: none Treatment compliance: not stated. Dosage was adjusted at the end of weeks 1 and 2 via an algorithm based on teacher and parent ratings
Outcomes	**ADHD symptoms** • IOWA CTRS: rated twice daily (morning and afternoon) Mondays through Thursdays **General behaviour** • CGI: parent-rated **Non-serious AEs** • Multi-Modality Treatment of ADHD (MTA) side effects scale: parent-rated weekly (Thursday evenings)
Notes	Sample calculation: no Ethics approval: no **Comment from trial authors** • Mean mg/kg dose for MPH non-responders was 0.43, which is less than the 0.3 mg/kg to 0.8 mg/kg dose known to be required for adequate response in some children with ADHD **Key conclusion of trial authors** • Both medications were superior to placebo for reducing inattentive and oppositional symptoms in the classroom and on the CGI Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes, 3 Funding source: Shire Richwood Incorporated Email correspondence with trial authors: January 2014. Supplemental information received from trial authors

Pliszka 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned: "We used a random number generator to determine which of the 3 groups the child was assigned to"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, children, teachers and treating physicians were blind to medication status. Medication was crushed, mixed with a blue food powder and placed in opaque capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo participants were randomly assigned to follow MPH or MAS treatment algorithm. The blinded psychiatrist could not determine the child's medication status simply by knowing which algorithm was being followed. Principal Investigator knew the medication status of participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Morning and afternoon IOWA scores were averaged at the end of the week Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported

Pliszka 2007

Study characteristics

Methods	5-week double-blind, cross-over, placebo-controlled trial, conducted to examine electrophysiological effects of MPH on inhibitory control in children with ADHD • MPH • Placebo
Participants	Number of participants screened: 12 Number of participants included: 12 (8 boys, 4 girls) Number of participants followed up: 12 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (100%)) Age: mean 12.3 years (range 9-15) IQ: not stated MPH-naive: 10 Ethnicity: white (67%), African American (8%), Hispanic (25%) Country: USA Setting: not stated

Pliszka 2007 *(Continued)*

	Comorbidity: ODD (45%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD, combined type • CGI: restless/impulsive ratings ≥ 1.5 SD above the mean for child's age and sex on both parent and teacher ratings **Exclusion criteria** • General Cognitive Ability on DIfferential Abilities Scale > 85 • Any substance abuse/dependence • Any neurological disease • Long-term use of any medicine • Learning disability
Interventions	Participants were randomly assigned to different possible drug condition orders of 5 mg, 10 mg, 15 mg, 20 mg MPH and placebo Mean MPH dosage: not stated Administration schedule: 3 time points Duration of each medication condition: 7 days Washout before trial initiation: not stated Medication-free period between interventions: 0 Titration period: none initiated before/after randomisation
Outcomes	**General behaviour** • Parents and Teacher CGI

Notes	Sample calculation: no
	
	Ethics approval: yes; trial approved by the Institutional Review Board of the University
	
	Comments from trial authors
	
	• "Several limitations of the study should be noted
	  ◦ Our sample was relatively small and was composed entirely of children with ADHD, combined type alone, and no other significant comorbidity other than ODD"
	  ◦ All participants were positive responders to MPH
	  ◦ Our sample was too small to examine for effects of sex and ethnicity, and results should be replicated in a larger sample"
	
	Key conclusions of trial authors
	
	• MPH may improve inhibitory control by enhancing brain mechanisms that trigger the inhibitory process and make stopping a motor act more probable (reflected by increased N200) and by increasing attentional resources to the task when unsuccessful inhibitions occur (as reflected by increased NoGo-P3)
	• These results are consistent with functional imaging studies, suggesting a role for the right frontal inferior cortex and the cingulate cortex in the pathophysiology of ADHD
	
	Comment from review authors

Pliszka 2007 *(Continued)*

- Although this study includes only good responders to MPH, this occurred by chance and not by design, as 10 out of 12 were treatment-naive

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: NIMH Grant R01 MH63986

Email correspondence with trial authors: May 2014. Trial authors could not give us the necessary data (e.g. separate data for each intervention period); therefore we could not use CGI data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information regarding generation of random sequence allocation to permit a judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	From email: "one investigator was assigned on the basis of chance; the other remained blinded"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind. One investigator assigned on the basis of chance; the other remained blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	One investigator assigned on the basis of chance; the other remained blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Pliszka 2017

Study characteristics

Methods	A 3 -week parallel trial with 2 arms: • DR-MPH and ER-MPH • Placebo Phases: 2
Participants	Number of participants screened: 163 Number of participants included: 163 (161 were included in the ITT analysis; 113 (70.2%) boys, 48 (29.8% girls) Number of participants followed up: 138 Number of withdrawals: 25

Pliszka 2017 *(Continued)*

Diagnosis of ADHD: DSM-5. 145 (90.1%) combined, 0 (0%) predominantly hyperactive-impulsive, 16 (9.9%) predominantly inattentive

Age: mean 9.3 years (SD 1.79, range 6-12 years) (of the ITT sample)

IQ: not stated

MPH-naive: 0%

Ethnicity: Hispanic/Latino (n = 34, 21.1%), non-Hispanic/Latino (n = 126, 78.3%), missing (n = 1, 0.6%) (of the ITT sample). Race was reported from the ITT sample: white (n =105, 65.2%), black/African American (n = 45, 28.0%), Asian (n = 1, 0.6%), American Indian/Alaska native (n = 1, 0.6%), other (n = 9, 5.6%)

Country: USA

Setting: day clinic/research clinic or hospital

Comorbidity: many disorders and somatic comorbidities were exclusion criteria

Comedication: psychotropics not allowed. No use of prescription medication except those specified in exclusion criterion 9 and 10

Sociodemographics: none

Inclusion criteria

- Participants must have a diagnosis of ADHD
- 6-12 years old (at the time of consent)
- ADHD-RS IV score of ≥ 90th percentile for age and gender and ≥ 26
- CGI-S score ≥ 4
- CGI - Parent score ≥ 10
- At least a partial clinical response to MPH (judged by investigators)
- Early Morning Functioning impairment and/or difficulties performing a morning routine of > 30 min in duration occurring between 6:00 and 9:00 am (parental or legal guardian confirmation)
- Body weight ≥ 20 kg
- Must be considered clinically appropriate for treatment with MPH and HLD200, including ability to swallow treatment capsules
- General good health based upon the medical history, physical, and laboratory examinations (including urine drug screen)
- Participant and parent or legal guardian must be able to read, write, and/or understand at a level sufficient to provide informed consent (parent/legal guardian) and assent (participant) prior to trial participation and to complete trial-related materials. Participant and parent or legal guardian must plan to be available for the entire trial period
- Female participants of childbearing potential (i.e. post-menarche) are required to have a negative result on urine pregnancy testing at screening (and will be given specific instructions for avoiding pregnancy during the trial)
- A medically highly effective form of birth control must be used during the trial and for 90 days thereafter for participants of either sex of childbearing potential. Examples of medically highly effective forms of birth control are as follows:
  - no sexual activity
  - use of acceptable methods of birth control including intra-uterine device, oral, implantable,or injectable contraceptives

Exclusion criteria

- History of, or current, medical condition or laboratory result which, in the opinion of the investigator, unfavourably alters the risk-benefit of trial participation, may jeopardise participant safety, or may interfere with the satisfactory completion of the trial and trial-related procedures
- Serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other cardiac problems that may place the participant at increased vulnerability to the sympathomimetic effects of a stimulant drug

Pliszka 2017 *(Continued)*

- History of seizure disorder (except febrile seizures prior to age 5 and with last occurrence at least 1 year prior to trial participation), Tourette's disorder, or intellectual disability of minor severity or greater (DSM-5 criteria)
- History of psychosis, bipolar disorder, anorexia nervosa, bulimia, or suicide attempt. Current depression, anxiety, conduct/behavior disorder, substance use disorder, or other psychiatric condition which, in the investigator's opinion, may jeopardise participant safety or may interfere with the satisfactory completion of the trial and trial-related procedures
- Active suicidal ideation as evidenced by an ideation score of ≥ 2 on the C-SSRS
- History of severe allergic reaction or intolerance to MPH
- ALT, AST, total bilirubin, or creatinine > 1.5 x the upper limit of normal (elevated bilirubin due only to Gilbert's syndrome is not exclusionary)
- History of alcohol abuse or illicit drug use
- Use of prescription medications (except per protocol allowed medications) within 7 days of Baseline (Visit 2), except for ADHD stimulant medication (72 h) and MAOIs (14 days), and over-the-counter medications (except birth control and allowed medications) within the 3 days preceding Baseline (Visit 2). Medications not covered in allowed medications or prohibited medications must be cleared by the medical monitor prior to enrolling the participant
- Use of psychotropic medications including antidepressants, mood stabilisers, and antipsychotics
- Participation in a clinical trial with an investigational drug within the 30 days preceding trial enrolment
- Previous treatment experience with HLD200
- Positive screening for illicit drug use or nicotine and/or current health conditions or use of medications that might confound the results of the trial or increase risk to the participant
- In the opinion of the investigator, the participant may have problems complying with the protocol or the procedures of the protocol, or for which the trial could pose unnecessary safety risks. This includes current health conditions or use of medications that might confound the results of the trial or increase risk to the participant
- A sibling or step-sibling that is concurrently participating in this trial who resides with and is cared for by the same parent/legal guardian as the participant

Interventions	Participants were randomly assigned to DR/ER-MPH oral capsules containing beads, titrated to 40, 60 or 80 mg (week 1, 2 and 3 respectively), or placebo matched to DR/ER-MPH oral capsules but containing microcrystalline cellulose beads in place of MPH for 3 weeks Number randomised to each group: DR/ER-MPH 82, placebo 81 Mean medication dosage: DR/ER-MPH 68.1 mg (at endpoint) Administration schedule: once daily in the evening at 8:00 pm ± 30 min; “Participants were also permitted to adjust the evening dose time between 6:30 and 9:30 pm in 30- or 60-minute increments per week to achieve optimal morning control of observed ADHD symptoms” Duration (of (each) medication): DR/ER-MPH titrated to 40 mg 1st week, 60 mg 2nd week, 80 mg 3rd week (if increases were not tolerated 1-down titration was allowed to a minimum of 40 mg), or placebo 3 weeks Washout before trial initiation: up to 2 weeks (phase 1). Stimulants, clonidine, and guanfacine required a ≥72-h washout, and any other medication used to treat ADHD required a ≥7-day washout before randomisation Treatment compliance: nothing stated besides percentage that completed the trial
Outcomes	**ADHD symptom severity** • ADHD-RS-IV **Serious AEs** • Spontaneous reporting • C-SSRS

Pliszka 2017 *(Continued)*

General behaviour

- Parent Rating of Evening and Morning Behavior-Revised, evening (PREMB-R PM) subscale (Sutton 2003)
- Parent Rating of Evening and Morning Behavior-Revised, morning (PREMB-R AM) subscale (Sutton 2003)
- Before School Functioning Questionnaire (BSFQ; Wilens 2010)

Non-serious AEs

- Spontaneous reporting
- Direct query at each visit for patients and parents on treatment emergent AEs of special interest (appetite suppression and insomnia, with sleep disturbances (onset, quality, and quantity))
- Vital signs
- ECGs
- Clinical laboratory tests
- Physical examination findings

Notes

Sample calculation: yes; 180 with an estimated dropout rate of 20%-25% = 70 participants per treatment arm after dropout

Ethics approval: yes; “All participants and parents/legal guardians provided informed assent and consent, respectively, under procedures approved by each site’s institutional review board”

Comments from trial authors

- “The short duration of the study limits the ability to extrapolate the findings over the long term. The study included school-age children (aged 6–12 years) only and, therefore, the applicability of these findings to other age groups (i.e., preschool children, adolescents, and adults) is unknown”.
- Enrolled participants have previously shown at least a partial response to MPH, and, therefore, the response and safety profiles in MPH-naïve patients may be different than those achieved in this study

Key conclusion of trial authors

- “The results of this trial demonstrated that 3 weeks of treatment with evening-dosed DR/ER-MPH is more effective than placebo in improving ADHD symptoms and at-home functional impairments from early morning to evening in children with ADHD.”
- “Evening dosed DR/ER-MPH was generally well tolerated and demonstrated a safety profile consistent with previously reported studies of MPH.”

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: yes, 5

Funding source: Ironshore Pharmaceuticals

Email correspondence with trial authors: September 2021. We received supplemental information regarding risk of bias assessment through personal email correspondence with the trial authors in September 2021 (Storm 2021f [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Medication randomisation will be performed using an interactive web response system (IWRS). The IWRS will assign subjects to a treatment group based on the pre-defined randomisation list."
Allocation concealment (selection bias)	Low risk	"A kit identification number corresponding to the assigned treatment will be assigned by IWRS."

Pliszka 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment assignments will be masked to the investigator, the sponsor, trial statistician, and the trial subjects." "If an investigator, site personnel performing assessments, or subject/parent/legal guardian is unblinded, the subject must be withdrawn from the trial, and procedures accompanying withdrawal are to be performed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment assignments will be masked to the investigator, the sponsor, trial statistician, and the trial subjects."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The ADHD-RS-IV was analysed by using a mixed-model repeated measures (MMRM) analysis that included the participant's intercept as a random effect; treatment, trial center, and visit-by-treatment interaction as fixed effects; and baseline ADHD-RS-IV total score at Visit 2 as a covariate. The BSFQ and ADHD-AM-RS were also analysed using the MMRM, as described for the primary efficacy analysis." Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	All outcomes reported

Quinn 2004

Study characteristics	
Methods	Cross-over trial with 3 interventions: • d,l-MPH • d-MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 32 Number of participants followed up: 31 (all boys) Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (combined (87.1%), hyperactive-impulsive (9.7%), inattentive (3.2%)) Age: not stated (range 9-12 years) IQ: > 80 MPH-naive: 0% Ethnicity: not stated Country: USA and Canada Setting: outpatient clinic Comorbidity: (0%) Comedication: 0% for other medications for ADHD Other sociodemographics: none

Quinn 2004 *(Continued)*

	Inclusion criteria • Male, between 9 and 12 years of age • Meet DSM-IV criteria for ADHD, as confirmed by the DISC • Clinical history of positive response to treatment with ≥ 20 mg/d of d,l-MPH for ≥ 1 month • Rating > 90th percentile on Parent and Teacher Versions of the SNAP ADHD-RS • IQ ≥ 80 as assessed by a validated intelligence test **Exclusion criteria** • Any associated CNS, cardiovascular, renal or respiratory disorder • Known sensitivity to MPH or receiving other medication for ADHD • Comorbid clinical disorders reported during clinical interview or identified during administration of the DISC
Interventions	Participants were randomly assigned to 1 of the possible drug condition orders of d-MPH, d,l-MPH and placebo. Both the order of drugs and the dose sequence were randomly assigned Mean MPH dosage: d-MPH 2.5 mg, 5 mg or 10 mg; d,l-MPH 5 mg, 10 mg or 20 mg Administration schedule: once at 8.30 am Duration of each medication condition: 1 day. Interventions were separated by ≥ 6 days Washout before trial initiation: 24 h Medication-free period between interventions: ≥ 24 h Titration period: none Treatment compliance: administered at the laboratory
Outcomes	**ADHD symptoms** • CLAM Scale: teacher-rated, at 2 h, 3.5 h and 6 h (CLAM aggressive/defiant, CLAM inattention/overactivity) • Conners' Hyperactivity Index: teacher-rated, at 2 h, 3.5 h and 6 h **Non-serious AEs** • AEs • Average pulse rate also measured
Notes	Sample calculation: no Ethics approval: approved by each centre's institutional review board **Comments from trial authors (limitations)** • Trial was conducted in a laboratory school setting (no healthy participants, high level of staffing, short and repetitive classroom period compared with a regular classroom setting) • Relatively small sample size • Narrow age range **Key conclusions of trial authors** • Efficacy of MPH resides in the d-isomer. Elimination of the i-isomer does not diminish the efficacy of an acute dose of MPH • This trial demonstrates that single low (2.5 mg), medium (5 mg) and high (10 mg) doses of d-MPH match the efficacy of equimolar single low (5 mg), medium (10 mg) and high (20 mg) doses of d,l-MPH over a 6-h period, based on repeated measurements of a surrogate measure of academic performance

Quinn 2004 *(Continued)*

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; included only children stable on MPH

Any withdrawals due to AEs: no

Funding source: Celgene

Email correspondence with trial authors: July -August 2014. We contacted trial authors to obtain safety data and supplemental information regarding randomisation, allocation concealment, blinding, handling of incomplete outcome data and outcomes, but we were not successful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised. Both the order of drugs and the dose sequence were randomly assigned
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Except for first practice day, on which only participants were blinded, administration of doses was double-blinded throughout the trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind. Blinded observers rated behaviour
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Trial authors report only 1 respondent LTFU, not related to side effects Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No protocol available

Ramtvedt 2013

Study characteristics

Methods	6-week, cross-over trial with 3 interventions: • MPH • placebo • dextroamphetamine Phases: 3
Participants	Number of participants screened: not stated Number of participants included: 36. Number of participants followed up: 36 (29 boys, 7 girls) (n = 34 for AE data) Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (combined (69%), hyperactive-impulsive (3%), inattentive (28%))

Ramtvedt 2013 *(Continued)*

	Age: mean 11.4 years (range 9-14) IQ: mean 90.9 MPH-naive: 100% Ethnicity: not stated Country: Norway Setting: outpatient clinic Comorbidity: anxiety/depressive disorder (n = 9, 25%), ODD (n = 20, 55%), learning disability (n = 22, 61%) and Asperger syndrome (n = 1, 3%) Comedication: no Other sociodemographics: none **Inclusion criteria** • ADHD diagnosis rated as > 2 SD above the mean on the CRS, DSM-IV Inattention and/or DSM-IV Hyperactivity-Impulsivity subscales • Between 9 and 14 years of age • No prior treatment with stimulants • Stimulant treatment that has been approved by a paediatrician or psychiatrist **Exclusion criteria** • Moderate to severe mental disability • Psychosis • Brain injury • Sensory deficits, motor impairment or both • Epilepsy • Factors that would substantially reduce the possibility of obtaining reliable observations from a parent or teacher
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of MPH (30 mg/d-40 mg/d), dextroamphetamine (10 mg/d-20 mg/d) and placebo Mean MPH dosage: not stated Administration schedule: MPH, 3 time points (morning, lunch and afternoon); dextroamphetamine, 2 time points (morning and afternoon) Duration of each medication condition: 2 weeks (1st week: low dose (30 mg/d), 2nd week: high dose (40 mg/d)) Washout before trial initiation: no; all were stimulant-naive Medication-free period between interventions: yes; Saturday and Sunday (48 h) Titration period: 2 weeks initiated after randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • DSM-IV Inattention and Hyperactive-Impulsive subscales from CRS – Revised, Long Version, Parent and Teacher Forms • 21-item ADHD questionnaire was developed for this trial (8 items reflecting inattention, 6 items reflecting hyperactive-impulsive behaviour and 4 items reflecting oppositional defiant behaviour), completed daily from Monday to Friday, every week by parents and teachers (Ramtvedt 2013)

Ramtvedt 2013 *(Continued)*

- Children's self-report scale - developed for this trial: 8 items, rated weekly by the children themselves

General behaviour

- CBCL
- Teacher Rating Form
- ADHD questionnaire - Inattentive subscale, teacher-rated

Non-serious AEs

- Barkley Side Effect Rating Scale: parents were instructed to rate side effects in co-operation with their child at the end of each week during the trial

Notes

Sample calculation: not stated

Ethics approval: yes

Comments from trial authors

- Drugs were not camouflaged in identical capsules, increasing the risk for identification of drug order
- In only 1 case, a parent identified the drug order with certainty. That particular child was removed from the study
- ADHD questionnaire, used to rate ADHD symptoms during the stimulant trial, was developed for this study and cannot be considered equivalent to well-established ADHD-RSs
- Sample size might not have been sufficient to detect subtle differences between stimulants at the group level

Key conclusions of trial authors

- MPH and dextroamphetamine were significantly effective. No significant superiority of 1 stimulant over the other was detected at the group level
- AEs associated with dextroamphetamine vs MPH appear similar at the group level but may differ substantially in individual children
- Overall, insomnia and decreased appetite were significantly associated with stimulants

Comments from review authors

- This does not seem to be a particularly useful paper because the main point (not explicitly stated) was to obtain an equivalence for the QbTest (measures the 3 core signs of ADHD). As a result of this, the medication regimen was dedicated to find the best effects of both medications
- Trial authors stated that the primary outcome measure was developed for the study and cannot be considered equivalent to known ADHD-RSs. Therefore, we have not used the data on ADHD symptoms in our analyses

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: first phase was conducted as part of ordinary clinical practice at Neuropsychiatric Unit, Østfold Hospital Trust. Second and third phases, data analysis and preparation of manuscript were sponsored by South-Eastern Norway Regional Health Authority, and also by Østfold Hospital Trust and National Resource Centre for ADHD, both under the umbrella of South-Eastern Norway Regional Health Authority

Email correspondence with trial authors: April 2015. We obtained supplemental information or data regarding comedication, randomisation and blinding

Risk of bias

Bias	Authors' judgement	Support for judgement

Ramtvedt 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants were randomly and evenly assigned to each of 6 possible drug orders. "The children were assigned to the 6 possible drug condition orders by drawing numbers"
Allocation concealment (selection bias)	Unclear risk	Not clear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, parents, teachers and test administrators were blinded to drug order. 1 parent identified the drug order. Tablets of similar colours, shapes and textures were administered, but the drugs were not camouflaged in identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No access to protocol

Rapport 1985

Study characteristics	
Methods	Triple-blind, randomised, cross-over trial with 4 interventions: • placebo • 5 mg MPH • 10 mg MPH • 15 mg MPH Phases • Week 1: baseline assessment • Weeks 2-5: cross-over trial
Participants	Number of participants screened: 22 Number of participants included: 14 (12 boys, 2 girls) Number of participants followed up: 11 Number of withdrawals: 1 Number of participants excluded during the trial: 2 Diagnosis of ADHD: DSM-III (subtype not stated) Age: 8.3/7.75 years (range 6-10) IQ: > 100 MPH-naive: not stated Ethnicity: white (86%), not stated (14%)

Rapport 1985 *(Continued)*

Country: USA

Setting: outpatient clinic

Comorbidity: not stated

Comedication: no

Other sociodemographics: low to middle socioeconomic status

Inclusion criteria

- DSM-III diagnosis of ADHD by the child's paediatrician and the clinic's directing clinical psychologist
- Maternal report of a developmental history consistent with ADD-H (Barkley 1981)
- Maternal rating of ≥ 2 SD above the mean for the child's age on the Werry-Weiss-Peters Activity Scale
- Teacher rating > 15 on the Abbreviated CTRS
- Children showing a favourable response to MPH (≥ 25% mean increase in classroom on-task behaviour and decrease ≥ 2 SD on the Abbreviated CTRS (compared with baseline levels) during any of the active medication weeks)
- Performance on the Matching Familiar Figures Test characteristic of a "fast-inaccurate or impulsive" responder (i.e. faster than average responses and higher than average error rates for the child's age)

Exclusion criteria

- Any gross neurological, sensory or motor impairment
- Those currently taking medication
- Those classified as non-responders, defined as neither improved (MPH-induced facilitation ≥ 25%) on the Paired Associates Learning test nor declined in relation to baseline and placebo

Interventions	Participants were randomly assigned to 1 of 24 possible drug condition orders of fixed doses of MPH (5 mg, 10 mg, 15 mg) and placebo. As a result of the small sample size, not all drug orders were used. Post hoc comparison showed that doses were distributed approximately equally across different positions in the sequence Administration schedule: once daily, in the morning Duration of each medication condition: 7 days Washout before trial initiation: none, but all weekly dosage changes occurred on Saturdays to control for potential rebound effects Titration period: none Treatment compliance: both used and unused envelopes with capsules were returned to control for medication compliance. No results regarding compliance were reported
Outcomes	**ADHD symptoms** • Abbreviated CTRS: teacher rated symptoms each Friday, in the morning, or at the end of each treatment condition • Dosage changes occurred on Saturdays No useable data
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusion of trial authors** • Results of the present investigation demonstrate a functional relationship between psychoactive medication and impulsivity, attention and behaviour of children with ADD in classroom settings

Rapport 1985 *(Continued)*

Comment from review authors

- Although trial authors refer in 1 of the articles to the other 2 articles as a recent trial and a past investigation, it seems to us that these articles discuss the exact same trial

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: not declared

Email correspondence with trial authors: July 2013. Trial authors informed us that original records were shredded after 20 years, and that they could not provide the requested data (Ramstad 2013c [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Order of drug administration was determined by randomly assigning each child to 1 of 24 possible drug disorders
Allocation concealment (selection bias)	Low risk	MPH was packaged by the pharmacist in coloured gelatin capsules to avoid detection of dose and taste. Capsules were placed in individually dated envelopes to ensure accurate dose administration
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind design (children, teachers and observers were blinded)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Teachers and observers were blind to when medication was administered and what specific doses were given
Incomplete outcome data (attrition bias) All outcomes	High risk	Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes, data from 2 of 12 children in the present investigation were not included in the statistical analyses because they were classified as non-responders according to results of the Paired Associates Learning test
Selective reporting (reporting bias)	Unclear risk	Not possible to receive a copy of the protocol

Rapport 1987

Study characteristics

Methods	Double-blind, placebo-controlled, cross-over trial with 2 interventions: • MPH (5 doses) • placebo Phases: 5 MPH doses were given in a randomly assigned, counterbalanced sequence. Children received each dose for 6 consecutive days

Rapport 1987 *(Continued)*

Participants	Number of participants screened: 134. Children were screened for inclusion after referrals from paediatricians, psychiatrists and school personnel over a 5-year period. Different publications reported different numbers of included children, ranging from 22-76 children. Trial authors stated: "this is a sample of children who were recruited across several years with publications presenting findings over that time period. Thus, there were slight differences in sample composition as more participants were added. But essentially these studies included the same sample". Different publications reported different figures for missing data, number of withdrawals and other important information. This was included in our risk of bias assessment and is reported in the risk of bias table. 1-day washout (Saturdays) was described in each publication Age: 10-12 years. Reported ages varied across publications but, in most publications, ranged from 6-11 years Diagnosis of ADHD: DSM-III diagnosis of ADHD (subtype not stated) IQ: mean 101. DuPaul 1993 (in Rapport 1987), stated that children were of average or above average intelligence Sex: 37 boys and 5 girls (Rapport 1987) MPH-naive: 100% (in both Rapport 1987 + other paper, DuPaul 1993). In Rapport 1987, 8 had experienced brief trials of stimulants within the previous 4 years Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: no children were taking medication before participating in the trial (DuPaul 1993 in Rapport 1987) Other sociodemographics: low to middle socioeconomic status (Hollingshead) (Rapport 1987 and DuPaul 1993 in Rapport 1987) **Inclusion criteria** • Independent diagnosis by the child's paediatrician and the Rhode Island Construction Leadership Council (CLC), directing clinical psychologists using DSM-III criteria for ADHD • Maternal report of a developmental history consistent with ADHD and problems in ≥ 50% of situations on the Home Situations Questionnaire • Maternal rating ≥ 2 SD above the mean for the child's age on the Werry-Weis-Peters Activity Scale • Teacher rating on the Abbreviated CTRS > 15 - the designated cut-off score for hyperactivity • Performance on the Matching Familiar Figures Test characteristic of a "fast inaccurate or impulsive" responder (i.e. faster than average responses and higher than average error rates for the child's age) • Absence of any gross neurological, sensory or motor impairment as determined by paediatric examination **Exclusion criteria** • none stated We believe that this trial consists of 13 articles. When trial authors were asked about that, Dr. DuPaul answered that many of the publications based on the Rhode Island Construction Leadership Council (CLC) Clinic "were fairly the same study". Even though some publications describe 6 inclusion criteria and others describe 5, we believe that the publications are based on the same trial (Ramstad 2013b [pers comm])
Interventions	Participants were randomly assigned to 1 of 5 possible drug condition orders of MPH and placebo. MPH was described by each child's paediatrician in the following doses: placebo, 5 mg, 10 mg, 15 mg and 20 mg. Fixed doses were prescribed (rather than mg/kg)

Rapport 1987 *(Continued)*

Administration schedule: children were seen once a week at the Rhode Island Construction Leadership Council (CLC) Clinic. Baseline measures were obtained during the child's second clinic visit to allow familiarisation with clinic personnel and testing procedures. On subsequent testing days, children were administered a capsule of the active agent (MPH) or placebo. This procedure continued until each child received each dose for 6 consecutive days. All weekly dosage changes occurred on Sundays, and no medication was administrated on Saturdays, to allow for needed washout due to inter-individual variation in serum and blood plasma levels following acute administration of MPH. All children described in the present trial were classified as favourable responders, whereas those whose performance did not improve to this extent were classified as non-responders. These criteria were established a priori. All children described in the present trial were favourable responders based on the given criteria. (Children showing drug-induced facilitation of performance ≥ 25% (i.e. a 25% drop in error rate) compared with baseline or placebo were classified as favourable responders, whereas those whose performance did not improve to this extent were classified as non-responders)

Treatment compliance: Rapport 1987 and DuPaul 1993 (in Rapport 1987): both used and unused envelopes were returned to the Rhode Island Construction Leadership Council (CLC) on a weekly basis to assess medication compliance. DuPaul 1993 and Denney 1999 (in Rapport 1987): Medication was properly administered nearly 100% of the time, with "make-up" observation days scheduled after rare occasions when compliance was not obtained

Outcomes

ADHD symptoms

- Abbreviated CTRS: once each week (1.5-2 h after morning medication)

Non-serious AEs

- Data from the Subjective Treatment Emergent Symptom Scale (no data reported on this scale. Additional data cannot be obtained from trial authors)
- Kelly 1988 (in Rapport 1987) measured heart rate. Each child's resting heart rate (average beats per minute) was measured for 5-min periods at 3 intervals (immediately before oral ingestion of MPH or placebo (intravenous), 120 min post-ingestion and 180 min post-ingestion). Each of these measurements was taken at the same relative time of day (between 2:00 pm and 6:00 pm) and on the same day of each week throughout the 6-week course of the trial

Notes

Sample calculation: no

Ethics approval: not stated. From Kelly 1988 in Rapport 1987: believe the trial was approved by the Institutional Review Board IRB at the University of Rhode Island (the site of the trial), but Dr. Rapport could confirm this (Ramstad 2013c [pers comm])

Key conclusions of trial authors

- Group results showed significant medication effects on classroom percentage of on-task behaviour, academic efficiency, teacher ratings of attention and continuous performance task omission errors
- Results indicate that higher dosages are linearly related to increasing levels of rate, and that these effects are dependent upon both the initial heart rate value and the time course of medication
- MPH had a significant effect on classroom measures of attention and academic efficiency, which were similar to those of normal control children. Still 25% of the sample failed to show normalised levels of classroom performance
- Results of the present investigation show that MPH effects were generally rate-dependent in the classical fashion (i.e. negative linear relationship between control response rate and output ratio) for responding that was controlled by schedules, which engendered both low and high response rates

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: not stated

Funding source: none, either external or internal. This project was supported in part by a Biomedical Research Support Grant (Number S07 RR05712), which was awarded to the first trial author by the Biomedical Research Support Grant Program, Division of Research Resources, NIH

Rapport 1987 *(Continued)*

Email correspondence with trial author: we contacted Dr. Rapport by email (Ramstad 2013c [pers comm]). He has stated that he does not have any supplementary data except those provided in these articles. We also contacted Dr. DuPaul (Ramstad 2013b [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Rapport 1987: "all children received each of the 5 MPH doses in a randomly assigned counterbalanced sequence"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All MPH and placebo doses were packaged in coloured gelatin capsules by the clinic's pharmacist. Capsules were sealed in individual daily-dated envelopes. All teachers were blinded as to time of administration and specific dose
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes (4 participants) All children described in the present trial were classified as favourable responders, whereas those whose performance did not improve to this extent were classified as non-responders. These criteria were established a priori. All children described in the present trial were favourable responders based on the given criteria. (Children showing drug-induced facilitation of performance ≥ 25% (i.e. a 25% drop in error rate) compared with baseline or placebo were classified as favourable responders, whereas those whose performance did not improve to this extent were classified as non-responders.
Selective reporting (reporting bias)	Unclear risk	No protocol found

Rapport 2008

Study characteristics

Methods	Double-blind, placebo-controlled, 5-week, cross-over trial with 2 interventions: • MPH (5 mg, 10 mg, 15 mg and 20 mg) • placebo Phases: baseline (1 week) and 5 cross-over phases (1 week placebo and 1 week MPH each)
Participants	Number of participants screened: not stated Number of participants included: 65 Number of participants followed up: 65 (58 boys, 7 girls) Number of withdrawals: none Diagnosis of ADHD: DSM-IV (all were of the combined subtype)

Rapport 2008 *(Continued)*

	Age: mean 8.56 years (SD 1.25; range 6-11) IQ: mean 102.8 (SD 10.0; range not stated) MPH-naive: 8 had experienced brief trials of stimulant therapy within the previous 4 years. None were prescribed psychostimulants immediately before the start of the current trial Ethnicity: white (100%) Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: low to middle **Inclusion criteria** • ADHD diagnosis confirmed by the K-SADS • Problems in ≥ 50% of the situations on the Barkley Home Situations Questionnaire • Maternal rating ≥ 2 SD above the mean on the Werry-Weiss-Peters Activity Scale • Teacher rating on the ADD/H Comprehensive Teacher Rating Scale ≥ 2 SD above the mean **Exclusion criteria** • CD; gross neurological, sensory or motor impairment
Interventions	Participants were randomly assigned to different possible drug condition orders of IR-MPH (5 mg/d, 10 mg/d, 15 mg/d, 20 mg/d) and placebo Mean MPH dosage: not stated Administration schedule: once daily, in the morning Duration of each medication condition: 1 week Washout before trial initiation: none were prescribed psychostimulants immediately before the start of the current trial Medication-free period between interventions: 1 day Titration period: none Treatment compliance: "nearly 100%; envelopes were returned on a weekly basis"
Outcomes	**Non-serious AEs** • Subject's Treatment Emergent Symptoms Scale of NIMH (adjusted to children for the children): rated weekly by observer interviewing parent and child
Notes	Sample calculation: not stated Ethics approval: yes **Comments from trial authors** • Increased frequency and/or severity of emergent symptoms reported by or observed in children receiving psychostimulant therapy are probable to the extent that dosing regimens differ from the parameters reported herein, particularly for symptoms highly specific to MPH, that is, children receiving multiple doses per day, single doses exceeding 20 mg, different MPH formulations and MPH over a longer duration of time are likely to experience greater frequency and/or severity of emergent symptoms

Rapport 2008 *(Continued)*

- IR-MPH formulary is currently used less frequently than that of newer formulations, and the generalisability of present findings to long-duration, ER and other variants is unknown

Key conclusion of trial authors

- "Collectively, our findings point to a clear need to develop psychometrically sound treatment-emergent symptom rating scales for the purposes of monitoring physical and behavioural complaints of children treated with psychostimulants"

Comment from review authors

- Trial authors used a design with a once-daily, IR-preparation of MPH. This seems to be exceptional compared with other studies

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: none

Email correspondence with trial authors: April 2014. Obtained supplemental information regarding data (Ramstad 2013c [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By email: "we used a computer-generated random assignment (without replacement) procedure with an additional stipulation that a nearly equal number of children had to be assigned to each of the possible drug condition orders. Children were entered onto the list as they entered the trial and followed that particular order (of which coders, parents, teachers and evaluators were unaware throughout the trial)" (Magnusson 2014b [pers comm])
Allocation concealment (selection bias)	Low risk	Same as above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	MPH and placebo dosages were packaged in coloured gelatin capsules by the clinic's pharmacist to avoid detection of dose and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Rater was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information received by email: no dropouts (Magnusson 2014b [pers comm]) Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting. All outcomes were reported

Reitman 2001

Study characteristics

Reitman 2001 *(Continued)*

Methods	A 20-day cross-over trial with treatment shifting daily between 2 arms: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 3 (1 boy, 2 girls) Number of participants followed-up: 3 Number of withdrawals: none Diagnosis of ADHD: not stated Age: 6.3 years (range 6-7) IQ: all participants were of normal intelligence. MPH-naive: no Ethnicity: not stated Country: USA Setting: outpatient, summer treatment camp Comorbidity: not stated Comedication: not stated Additional sociodemographics: none **Inclusion criteria** • Had a psychiatric diagnosis of ADHD • Had a T-score of at least 70 on the ADHD Index of the CPRS-Revised • Had a T-score of at least 70 on the Attention subscale of the CBCL • Had a T-score of at least 70 on the Social Problems subscale of the CBCL **Exclusion criteria** • Diagnosed with a developmental delay
Interventions	Participants were randomly assigned to receive either MPH at individual dosage or placebo in a day-by-day cross-over design. Placebo and MPH were combined with behavioral treatment and no treatment Number randomised to each group: not stated Mean medication dosage: 10 mg, 10 mg and 15 mg Administration schedule: not stated Duration (of (each) medication): not clearly stated, but from the text we assume that they received MPH and placebo for 10 days each Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: dosages were the ones that the children had responded to in a trial with classroom behaviour

Reitman 2001 *(Continued)*

	Treatment compliance: children received either medication or placebo each morning at home, and medication administration integrity was checked via phone or face-to-face confirmation each afternoon
Outcomes	**ADHD symptoms** • CTRS-Revised
Notes	Sample calculation: no Ethics approval: not stated **Comments from trial authors** • "Future studies need to be conducted to refine our understanding of the potential benefits of behavioral and pharmacologic interventions in social contexts such as athletics." **Key conclusion of trial authors** • Contrary to other research, when the token economy and medication were compared in isolation, the token system appeared more effective in reducing disruptive behavior for 2 of the 3 participants. In addition, the token system generally enhanced the effects of stimulant medication. Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes, all children had shown previous response to their individual dosage Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: none. We did not request supplemental information from the trial authors as no contact information was available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Pill boxes were used to facilitate medication administration
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both staff and children were blind to medication status
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The observers were blind to medication status and completed the Conners ADHD index following the game each day
Incomplete outcome data (attrition bias) All outcomes	Low risk	No data imputed Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Riggs 2011

Study characteristics	
Methods	16-week, randomised, 11-centre, parallel-group trial with 2 arms: • OROS-MPH • placebo Participants in both medication groups received manual-standardised, individual CBT through motivational enhancement approaches throughout the 16-week medication trial
Participants	Number of participants screened: 1334 prescreened, 450 were consented and screened. An unknown number was included in the pre-randomisation titration phase. Number of participants included: 303 (239 boys, 64 girls) Number of participants followed up: 303 (MPH 151, placebo 152) Number of withdrawals 76 (MPH 33, placebo 43) Diagnosis of ADHD: DSM-IV (combined (68.6%), hyperactive-impulsive (2.6%), inattentive (28.1%)) Age: mean 16.5 years (SD 1.3; range 13-18) IQ: all participants were cognitively normal MPH-naive: not stated Ethnicity: Hispanic (15.2%) Race: white (61.7%), African American (23.2%), Asian (1.3%), Native American/Alaskan (1.0%), other (12.7%) Country: USA Setting: outpatient clinic Comorbidity: major depressive disorder (12.5%), CD (32.3%), non-nicotine substance use disorder (100%) Comedication: drug/alcohol use Other sociodemographics: none Differences between groups : No statistically significant differences in baseline demographics were noted between the 2 groups **Inclusion criteria** • Meets DSM-IV diagnostic criteria for ADHD • Meets DSM-IV diagnostic criteria for ≥ 1 non-nicotine substance use disorder • DSM-IV ADHD Symptom Checklist score ≥ 22 derived from the adolescent-completed checklist **Exclusion criteria** • Serious medical illness or cardiac illness • History of tic disorder • Pregnant or breastfeeding • Meets DSM-IV criteria for current or lifetime psychotic disorder • Meets DSM-IV criteria for current or lifetime bipolar disorder • Requires/or prescribed other concurrent psychotropic medication • Taking any medications that may produce interactions with OROS-MPH

Riggs 2011 *(Continued)*

Opiate dependence

- Methamphetamine abuse, dependence or past month use
- Suicidal risk
- Enrolled in an inpatient, residential, day treatment or outpatient substance abuse programme within 28 days before signing consent
- Participation in other substance or mental health treatment

Exploratory analyses of treatment response (ADHD-RS)

- ADHD subtypes
  - Defined according to DSM-IV criteria (i.e. inattentive subtype with ≥ 6 inattentive symptoms and not ≥ 6 hyperactive-impulsive symptoms)
    - Number of participants excluded: 13 because they did not meet criteria for a subtype, 14 because they did not meet criteria for hyperactive-impulsive subtype
    - Number of participants included: inattentive subtype 103, combined subtype 173. Subtypes did not differ with regard to age or ethnicity but did differ with regard to sex, comorbid CD, inattentive and hyperactive-impulsive symptoms and dependence diagnoses
  - More strictly defined subtypes (i.e. strict inattentive subtype with ≥ 6 inattentive symptoms and ≤ 3 hyperactive-impulsive symptoms; strict combined type with ≥ 6 inattentive symptoms and ≥ 8 hyperactive-impulsive symptoms)
    - Number of participants included: inattentive subtype 52, combined subtype 97
- Major depressive disorder comorbidity
  - 38 participants with major depressive disorder, 265 without major depressive disorder
  - Number of participants randomly assigned
    - MPH: 19 with major depressive disorder, 133 without major depressive disorder
    - placebo: 19 with major depressive disorder, 132 without major depressive disorder
  - No significant differences between groups were noted with regard to ADHD symptom severity, comorbid CD or substance abuse or dependence diagnoses. Differences between groups were noted with regard to age, sex, court mandate to substance treatment and days of past-month non-nicotine substance use
- Comorbid CD
  - 299 participants included in this analysis. 4 were excluded because they did not have a non-tobacco substance use disorder or did not meet inclusion criteria for ADHD
  - Number of participants randomly assigned: MPH 48 with CD, placebo 49 with CD

Interventions	Participants were randomly assigned to OROS-MPH or placebo Number randomised to each group: MPH 151, placebo 152 Mean MPH dosage at the end of treatment: 68 mg Administration schedule: single dose in the morning Duration of intervention: 16 weeks Titration period: 2 weeks post-randomisation Treatment compliance: 79% (pill counts), 82.3% (self-reports)
Outcomes	**ADHD symptoms** • ADHD-RS, clinician-administered, adolescent informant: rated at baseline and weekly for 16 weeks • ADHD-RS, clinician-administered, parent informant: rated at weeks 8 and 16 **Serious AEs** • Systematically assessed by medical clinicians during weekly visits **Non-serious AEs**

Riggs 2011 *(Continued)*

- Systematically assessed by medical clinicians during weekly visits
- Laboratory assessments ascertained at baseline and at 16 weeks included liver function testing, complete blood count with differential and urinalysis
- Massachusetts General Hospital Abuse and Diversion Questionnaire, self-administered and completed monthly
- Massachusetts General Hospital Liking Scale completed at trial weeks 4, 8, 12 and 16. Relevant subscales: feeling high, feeling depressed, craving medication, craving substances

Notes

Sample calculation: yes; sample size of 300 participants was calculated for ADHD-RS

Ethics approval: yes; Institutional Review Boards approved the protocol before participant enrolment

Comments from trial authors

- One participant did not meet diagnostic criteria for ADHD, and 1 did not have a score ≥ 22 on the ADHD-RS, but both were included in analyses
- 2 participants did not meet diagnostic criteria for a non-tobacco substance use disorder but were included in analyses
- Results of this study add to the growing suspicion that CBT (for substance use disorder) may contribute to ADHD treatment response and warrants further investigation
- Limitations: this study was not powered to address safety, and no current consensus exists regarding the most valid outcome measures for ADHD in adolescents with or without substance use disorder

Key conclusions of trial authors

- OROS-MPH did not show greater efficacy than placebo for ADHD or greater reduction in substance use among adolescents concurrently receiving individual CBT for co-occurring substance use disorders
- OROS-MPH was relatively well tolerated and was associated with modestly greater clinical improvement on some secondary ADHD and substance outcome measures
- With good monitoring, and in the context of substance abuse treatment, OROS-MPH can be used safely in adolescents with a substance use disorder despite non-abstinence
- Higher baseline use of alcohol and cannabis was associated with increased risk of experiencing a treatment-related AE with OROS-MPH, but baseline use did not increase the risk of serious AEs or of any particular category of AEs
- For adolescent misuse/diversion of OROS-MPH, results suggest that OROS-MPH was not misused/diverted to a greater extent than placebo and was not impacted by baseline substance use severity
- Despite baseline differences, both inattentive and combined subtypes responded equally to treatment, suggesting limited relevance for subtype designation in treatment planning
- ADHD symptom severity (based on DSM-IV ADHD-RS) followed a slightly different course of improvement, although with no differences between the group with comorbid major depressive disorder and the group without major depressive disorder in baseline or 16-week symptom severity, or in 16-week reduction: presence of major depressive disorder was not associated with ADHD treatment response in this sample
- Interaction effects showed that OROS-MPH improved substance use disorder outcomes among adolescents with comorbid CD compared with placebo
- Although severe substance use disorder may require more intensive psychosocial treatment, OROS-MPH may improve substance treatment outcomes among adolescents with comorbid attention and conduct problems

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: unclear. Participants underwent a 2-week titration period prior to randomisation. It is not reported if any participants withdrew during the titration period due to AEs or lack of efficacy.

Any withdrawals due to AEs: reasons for withdrawals not stated

Funding source: OROS-MPH and matching placebo were supplied to the Clinical Trials Network contract pharmacy (EMINENT Services Corporation) by McNeil Consumer and Specialty Pharmaceuticals (distributor for Concerta), at no cost.

Riggs 2011 *(Continued)*

Comment from review authors

- Data are influenced by drug abuse, especially data on AEs, but no statistically significant differences between OROS-MPH and placebo in self-reported medication abuse were noted.

Email correspondence with trial authors: December 2013. We obtained supplemental information (IQ, allocation concealment and detailed description of 1 of the serious AEs)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned to OROS-MPH or matching placebo in a 1:1 ratio, stratified by site and completed by computer at a centralised location
Allocation concealment (selection bias)	Low risk	Product was supplied in pre-randomly assigned kits containing individual bottles. Kits and bottles were labelled with the protocol number and treatment/randomisation number. Labeling protected the trial, ensuring that it remained blinded, and indicated that the medication was investigational
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sites were provided blinded medication bottles for each randomly assigned participant Masking: double-blinded (participant, caregiver, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking: double-blinded (participant, caregiver, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary analyses were ITT, including all randomly assigned trial participants Completers (N = 227) were not different from non-completers (N = 76) in baseline demographic or clinical characteristics, and the proportion of completers did not differ by treatment assignment Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting.

Rubinsten 2008

Study characteristics

Methods	5-day, randomised, double-blind, placebo-controlled, cross-over trial with 4 interventions and 11 possible orders: • MPH, in 3 different dosages • placebo
Participants	Number of participants screened: 170 Number of participants included: 18 Number of participants followed up: 18 (15 boys, 3 girls) Number of withdrawals: 0

Rubinsten 2008 *(Continued)*

	Diagnosis of ADHD: DSM-IV (combined (28%), hyperactive-impulsive (0%), inattentive (72%))
	
	Age: mean 9.73 years (range not reported)
	
	IQ: mean 104.44
	
	MPH-naive: 0%
	
	Ethnicity: not stated
	
	Country: Canada
	
	Setting: outpatient clinic
	
	Comorbidity: not stated
	
	Comedication: no
	
	Other sociodemographics: none
	
	Inclusion criteria
	
	• Completed the same research protocol in an acute, randomised placebo-controlled, cross-over trial
	• IQ ≥ 82
	• No current evidence on or history of neurological dysfunction, poor physical health, uncorrected sensory impairments or history of psychosis
	• At least average reading scores
	• ADHD according to DSM-IV
	• 1 group of patients needed to have a score < 79 (n = 6)
	  ◦ 1 group had a score between 80 and 89 on the Wide Range Achievement Test (n = 6 of 9 meeting criterion)
	  ◦ 1 group had a score ≥ 90 on the Wide Range Achievement Test (n = 6 of 83 meeting criterion)
	• Free of medication for minimum of 24 h before diagnostic assessment and participation in the medical trial
	
	Exclusion criteria
	
	• Not stated

Interventions	Participants were randomly assigned to 1 of 11 possible drug condition orders of MPH (10 mg, 15 mg and 20 mg) and placebo Mean MPH dosage: 0.27 mg/kg, 0.42 mg/kg and 0.58 mg/kg, respectively Administration schedule: not stated Duration of each medication condition: 1 day Washout before trial initiation: 24 h Medication-free period between interventions: not stated Titration period: none Treatment compliance: not stated
Outcomes	**Non-serious AEs** • Examiner observed the child for possible side effects of medication
Notes	Sample calculation: no Ethics approval: not stated

Rubinsten 2008 *(Continued)*

Comment from trial authors

- "This was a sample of small children, so we do not know whether the same results would hold for adolescents or adults"

Key conclusion of trial authors

- "We found clear dissociation of MPH functions: MPH improved working memory functions but did not improve specific cognitive functions such as quantity manipulation. Moreover, MPH showed decreased efficacy for arithmetic performance in ADHD + developmental dyscalculia, highlighting the need for additional intervention in this subgroup"

Comment from review authors

- Trial authors selected 12 patients from a larger population but did not describe how this was done

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: research was completed while Dr. Rubinsten was a post-doctoral fellow at the Hospital for Sick Children (HSC), in Toronto, Canada, and was supported by the Rothschild Fellowship from Israel. It was undertaken, in part, through funding received from the Canadian Institutes of Health (CIHR: grant #MOP 64312), a CIHR post-doctoral fellowship (A-CB), and the Canada Research Chairs Program (RT)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Master randomisation tables were prepared by the research support pharmacist at the hospital using simple randomisation with restrictions. A balanced block 22 design was used
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment provided to permit a judgement of low or high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Examiner, psychiatrist, child and child's family were not informed about the child's randomisation order or daily medication status until trial completion. Placebo and active medication were prepared by the hospital pharmacist as powdered and packaged in an opaque gelatin capsule to prevent identification of content by colour, taste or volume. Each child's medication was placed in an individually named and dated envelope to ensure accurate administration
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiner, psychiatrist, child and child's family were not informed about the child's randomisation order or daily medication status until trial completion
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Samuels 2006

Study characteristics	
Methods	Double-blind, randomised, cross-over trial with 2 interventions: • MPH • placebo Phases: 2
Participants	Number of participants screened: not stated Number of participants included: 6 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean (not stated) IQ: mean (not stated) MPH-naive: not stated Ethnicity: white (100%) Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Children 5-15 years of age • Long-term stable dose of stimulant medicine for treatment of ADHD • Recruited from local private paediatrician and psychiatric offices **Exclusion criteria** • Receiving concomitant medication that might increase BP • Documented hypertension requiring antihypertensive therapy
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Mean MPH dosage: not stated Administration schedule: each child was kept on his or her previous regimen of treatment and a corresponding placebo Duration of each medication condition: 24 h Washout before trial initiation: 3-day run-in Titration period: children were kept on stable medication doses and schedules Treatment compliance: not stated
Outcomes	**Non-serious AEs**

Samuels 2006 *(Continued)*

	• 24-h ambulatory BP monitoring was performed on and off medication No separate data were available for MPH
Notes	Sample calculation: no Ethics approval: not stated **Key conclusion of trial authors** • This trial provides evidence of a possible negative cardiovascular effect of stimulant medications in children with ADHD. This potential cardiovascular risk should be balanced against the beneficial behavioural effects of this class of medication Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, all participants were already on a stable dose of MPH Any withdrawals due to AEs: unclear Funding source: not declared Email correspondence with trial authors: July 2014. Emailed trial authors to ask for additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described; "randomized in double-blind fashion"
Allocation concealment (selection bias)	Unclear risk	"Randomized in double-blind fashion"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blind". All medications and placebo were identically packaged by the research pharmacy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants who successfully underwent an ambulatory BP monitoring trial at the end of each phase were included in the primary analyses. The first trial included 17 participants, 13 of whom underwent the second trial. Of these, data from 11 participants (of whom 6 received MPH) were analysed. Unclear why the rest were not included. Selection bias (e.g. titration after randomisation → exclusion): unclear
Selective reporting (reporting bias)	Unclear risk	Protocol not found

Schachar 1997a

Study characteristics

Methods	12-month, parallel RCT with 4 arms

Schachar 1997a *(Continued)*

- MPH + parent training
- MPH + parent support
- placebo + parent training
- placebo + parent support

Follow-up at baseline (before treatment), at end of titration (3-4 weeks) and after 4, 8 and 12 months of treatment

Follow-up trial of cohort completing the 12-month RCT: participants were evaluated annually for 5 years

Participants	Number of participants screened: 302
	Number of participants included: 91 included in the RCT (74 boys, 17 girls)
	Number of participants followed up: 63 (MPH 45, placebo 18)
	Number of withdrawals: 28 (MPH 1, placebo 27)
	Diagnosis of ADHD: DSM-III-R diagnosis of ADHD (subtype not stated)
	Mean age: MPH 8.4 years, placebo 8.3 years (range 6-12)
	IQ: mean (MPH 110.3; placebo 107.6)
	MPH-naive: 100%
	Ethnicity: not stated
	Country: Canada
	Setting: research unit at hospital
	Comorbidity: ODD (MPH 56.5%, placebo 44.4%), CD (MPH 6.5%, placebo 20.0%), anxiety (MPH 21.7%, placebo 24.4%)
	Comedication: no
	Other sociodemographics: placebo group had a higher score at baseline for psychosocial adversity than those assigned to the MPH group
	Psychosocial risk index: MPH 1.5%, placebo 2.7%
	Inclusion criteria
	Screening
	• Age between 6 and 12 years • ≥ 6 of 14 ADHD symptoms on the ADHD-RS (DuPaul 1991a) • Parental report of some ADHD symptoms at school • No previous treatment with MPH • Willingness to participate in a trial that involved random assignment to treatments for ADHD (both pharmacological and non-pharmacological) • ≥ 1 parent able to communicate in English
	Diagnostic evaluation
	• Exhibit pervasive ADHD, defined as ≥ 8 of the 14 DSM-III-R criteria for ADHD, in 1 setting (at home on the PICS, or at school on the Teacher Telephone Interview (prepared by trial authors)) and ≥ 5 ADHD criteria in the other setting • History of ADHD symptoms of ≥ 6 months' duration before the age of 7 years
	Final inclusion criteria

Schachar 1997a *(Continued)*

- Exhibit pervasive ADHD, defined as ≥ 8 of the 14 DSM-III-R criteria for ADHD in 1 setting and ≥ 5 ADHD criteria in the other setting
- History of ADHD symptoms of ≥ 6 months' duration before the age of 7 years
- Estimated full-scale IQ > 80
- No primary anxiety or affective disorder

Exclusion criteria

- Attending a full-time residential or day treatment programme
- Has received regular medication for a medical problem
- Chronic medical condition including a severe motor or vocal tic disorder and Tourette's syndrome
- Prior treatment for tics

Interventions	Randomly assigned to 1 of the 4 treatment groups after stratification based on comorbid, conduct or oppositional disorder: MPH + parent training/parent support, placebo + parent training/parent support Number of participants randomised: MPH 46, placebo 45 Titration period: 3-4 weeks (depending on child's weight) after randomisation Mean MPH dosage: target dose 0.7 mg/kg body weight, twice daily Administration schedule: breakfast and lunch Duration of intervention: 12 months Treatment compliance: MPH 80%, placebo 64%
Outcomes	**ADHD symptoms** • Parent- and teacher-rated IOWA CRS at baseline, at end of titration and at 4 months **General behaviour** • Parent- and teacher-rated telephone interview probe (TIP) ("(Corkum et al., unpublished data available from authors)" Schachar 1997a, p. 756) questionnaire at baseline and at 4 months. Grouped into 4 factors: inattention, hyperactivity-impulsivity, oppositional behaviour, difficulty experienced by rater in dealing with typical daily problem situations **Non-serious adverse effects** • Parent- and teacher-rated questionnaire with 14 common side effects (modified from Barkley 1990) administered by telephone at baseline, at end of titration and at 4 months. Grouped into 4 factors: affective, overfocusing, physiological and tics. Parent-rated questionnaire with 16 possible adverse effects (also modified from Barkley 1990) at annual evaluations (telephone interviews) • Height and weight were measured at baseline, at week 3- 4 and at 4 months in the RCT, and annually in the follow-up trial. Standing height was measured in cm without shoes from floor to vertex of head. Weight in indoor clothing, without shoes, was measured in kg. Baseline and annual measures of height and weight were ascertained with the same stadiometer • Presence and severity of tics were rated at baseline, end of titration, 4 months, 8 months and 12 months by research assistants interviewing parents and teachers. Moderate and severe Tourette's-like symptoms were assessed and diagnosed by the supervising psychiatrist
Notes	Sample calculation: yes Ethics approval: yes **Comments from trial authors** • Current RCT is limited by sample size and by medium statistical power • This cannot be generalised to situations in which higher doses of MPH may be used, or to children with more than moderate tics

Schachar 1997a *(Continued)*

- Instrument used to measure adverse effects was originally designed for short-term pharmacological studies and could fail to identify potentially long-term health concerns in the follow-up trial
- Sample in the follow-up trial of previous participants in an RCT would be biased in favour of adherence relative to a cohort chosen and followed from the time of identification
- Infrequent contact with participants and lack of an untreated control group are additional limitations of the follow-up trial
- Study did not include pubertal staging

Key conclusions of trial authors

RCT

- Positive effects of MPH on behaviour are evident in the classroom, but with MPH given twice daily, parents did not report that MPH improved behaviour at home
- Comorbid anxiety did not appear to influence development of side effects or behavioural response to MPH when dose was titrated as in standard clinical practice
- Doses of MPH based on the typical clinical titration procedure did not produce significantly more tics than placebo in children with or without pre-existing (mild to moderate) tics

Follow-up trial

- Psychostimulants improve ADHD symptoms for up to 5 years, but adverse effects persist
- Long-term use of high doses of stimulants during a period of 1-5 years is likely to have measurable effects on rate of growth in school-aged children with attention deficit hyperactivity disorder

Comments from review authors

- Data in both Schachar 1997a and Diamond 1999 (secondary reference under Schachar 1997a) are preliminary (interim results of first 4 months of treatment). Data from the 2 placebo groups (cointervention: parent training and parent support) and the 2 MPH groups (same 2 cointerventions) are combined (placebo vs MPH). No final report focuses on ADHD symptoms
- As participants are allowed to switch from the allocated intervention group during the trial, we can use only data regarding adverse effects

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: yes. “Side effects were the stated reason for discontinuing MPH in five cases”

Funding source: Medical Research Council of Canada, National Health Research Development Program of Canada and the Department of Psychiatry, The Hospital for Sick Children, Toronto. Placebo pills were provided by Ciba Geigy, Canada, Ltd

Email correspondence with trial authors: September-October 2013. Unfortunately, they were not able to provide supplemental data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned after stratification based on the presence of comorbid conduct or oppositional disorder and assigned to 1 of the 4 treatment groups. Randomly assigned based on a random number table
Allocation concealment (selection bias)	Low risk	Concealed from the physician and participants before randomisation and maintained throughout the trial
Blinding of participants and personnel (performance bias)	Low risk	All participants (child, research staff, parents and teachers) were blinded to the medication assignment

Schachar 1997a *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants (child, research staff, parents and teachers) were blinded to the medication assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	No imputation method: the effect of treatment was analysed among participants who adhered to their original medication assignment. At the 4-month point, children not taking any medication were grouped with those taking placebo. When a participant switched from placebo to MPH treatment, they were counted within the MPH group Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	Not possible to find protocol

Schachar 2008

Study characteristics	
Methods	Single-centre, randomised, double-blind, 3-way cross-over trial with 2 interventions: • MPH (IR or ER) • Placebo Phases: IR-and multi-layer (ER)-release
Participants	Number of participants screened: not stated Number of participants included: 18 Number of participants followed up: 17 (15 boys, 2 girls) Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV diagnosis of ADHD (combined (100%)) Age: mean 11.3 years (range 6.8-15.3) IQ: ≥ 85 MPH-naive: 5 (29.4) Ethnicity: not stated Country: USA Setting: outpatient clinic, laboratory classroom setting Comorbidity: no Comedication: not stated Other sociodemographics: none **Inclusion criteria** • 6-15 years of age • IQ ≥ 85 within previous 12 months • Mentally and physically competent to provide written informed consent

Schachar 2008 *(Continued)*

- Ability to read, speak and understand English
- Otherwise able to comply with trial protocol

Exclusion criteria

- Allergic to MPH or amphetamines, or had a history of serious adverse reactions to MPH or lack of response to MPH
- Serious or unstable medical illness, comorbid psychiatric illness of sufficient severity to require treatment or currently receiving psychotropic medications or herbal treatments
- Disorders of the sensory organs (particularly deafness), autism, psychosis or any unstable psychiatric conditions

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of IR-MPH and ER-MPH and placebo Mean MPH dosage: 31.2 mg/d (SD 11.7 mg/d; range 20-60 mg/d), 1.2 mg/kg Administration schedule: twice daily, in the morning and at noon (4 h apart) Duration of each medication condition: 6 days Washout before trial initiation: 1 day Titration period: none. Participants who were receiving MPH at the time of trial entry received the dose of MPH that they were taking before entry into the trial Treatment compliance: not stated
Outcomes	**ADHD symptoms** • IOWA: parent-rated weekly (8 times in 1 day) • Conners' Continous Performance Task: rated weekly (8 times in 1 day) **Non-serious AEs** • Clinical Assessment of Side Effects Scale: parents and teachers separately, rated weekly 1 day before other assessments • Spontaneously reported AEs: investigator, collected weekly
Notes	Sample calculation: no Ethics approval: yes **Key conclusion of trial authors** • Both ER-MPH and IR-MPH compared with placebo demonstrated significant improvement on IOWA-CRS average total score, with onset of action observable by 1 h Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes Any withdrawals due to AEs: no Funding source: Purdue Pharma (Canada) Email correspondence with trial authors: May 2014. Emailed trial authors to ask for supplementary information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement

Schachar 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomly assigned to a treatment sequence according to a Latin square
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind; not further described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; not further described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 withdrawal due to inability to swallow capsules, all other participants were included in efficacy analyses. All participants were included in safety analyses. Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol was published

Schrantee 2016

Study characteristics	
Methods	A 16-week parallel-trial with 2 arms: • MPH • placebo Phases: 2:4 (1-week actigraphy baseline, 16-week parallel trial followed by 1-week washout, 1-week actigraphy follow-up)
Participants	Number of participants screened: 75 boys Number of participants included: 50 (100% boys) Number of participants followed-up: 48 (46 for sleep measurements) Number of withdrawals: 2 from the placebo group. Sleep outcomes were excluded for another 2 participants due to analytic errors Diagnosis of ADHD: DSM-IV (21 combined, 1 hyperactive-impulsive and 28 inattentive type) Age: placebo 11.3 MPH 11.4 (range 10-12) IQ: MPH 103.22 (SD 21.01), placebo 103.35 (15.05) MPH-naive: 100 % Ethnicity: not stated Country: the Netherlands Setting: outpatient Comorbidity: many were an exclusion criterion

Schrantee 2016 *(Continued)*

	Comedication: many were an exclusion criterion Additional sociodemographics: none **Inclusion criteria** • Male outpatients newly diagnosed with ADHD all subtypes as defined in the DSM-IV **Exclusion criteria** • Co-morbid Axis I psychiatric disorders requiring treatment with medication at trial entry, and a history of major neurological or medical illness (including epilepsy, traumatic brain injury and chronic severe tics or Tourette syndrome) • IQ < 80 ("(as measured by a subtest of the Wechsler Intelligence Scale for children-Revised (WISC-R), National Adult Reading Test (NART), authorized Dutch translation [23])" Bottelier 2014 p. 4, secondary reference under Schrantee 2016) • Current or previous treatment with medications that influence the dopamine system (for adults before 23 years of age) such as: neuroleptics, antipsychotics, D2/D3 agonists (pramipexole and ropinirole) • Current or previous dependency of drugs that influence the DA system (for adults before 23 years of age), such as: MDMA, amphetamine, methamphetamine, cocaine, heroin and LSD Version 6, November 2013 17 of 44Protocol ID/34509.000.10 ePOD-MPH • Contraindications to MPH treatment: cardiovascular diseases such as hypertension, arrhythmia, hyperthyroidism, glaucoma, suicidality, psychosis, Tourette disorder • Prenatal use of MPH by mother of the patients • Contraindications to MRI (metal implants, pacemakers, claustrophobia, etc.)
Interventions	Participants were randomly assigned to 2 different interventions, either flexible dose MPH (starting with 0.3 mg/kg day in 1-2 doses) or placebo Number randomised to each group: 25 Mean medication dosage: MPH-group 31.3043 mg/d (information from 23 participants) Administration schedule: individually fixed times during the day. 1-2 times Duration (of (each) medication): 16 weeks Washout before trial initiation: NA Titration period: trial dosage can be increased weekly with 5-10 mg/d to a maximum of 60 mg daily Treatment compliance: adherence to the trial medication was monitored at each of the 5 control visits
Outcomes	**Serious AEs** • Spontaneous reporting **Non serious AEs** • Quality of sleep measured by: SE prior to, during, and one week after treatment discontinuation, assessed using actigraphy, sleep onset latency, total sleep time, TIB, WASO, number of wake bouts (WBnumber), mean wake bout time (WBmean), interdaily stability (IS), intradaily variability (IV), the amount of activity during the 5 h with the lowest activity (L5) and during the 10 h with the highest activity, the amplitude of the sleep-wake rhythm (AMP)
Notes	Sample calculation: no Ethics approval: yes. The institutional review board of the Academic Medical Center approved the trial. **Comments from trial authors** • "Owing to its complexity, the power of the trial was limited, especially because we examined 3 different brain regions, which could have increased the risk of a type I error."

Schrantee 2016 *(Continued)*

Key conclusion of trial authors

- Because significant relationships between changes in cortical ROIs and changes in symptom severity were not observed, the functional significance remains uncertain.
- The results of this RCT yield partial support for the hypothesis that MPH treatment in development is associated with reduced cortical thinning in childhood, but not adulthood.
- "We found a strong, positive effect of 16 weeks MPH treatment on the timing, duration and quality of sleep in boys with ADHD."

Comments from review authors

- As data for the population aged 10-12 are available separately, we have included these data as a part of a larger study, in which 49 men between 23-40 also participated.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no

Any withdrawals due to AEs: yes, 1 in the placebo group

Funding source: this trial was funded by faculty resources of the Academic Medical Center, University of Amsterdam, and by grant 11.32050.26 from the European Research Area Network Priority Medicines for Children (Sixth Framework Programme). Dr Rombouts was supported by Vici (Netherlands Organisation for Scientific Research), and Dr Andersen was supported by grant DA-015403 from the National Institute on Drug Abuse.

Email correspondence with trial authors: September 2021. We received supplemental information regarding mean medication dosage and vested interest through personal email correspondence with the trial authors in September 2021. (Storm 2021g [pers comm]).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1) using a permuted block randomisation scheme generated by the local Clinical Research Unit to either IR-MPH or matching placebo treatment for 16 weeks
Allocation concealment (selection bias)	Low risk	The hospital pharmacy (Alkmaar) assigned participants to a specific allocation, using sequentially numbered containers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The placebo tablet was identical to the MPH tablet with respect to appearance and was manufactured and labelled according to guidelines (2003/94/EG). The treating physician prescribed the medication under double-blind conditions on clinical guidance (reduction in ADHD symptoms), in accordance with Dutch treatment guidelines. After trial end, blinding was checked with the participant and his psychiatrist as well as the trial investigators.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants as well as care providers and research personnel were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**"**Missing values for the CBF (3.6% [14 of 392] due to dropout and 10.7% [42 of 392] in total) and clinical assessments (3.6% [14 of 392] due to dropout and 18.9% [74 of 392] in total) were replaced using nearest neighbor interpolation within age and medication group." **Comment:** High-risk method of analysis. Only 2 withdrawals from outcomes other than sleep, therefore low risk for general behaviour.

Schrantee 2016 *(Continued)*

		Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All outcomes from trial protocol reported

Schulz 2010

Study characteristics	
Methods	Double-blind, randomised, multi-centre, triple cross-over design with 3 interventions: • ER-MPH (Ritalin) 20 mg once daily • ER-MPH (Medikinet Retard) 20 mg once daily • Placebo
Participants	Number of patients screened: 147 Number of participants included: 147 (119 boys, 28 girls) Number of participants followed up: 139 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV diagnosis (combined (55%), hyperactive-impulsive (8%), inattentive (37%)) Age: mean 10.2 years (range 6-14) IQ: not stated MPH-naive: 0% Ethnicity: not stated Country: Germany Setting: outpatient clinic Comorbidity: 6.8% (disturbance in social behaviour (2.7%), initial insomnia (0.7%), ODD (1.36%), dysphaemia (0.68%), encopresis (0.68%)) Comedication: no Other sociodemographics: none **Inclusion criteria** • DSM-IV diagnosis of ADHD confirmed by K-SADS in the German Version • All children had to be on a stable and well-tolerated dose of 20 mg-equivalent MPH for ≥ 1 month before screening **Exclusion criteria** • Patients with known previous non-response to MPH • Children with relevant somatic or psychiatric comorbidity requiring pharmacological treatment (e.g. psychosis, major depression) • Patients with warnings as described in the prescribing information for ER-MPH (Ritalin), including tic disorders

Schulz 2010 *(Continued)*

Interventions	Pre-randomisation phase and 3 treatment periods of 7 days each. Participants were randomly assigned to 1 of 6 possible drug condition orders of 20 mg ER-MPH (Ritalin), 20 mg ER-MPH (Medikinet Retard) and placebo Number of participants: not stated Mean MPH dosage: 20 mg daily Administration schedule: once daily, morning Time points: 9:00 am Duration of each medication condition: 7 days Washout before trial initiation: none Medication-free period between interventions: none Titration period: none Treatment compliance: not stated

Outcomes	**ADHD symptoms**
	
	• SKAMP (Wigal 1998) by 3 treatment-blinded observers: rated at 1.5, 3.0, 4.5, 6.0 and 7.5 h after drug intake at the end of each treatment week
	
	SeriousAEs
	
	• One serious AE was reported: a case of acute appendicitis during treatment with ER-MPH (Ritalin). This was judged to be not treatment-related
	• 4 events were reported as "severe" and drug-related: placebo: 2× aggressive behaviour; placebo: 1× lack of attention; ER-MPH (Medikinet) 1× aggressive behaviour
	
	General behaviour
	
	• Nisonger Child Behavior Rating Form (NCBRF-TIQ) to assess behaviour in children applied once at the end of each treatment period
	
	Non-serious AEs
	
	• Monitoring and recording of all AEs by
	  ○ "Non-directive questioning" at every visit
	  ○ "Regular monitoring of vital signs"
	  ○ Participants were called by phone every midweek and were asked about AEs
	  ○ Clinical abnormality in BP defined as increase or decrease ≥ 20 mmHg from age-dependent normal values (ages 6-9: SBP 90 mmHg, DBP 60 mmHg; age > 10 years: SBP 110 mmHg, DBP 75 mmHg)
	
	Clinically notable increased values for SBP were recorded under all 3 treatments: 15% on placebo, 17% on ER-MPH (Ritalin) and 18% on ER-MPH (Medikinet). Abnormal increases in DBP were noted in 5% of participants taking placebo and LA MPH (Ritalin) and in 3% of participants given ER-MPH (Medikinet). Abnormal values in SBP among participants who had normal values at screening and at baseline were recorded in only 7 participants (3 given placebo, 3 taking ER-MPH (Medikinet) and 2 taking ER-MPH (Ritalin) - as reported in the article). Changes in vital signs were attributed to sympathomimetic effects of MPH and were not considered clinically relevant

Notes	Sample calculation: yes Ethics approval: yes **Comments from trial authors** • Another factor to be considered a limitation is that all participants were known MPH responders. This decision was made to ensure that study objectives regarding efficacy were met. However, it might

Schulz 2010 *(Continued)*

have led to overestimation of treatment effect and tolerability in the overall population, as no treatment-naive participants were included in this trial
- Individual dose titration as a standard approach in everyday practice was not allowed during this trial; therefore treatment response might not have been optimal for all children
- Inclusion of many other children, all with ADHD, as well as other experimental factors might have influenced the behaviour of the individual child
- Encapsulation might have altered the pharmacokinetics of active substances

Key conclusions of trial authors

- Compared with placebo, both ER-MPH (Ritalin) and ER-MPH (Medikinet Retard) demonstrated robust treatment effects on core inattentive and hyperactive symptoms for up to 7.5 h in children with ADHD in a laboratory classroom
- Treatment with ER-MPH (Ritalin) and ER-MPH (Medikinet Retard) was generally well tolerated
- No participant had to discontinue participation in the trial because of AEs
- Although almost every third participant was affected by ≥ 1 AE, almost all AEs were of mild intensity

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; efficacy trial to prove non-inferiority of ER-MPH (Ritalin) vs ER-MPH (Medikinet). Highly restrictive inclusion criterion - responders only. Trial authors acknowledge "it might overestimate the treatment effect and the tolerability in the overall population, as no treatment naive patients have been included in this trial"

Any withdrawals due to AEs: no

Funding source: not declared. Trial aimed at showing efficacy of ER-MPH (Ritalin) with purpose of obtaining marketing authorisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was centrally generated with a validated system that automated the random assignment of treatment sequences to randomization numbers in a specified ratio"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All treating physicians, other site staff, and patients, as well as data analysts and Novartis in-house personnel, remained blinded from the time of randomization until database lock. The raters also did not have access to information about adverse events to maintain the blind" "To ensure blinding of the study, all capsules were overencapsulated in an identical optical design"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The scale was rated by three treatment-blinded observers in the classroom who were specifically trained on the SKAMP scale"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants were included in the ITT population. Missing values for the primary endpoints were replaced by the worst value observed in another participant under the same treatment at the same assessment time. For non-inferiority comparisons, the per-protocol (PP) population consisting of participants without major protocol violations was considered primary Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no

Schulz 2010 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol identified

Schwartz 2004

Study characteristics	
Methods	2-week, double-blind, placebo-controlled, cross-over, randomised clinical trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 44 (37 boys, 7 girls) Number of participants followed up: 44 Number of withdrawals: none Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.2 years (range 6-12) IQ: > 70 MPH-naive: 16 Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: CD (39%), ODD (32%), separation anxiety disorder (16%), major depression (7%) Comedication: no Other sociodemographics: income level category, mean 3.7 **Inclusion criteria** • ADHD diagnosis **Exclusion criteria** • IQ < 70 • Tourette's syndrome • Pervasive developmental disorder • Psychosis • Taking any medication other than MPH • Previous intolerance or allergic reaction to any psychostimulant
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of (0.5 mg/kg) MPH and placebo Mean MPH dosage: not stated Administration schedule: twice/day: morning/noon time points Duration of each medication condition: 7 days

Schwartz 2004 *(Continued)*

	Washout before trial initiation: yes (2 weeks) Medication-free period between interventions: not stated Titration period: none stated Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS, CTRS • Restricted Academic Situation Scale **Non-serious AEs** • Actigraphic monitoring of sleep
Notes	Sample calculation: post hoc power calculation Ethics approval: yes **Comment from trial authors** • Good responder participants showed improvement in behaviour when taking MPH but no difference in sleep-onset latency compared with those given placebo (average 49 min). However, this latency was rather long, and this was an open trial with no comparison group with poor or no response to MPH **Key conclusions of trial authors** • MPH induces a 4% reduction in ActiGraph (slight but significant sleep disturbance) • Children who responded well to MPH did not exhibit increased motor activity in sleep compared with those who did not respond or who responded poorly • Therapeutic efficiency does not come with more sleep side effects Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; exclusion of children with history of intolerance Any withdrawals due to AEs: no Funding source: grants from Le Fonds de la Recherche en Santé du Québec and the Canadian Institutes of Health Research. Email correspondence with trial authors: March-April 2014. We emailed trial authors twice to ask for supplemental information regarding data on ADHD symptoms but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After baseline assessments, children randomly received either placebo or (...)"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	No information

Schwartz 2004 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Sharp 1999

Study characteristics	
Methods	Cross-over trial with 3 interventions: • MPH • dextroamphetamine • placebo Phases • 3-week medical-free baseline, randomised administration of MPH, dextroamphetamine and placebo followed by breakfast and lunch daily • Stepwise increase in stimulant dose each week • Each phase lasted 3 weeks • Dosage range: MPH 10 mg/d-70 mg/d, dextroamphetamine 5 mg/d-30 mg/d
Participants	Number of participants screened: 150 (girls) Number of participants included: 42 girls and 56 comparison boys Number of participants followed up: 42 Number of withdrawals: 1 girl given placebo at each phase Diagnosis of ADHD: DSM-IV (subtype not stated) Mean age: 9.1 years (range 6.0-12.7) Mean IQ: boys 109.3, girls 105.2 MPH-naive: Some of the participants had no previous experience with stimulants. No information on exact number. Ethnicity: girls: white (67%), African American (19%), Hispanic (14%); boys: white (73%), African American (21%), Hispanic (4%), Asian (2%) Country: USA Setting: outpatient clinic, laboratory classroom setting Comorbidity: 71% boys, 69% girls; ODD (33% boys, 50% girls), CD (7% boys, 2% girls), major depression (0% boys, 7% girls), separation anxiety (0% boys, 2% girls), specific phobias (0% boys, 7% girls), trichotillomania (2% boys, 0% girls), tic disorders not otherwise specified (13% boys, 2% girls), enuresis (18% boys, 12% girls), reading disorder (5% boys, 8% girls) Comedication: not stated Other sociodemographics: socioeconomic status mean score 48.0 ± 25.8 (girls), 52.4 ± 26.9 (boys)

Sharp 1999 *(Continued)*

	Inclusion criteria • Girls with a history of severe hyperactivity, impulsivity and inattentiveness that interfered with home and school functioning • Symptoms of ADHD present in ≥ 2 settings • Conners' Hyperactivity factor scores from home teachers were ≥ 2 SD greater than age and sex norms **Exclusion criteria** • Full-scale IQ < 80 on WISC-R • Chronic medical or neurological disease, including Tourette's disorder and chronic tic disorders
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of MPH, dextroamphetamine and placebo Sharp 1999 Mean MPH dosage: week 1 mean dose 0.45 mg/kg, week 2 mean dose 0.85 mg/kg and week 3 mean dose 1.28 mg/kg Administration schedule: breakfast and lunch - 5 days per week administered by nurse; administered by parent on weekends Elia 1991 (secondary reference under Sharp 1999): Mean MPH dosage: week one 0.9 mg/kg, week two 1.5 mg/kg and week three 2.5 mg/kg Administration schedule: 9:00 am and 1:00 pm throughout the entire week (7 days) Duration of each medication condition: 3 weeks Washout before trial initiation: 3-week medication-free period before trial Medication-free period between interventions: none Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Conners' Hyperactivity and Conduct factors score: teacher-rated • Wender Utah Rating Scale (WURS): parent-rated • Abbreviated CTRS: completed weekly • CTRS: completed weekly **Serious AEs** Mean beneficial and adverse effects of dextroamphetamine and MPH were nearly identical for all ratings, including ratings of appetite problems. However, objectively verified significant decreases in body weight (drug main effect, F 10.27; P = 0.0002) were significantly greater for dextroamphetamine (mean change −1.1 ± 1.0 kg from baseline; P = 0.02) than for MPH (−0.4 ± 1.1 kg; not significant) Stimulant-related AEs and body weight **General behaviour** • CBCL: parent-rated • Woodstock-Johnson Achivement Battery: observer (psychologist)-rated • Teachers Report Form (TRF): teacher-rated • Conners' Parent Questionnaire (CPQ): completed weekly by parents • Children's Psychiatric Rating Scale (CPRS): completed weekly by psychiatric staff • Activity monitor (measuring truncal motor activity): from 9:00 am-4:00 pm

Sharp 1999 *(Continued)*

Non-serious AEs

- Subject Treatment Emergent Symptom Scale (STESS): physicians and parents
- Some items on the CPRS, such as nervous mannerisms and obsessive thinking: rated as AEs (Elia 1991, secondary reference under Sharp 1999)
- 24-h urine and blood studies: at baseline and at third week for each treatment

Notes

Sample calculation: no

Ethics approval: no information available

Key conclusion of trial authors

- Sharp 1999: "Our primary conclusion is that our sample of girls demonstrated very similar patterns of comorbidity and impairment and identical patterns of drug response"

Comment from review authors

- We need a lot of information on the girls

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: not declared

Email correspondence with trial authors: June 2014. We received supplemental information from Dr. Castellanos

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Order of medication (MPH, placebo or dextroamphetamine) was randomly assigned on the basis of a table administered by the research pharmacy. Dose escalation was fixed, with 2 ranges, depending on body weight (> or < 30 kg). 3 weeks (1 dose per week) in each phase. For most children, this was followed by random assignment to pemoline vs placebo after another washout period
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	MPH, dextroamphetamine and placebo were packaged in identical capsules by the NIH pharmacy and were administered by NH nurses in double-blinded randomly assigned order
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All ratings were performed blind to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Did not describe what they did with the missing data Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol published.

Shiels 2009

Study characteristics	
Methods	3-day, double-blind, placebo-controlled cross-over trial with 3 arms: • LD-MPH • HD-MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 49 (80% boys, 20% girls) Number of participants followed up: not stated Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined 35 (71%), hyperactive-impulsive 3 (6%), inattentive 11 (23%)) Age: mean 10.5 years (range 9-12) IQ: mean 104 (range not stated) MPH-naive: not stated Ethnicity: white (76%), African American (14%), other (10%) Country: USA Setting: outpatient clinic (summer research programme) Comorbidity: ODD (43%), CD (22%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-IV ADHD diagnosis • Attending ADHD summer research programme **Exclusion criteria** • Full-scale IQ < 80 • History of seizures or other neurological problems or medication to prevent seizures • History of other medical problems for which psychostimulant treatment may involve considerable risk • Current use of psychotropic medications other than for ADHD (i.e. antipsychotics, mood stabilisers, antidepressants and anxiolytics) • History or concurrent diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders • Absence of functional impairment • Vision or hearing problems that would make it difficult to complete discounting tasks (or other tasks; data not reported)
Interventions	Participants were assigned to extended-release MPH in "high" or "low" dose (range 18-90 mg/d) No of participants randomised: not stated Mean MPH: LD 39 mg (Concerta), HD 73 mg (Concerta) Administration schedule: once daily

Shiels 2009 *(Continued)*

	Time points: in the morning, 90 min before cognitive task Duration of intervention: 7:30 am-5:00 pm, Monday through Thursday Titration period: not stated Treatment compliance: not stated Washout before trial initiation: MPH 1 week if taking atomoxetine, 24 h if taking MPH
Outcomes	**General behaviour** • Impairment Rating Scale (IRS; Fabiano 2006) **Non-serious AEs** • Pittsburgh Side Effects Rating Scale, BP and heart rate assessed daily during times of peak medication effects
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusions of trial authors** • These findings provide initial evidence that stimulant medication reduces delayed discounting among those with the disorder • MPH, an effective pharmacological treatment for ADHD, reduced the preference for smaller immediate rewards over larger delayed rewards when delays and rewards were actually experienced by the child. This raises the possibility that stimulant medication improves real-world behaviour of children with ADHD by altering delay-related impulsivity **Comment from review authors** • This study focused on effects of MPH on "delay discounting", a function of impulsivity. However, no data are available on the effects of MPH on ADHD symptoms more generally, nor are data available regarding side effects or changes in blood pressure and pulse. Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: none Funding source: National Institute of Mental Health Email correspondence with trial authors: July 2014. Emailed trial authors to request additional information but have not received a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To maintain blinding, participants were given the same number of opaque capsules per day regardless of actual MPH dose"

Shiels 2009 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Silva 2005a

Study characteristics	
Methods	6-week, randomised, single-blind, placebo-controlled, cross-over trial with 5 interventions: • ER-MPH 20 mg • ER-MPH 40 mg • OROS-MPH 18 mg • OROS-MPH 36 mg • Placebo
Participants	Number of participants screened: not stated Number of participants included: 54 (34 boys, 20 girls) Number of participants followed up: 53 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (combined (70.4%), hyperactive-impulsive (1.9%), inattentive (27.8%)) Age: mean 9.4 years (range 6-12) IQ: > 80 MPH-naive: 0% Ethnicity: white (63.0%), African American (14.8%), Asian (0%), other (22.2%) Country: USA Setting: laboratory classroom Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Children 6-12 years old • Meeting DSM-IV criteria for primary diagnosis of ADHD • Written consent from parents • Treated and stabilised on total daily dose of 20 mg-40 mg MPH for ≥ 2 weeks before enrolment • Girls are required to be pre-menarchal, sexually abstinent or using an approved method of contraception

Silva 2005a *(Continued)*

- Girls of childbearing potential are required to have a negative pregnancy test before enrolment

Exclusion criteria

- IQ level ≤ 80
- Diagnosed with Tourette's syndrome or a tic disorder
- Deemed by investigator to be unable to comply with trial instructions
- Significant concurrent medical or psychiatric illness or substance abuse disorder
- History of sensitivity to MPH
- History of substance abuse
- Currently taking atomoxetine
- Have taken, or is currently taking or planning to take, any investigational drug within 30 days of trial start date

Interventions	Participants were randomly assigned to 1 of 10 possible drug condition orders of 20 mg ER-MPH, 40 mg ER-MPH, 18 mg OROS-MPH, 36 mg OROS-MPH and placebo Mean MPH dosage: not stated Administration schedule: once Duration of each medication condition: 1 day Washout before trial initiation: 1 day Medication-free period between interventions: participants were instructed to continue to take their regularly prescribed medication Sundays through Thursdays between trial days; no medication was administered on Fridays to avoid possible carry-over effects during the Saturday treatment period Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP: by blinded raters, −0.5, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose. Primary analysis time point was 2 h post-dose **Non-serious AEs** • AEs were assessed throughout the classroom period day Only 1 AE was considered to be drug-related
Notes	Sample calculation: yes; 46 Ethics approval: approved by an independent investigational review board **Comments from trial authors** • As available formulations of ER-MPH contain 11% more MPH than their OROS-MPH counterparts, outcomes might appear to be biased toward ER-MPH • OROS-MPH releases a third bolus of active drug between 8 and 12 h after dosing, whereas ER-MPH releases its last bolus at 4 h post dose. Hence, outcomes during the last 4 h of the day might, theoretically, be biased towards OROS-MPH • Study was conducted in a controlled laboratory classroom • These results are representative of participants who are known responders to MPH • All participants had been previously stabilised on ADHD medication, so they may have been able to detect a difference between active treatment and placebo **Key conclusions of trial authors**

Silva 2005a *(Continued)*

- Efficacy of ER-MPH 20 mg is similar to that of OROS-MPH 18 mg and 36 mg during the first 8 h post-dose
- Statistically greater benefits are observed with extended-release MPH 40 mg than with OROS-MPH 36 mg and persist through h 8
- Active treatments show comparable efficacy from 8-12 h post-dose
- Both doses of each MPH formulation are well tolerated

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes

Any withdrawals due to AEs: no

Funding source: Novartis Pharmaceuticals Corporation

Email correspondence with trial authors: April 2014. Sent an email to trial authors to ask for additional data but have not receive a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All trial personnel, with the exception of the nurse, pharmacist or physician dispensing medication, were blinded Trial medications were administered in an opaque container with a small aperture, so participants could not see them during administration
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The SKAMP was completed by blinded raters
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant received ER-MPH 20 and 40 mg before discontinuing the trial. Reason not stated Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol found

Silva 2006

Study characteristics

Methods	Cross-over trial with 2 interventions: • d-MPH-ER 20 mg once daily • placebo Phases: 2 cross-over phases
Participants	Number of participants screened: not stated Number of participants included: 54 (38 boys, 16 girls)

Silva 2006 *(Continued)*

Number of participants followed up: 53

Number of withdrawals: 1

Diagnosis of ADHD: DSM-IV (combined (90.7%), hyperactive-impulsive (0%), inattentive (9.3%))

Age: mean 9.4 years (range 6-12)

IQ: not stated

MPH-naive: none

Ethnicity: predominantly white

Country: USA

Setting: laboratory classroom

Comorbidity: not stated

Comedication: not stated

Other sociodemographics: none

Inclusion criteria

- Boys and girls
- Age 6-12 years
- Diagnosed with ADHD
- Must have been stabilised on MPH 20 mg/d to 40 mg/d for ≥ 1 month
- For girls: pre-menarchal, sexually abstinent or using reliable contraceptive and have negative urine pregnancy test

Exclusion criteria

- Investigator deemed IQ below average or evidence of IQ < 80; home-schooled
- Tourette's syndrome
- Tic disorder
- Significant medical illness
- Significant psychiatric illness (schizophrenia, bipolar disorder, autism)
- Parents or guardians unable to understand or follow instructions
- Taking antidepressants
- Initiated psychotherapy 3 months before screening
- Positive urine drug screening
- Poor response to MPH
- Currently taking other medications for ADHD
- Taking or planning to take another investigational drug within 30 days of trial start; previously participated in ER-d-MPH trial

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 20 mg/d d-MPH-ER and placebo Mean MPH dosage: 20 mg/d Administration schedule: once daily; morning Duration of each medication condition: 1 week Washout before trial initiation: 1 day Medication-free period between interventions: 1 day

Silva 2006 *(Continued)*

	Titration period: none Treatment compliance: 100% in laboratory classroom sessions
Outcomes	**ADHD symptoms** • SKAMP: once weekly, observer-rated **Non-serious AEs** • Recorded AEs described by parents and children, as well as in laboratory school setting, 1 day each week
Notes	Sample calculation: yes Ethics approval: not stated **Comments from trial authors** • "One of the inclusion criteria in this study was that participants were known to be currently stable on another MPH preparation" • "We listed all side effects, irrespective of whether they were reported by parent or child. These were gathered both during the week preceding laboratory observation days and during the laboratory classroom day" • "We did not systematically analyse compliance data during the week preceding the laboratory classroom." **Key conclusion of trial authors** • "In this study, once-daily d-MPH-ER 20 mg was a safe and effective treatment for paediatric participants with ADHD symptoms" Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes Any withdrawals due to AEs*:* yes; 1 (during placebo) Funding source: Novartis Email correspondence with trial authors: June 2014. Sent twice to trial author to ask for additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by computerised random number assignment
Allocation concealment (selection bias)	Low risk	Trial medication comprised 1 bottle of 5 capsules of blinded trial medication or 1 bottle of 5 matching placebo capsules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Trial medication comprised 1 bottle of 5 capsules of blinded trial medication or 1 bottle of 5 matching placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	3 independent blinded raters

Silva 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Safety population consisted of all participants who received ≥ 1 dose of trial medication. Efficacy population comprised all randomly assigned participants who provided valid efficacy measurements for both treatment periods Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Silva 2008

Study characteristics	
Methods	Randomised, multi-centre, double-blind, placebo-controlled, cross-over design with 2 interventions: • ER-d-MPH • placebo
Participants	Number of participants screened: 68 (45 boys, 23 girls) Number of participants included: 68 Number of participants followed up: 67 Number of withdrawals: 1 (from the placebo group) Diagnosis of ADHD: DSM-IV (combined (82.4%), hyperactive-impulsive (0%), inattentive (17.6 %)) Age: mean 9.5 years (range 6-12) IQ: > 70 MPH-naive: none Ethnicity: white (50%), African American (22.1%), Asian (0%), Hispanic (19.1%), other (8.8%) Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • 6-12 years of age • DSM-IV diagnosis of ADHD • Participants had to be clinically and behaviourally stable in the opinion of the referring physician and the site's principal investigator • Have taken their current dose of medication without adjustment for ≥ 2 weeks (this was required to be a total daily dose or nearest equivalent of MPH 40 mg or IR-d-MPG 20 mg (Concerta 36 mg was allowed)) • Parents and/or guardians had to provide informed consent • Female participants were required to be pre-menarchal or sexually abstinent, or had to be using an adequate and reliable contraceptive method (e.g. double-barrier method), which was documented in the medical record. Girls who were sexually active were required to have a negative result on a urine pregnancy screening test

Silva 2008 *(Continued)*

	Exclusion criteria • Children were excluded if they or their parents/guardians were unable to understand or follow instructions necessary to participate in the trial • If they were deemed by the investigator to have below-normal cognitive capacity, or if they were home schooled • Diagnosed with Tourette's disorder or a tic disorder, or had a history of, or concurrent, significant medical or psychiatric illness or substance abuse disorder • Children taking an antidepressant medication, those who initiated psychotherapy within the 3 months preceding screening and those with a positive urine drug screen • Also excluded were children with poor response or intolerance to MPH, who were currently taking other medications for ADHD or were taking or planning to take any other investigational drug within 30 days of trial start or who had previously participated in ER-d-MPH studies
Interventions	Participants were randomly assigned to ER-d-MPH or placebo Mean MPH dosage: 20 mg/d Administration schedule: once daily, in the morning Duration of each medication condition: 7 days Washout before trial initiation: 2 days Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Combined score on the SKAMP: measured at time points 1, 3, 4, 5, 7, 9, 10, 11 and 12 h post-dose by independent blinded raters. Rated at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (visit day 15) • Attention and deportment scores on the SKAMP, obtained from 0.5 h up to 12 h by independent blinded raters. Rated at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (visit day 15) • Combined score on the SKAMP, measured at time point 0.5 by independent raters. Rated at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (15) **Non-serious AEs** • Vital signs obtained at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (15) • Recording of spontaneously reported AEs
Notes	Sample calculation: no Ethics approval: yes **Comment from trial authors** • Unequal carry-over effects: as a result of the design used in this trial, a test for carry-over effects could not be performed. Instead, tests of sequence effects in the analysis of the co-variance model were examined. If tests on sequence factors among time points were statistically significant (P = 0.05), analyses were performed by each period Limitations • Each participant took ER-d-MPH for only 1 week • Only 1 dose (20 mg/d) was used, meaning that results may not be generalisable to other doses • Trial was confined to school-aged children, so applicability of results to pre-school children, adolescents or adults is unknown

Silva 2008 *(Continued)*

- All participants in this trial had been previously shown to respond to and tolerate MPH or d-MPH
- Children who received placebo during the week before the laboratory classroom day showed statistically better pre-dose performance than children who received active medication on all measures except the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale

Key conclusions of trial authors

- In this study, once-daily ER-d-MPH 20 mg was effective in treating both inattentive and behavioural symptoms in paediatric patients over a 12-h laboratory classroom day
- Primary efficacy variable - combined score on the SKAMP - showed significant superiority over placebo at all time points from 1-12 h
- Secondary efficacy variables indicated that onset of effect was rapid (0.5 h) and duration of effect was relatively long (12 h post dose)
- In this sample, the drug was safe and well tolerated
- Changes in vital signs were comparable with those of placebo

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes

Any withdrawals due to AEs; yes

Funding source: Novartis

Email correspondence with trial authors: October 2013. We received supplemental information from trial authors regarding ethics approval and data. We were not able to obtain first period data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random assignment
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All trial medications were identical in appearance for blinding purposes; double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Safety population consisted of all participants who took ≥ 1 dose of trial medication. Efficacy population included all randomly assigned participants who provided valid efficacy measurements for both treatment periods. Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Outcomes according to protocol

Smith 1998

Study characteristics

Smith 1998 *(Continued)*

Methods	**Main trial:** 8-week intensive Summer Treatment Program, including a 6-week, double-blind, cross-over trial with 4 interventions: • 3 different doses of MPH • Placebo **Follow-up trial:** retrospective follow-up trial of 16 individuals who completed double-blind, placebo-controlled, cross-over studies during 2 separate Summer Treatment Programs
Participants	**Main trial** Number of participants screened: not stated Number of participants included: 49 Number of participants followed up: 46 (41 boys, 5 girls) Number of withdrawals: 3 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 13.8 years (range 12-17) IQ: mean 101 (range 65-129) MPH-naive: 28% Ethnicity: white (85%), African American (15%) Country: USA Setting: outpatient clinic (summer treatment program) Comorbidity: ODD (50%), CD (15%) Comedication: no Other sociodemographics: median family income USD 38,500 **Inclusion criteria** • Meeting DSM-III-R diagnostic criteria for ADHD • 12th birthday before the protocol began • Verbal IQ > 80 • No conditions that precluded a trial of stimulant medication or full participation in Summer Treatment Program academic and athletic activities **Exclusion criteria** • No information **Follow-up trial** (Not used in this review) Number of participants included: 16 (all boys) Number of participants followed up: 16 Number of withdrawals: none Diagnosis of ADHD: DSM-III-R Age: mean (children) 10.2 years (range 8-11); mean (adolescents) 12.7 years (range 12-14.5) IQ: mean (children) 109; mean (adolescents) 107

Smith 1998 *(Continued)*

	MPH-naive: 4 (25%) Ethnicity: white (100%) Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: family income (children USD 37,943; adolescents USD 49,650)
Interventions	**Main trial** Participants were randomly assigned to 1 of the possible drug condition orders of 25 mg/d, 50 mg/d or 75 mg/d MPH and placebo Mean MPH dosage: 0.17 mg/kg Administration schedule: 3 times/d: 7:45 am, 11:45 am, 3:45 pm Duration of each medication condition: 6 days Washout before trial initiation: 2 weeks Medication-free period between interventions: 16 h Titration period: none Treatment compliance: not stated **Follow-up trial** (Not used in this review) Participants were randomly assigned to 1 of the possible drug condition orders of 0.3 mg/kg MPH and placebo Mean MPH dosage: 0.3 mg/kg Administration schedule: twice/d: 8:00 am and 12:00 pm Duration of each medication condition: 1 day Washout before trial initiation: 2 weeks Medication-free period between interventions: 20 h Titration period: none Treatment compliance: not stated. Adolescents were evaluated on a protocol that included placebo and 3 doses of MPH. To facilitate comparison, doses for adolescents were converted to milligrams per kilogram, and the dose closest to 0.3 mg/kg was used in this trial
Outcomes	**ADHD symptoms** • IOWA CRS (subscale: Inattention/Overactivity): completed every day by counsellors and classroom teachers **General behaviour** • IOWA CRS (subscale: Oppositional Defiant): completed every day by counsellors and classroom teachers **Non-serious AEs** • Smith 1998: "side effects rating form (rating 12 potential side effects associated with stimulant medication on a 4-point scale. A side effect rating of 3 (severe) was defined as troubling enough to con-

Smith 1998 *(Continued)*

traindicate that dose of medication): completed every day by counsellors and parents during medication assessment"

- Evans 1997 (secondary reference under Smith 1998): "ratings on major side effects associated with MPH: completed each day by classroom teachers"

Notes

Sample calculation: no
Ethics approval: not stated

Comments from trial authors

Main trial

- One participant had a full-scale IQ of 65 but was judged to be sufficiently intelligent to understand the behavioural contingencies, activity rules and social skills training provided in the programme
- Comment on high response rate in this study compared with other studies of adolescents with ADHD
  - Higher response rate in this study may be due to greater statistical and methodological power to detect medication effects compared with previous studies, including (1) a larger sample, (2) a broader range of doses, (3) measurement in a well-controlled, naturalistic setting, (4) repeated replications of medication conditions and (5) a statistical cutoff of 0.5 to define a positive response to medication

Follow-up trial

- For data compared in this study, randomisation and medication administration procedures were identical for children and adolescents, except that adolescents were evaluated on a protocol that included placebo and 3 doses of MPH. To facilitate comparison, doses for adolescents were converted to milligrams per kilogram, and the dose closest to 0.3 mg/kg was used in this study
- Sample included only white males
- Only one third of participants in the adolescent programme had completed the summer treatment programme for children
- Students exhibited a much higher than expected positive response to stimulant medication

Key conclusions of trial authors

Main trial

- Results show that the shape of the dose-response curve is influenced by the measurement method; most adolescents exhibited improved social behaviour when treated with MPH, most positive effects of MPH were achieved at the lowest dose and diminishing positive effects and increasing risk of negative effects were noted with successively higher doses

Follow-up trial

- Stimulant medication is equally effective with children and adolescents with ADHD who are engaged in similar activities

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: grants from the National Institute on Drug Abuse, the NIMH, the National Institute on Alcohol Abuse and Alcoholism and the National Institute of Child Health and Human Development

Email correspondence with trial authors: September 2014. We contacted trial authors twice to ask for supplemental information/data but have received no response

Risk of bias

Bias	Authors' judgement	Support for judgement

Smith 1998 *(Continued)*

Random sequence generation (selection bias)	Low risk	Medication conditions were randomly assigned daily, with each condition occurring once a week. Thus, adolescents received a mode of 6 replications of each medication condition
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind; no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Some missing data was caused by holidays or absences from the program" Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol

Smith 2004

Study characteristics	
Methods	n-of-1 randomised, double-blind, cross-over trial investigating the effects of MPH (Ritalin) on the disruptive behaviour of a child diagnosed with ADHD. 1-day antecedent analysis in the clinic followed by an extended school-based trial, during which participants received MPH or placebo before evaluation Duration: 15 days
Participants	Number of participants screened: not stated Number of participants included: 1 boy Number of participants followed up: 1 Number of withdrawals: none Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 11 years IQ: 124 MPH-naive: no Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none

Smith 2004 *(Continued)*

	Inclusion criteria • Not stated **Exclusion criteria** • Not stated
Interventions	Participant was randomly assigned to 1 of 2 possible drug condition orders of (20 mg/d) IR-MPH and placebo Outpatient clinic setting, duration 1 day: ingestion of 20 mg MPH or placebo 45 min before evaluation (randomised) Cross-over 4 h later followed by 2nd evaluation School setting: 15 days (3 school weeks) Administration schedule: once daily, mornings, 45 min before 1st evaluation Medication-free periods: on weekends; a total of 9 days with medication and 6 days without, randomly assigned throughout the trial period Titration period: no Washout period before trial initiation: none other than weekends Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV - School Version (18 items): completed by the teacher and an independent observer in the classroom. Classroom assessments were conducted within normal classroom activities in the morning (first 4 h of school). Mean inter-rater reliability 79% (range 56%-100%)
Notes	Sample calculation: no Ethics approval: not stated **Comments from trial authors** • A major problem with single data point analyses is the difficulty involved in generalising outcomes to other settings and times • Another difficulty involved inclusion of only 1 participant. However, the objectivity of clinic data in combination with checklist outcomes provides generalisable results, which reduces some of these limitations **Key conclusion of trial authors** • The investigation suggests that the 1-day antecedent analysis procedure could be used as an initial evaluation of the use of MPH (Ritalin) Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: October 2013. We received from trial authors supplemental information regarding diagnostic criteria
Risk of bias	

Smith 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A third party, who was not involved in the clinical procedure, determined the selection of actual medication packs
Allocation concealment (selection bias)	Low risk	A third party, who was not involved in the clinical procedure, determined the selection of actual medication packs
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A third party, not involved in the clinical procedures, determined the selection of actual medication packs. Thus, people conducting the direct evaluation were blinded to all medication manipulations (i.e. the child, parents, therapists and data collectors). However, no description was provided about whether medication and placebo pills were identical. "Prior to clinical assessment, two packets of medication were provided to the participant's parent. One package contained 20 mg of Ritalin and the other package contained a placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A third party, who was not involved in the clinical procedure, determined the selection of actual medication packs. Thus, people conducting the direct evaluation were blinded to all medication manipulations (i.e. the child, parents, therapists and data collectors)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified and no email from trial author

Smithee 1998

Study characteristics	
Methods	Cross-over trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 26 (20 boys, 6 girls) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (combined (77%), inattentive (23%)) Age: mean 9.63 years (range 6.5-12) IQ: mean 99.71 MPH-naive: 24 Ethnicity: not stated Country: USA Setting: outpatient clinic

Smithee 1998 *(Continued)*

	Comorbidity: ODD/CD (n = 13), anxiety disorders (n = 13), nocturnal enuresis (n = 4), vocal tics (n = 4), motor tics (n = 3) Comedication: not stated Other sociodemographics: middle class status; mean social class of 2.12 **Inclusion criteria** • 6.5-12 years of age • Full-scale, verbal or performance IQ ≥ 85 • Normal or corrected vision and hearing • No physical handicaps • No history of psychotic or neurological disorder • No previous psychotropic treatment except for brief interventions of at most a couple of months (n = 2) **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Mean MPH dosage: 0.78 mg/kg/d Administration schedule: 3 times daily for 14 days per medication conditions Time points: morning, noon and 4:00 pm Duration of each medication condition: 14 days Washout before trial initiation: not stated Medication-free period between interventions: no Titration period: on days 1-3, participants received a dose 2.5 mg below their target dose of 0.3 mg/kg twice/d. On days 4-7, dose was raised to 0.3 mg/kg twice/d, and on day 8, the 4:00 pm dose was added Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Abbreviated Conners' Hyperactivity Questionnaire, parent and teacher: before trial and at each phase of 14 days • IOWA, parent and teacher: before trial and at each phase of 14 days • Hyperactivity Attention and Aggression Scales of the TOTS, parent and teacher: before trial and at each phase of 14 days **Non-serious AEs** • Weight with clothes but without shoes: observer, before and last day of each phase • Interview to assess the presence of side effects: 11 somatic side effects and 3 mood problems • Appetite decrease, increased thirst, dry mouth, stomachaches, nausea, headaches, dizziness, tremors, drowsiness, sleep problems, tics, crying, anger and sadness, EEG Relatively few side effects were reported, probably in part because of adjustment in dosages in response to emergent symptoms
Notes	Sample calculation: no Ethics approval: not stated **Comment from trial authors**

Smithee 1998 *(Continued)*

- "Teachers tended to detect greater improvement with medication than did parents. (...) Nevertheless, both parents and teachers detected significant improvement with treatment."

Key conclusion of trial authors

- "Stimulant treatment increased accuracy and speed among younger children and curtailed variability of reaction time for the sample as a whole. However, MPH did not affect ERPs [event-related potentials]. In combination, results imply that enhancement of performance by MPH does not involve the demands of response selection examined in this trial."

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: unclear, not stated

Funding source: NIMH Grant MH 38228; Rafael Klorman

Email correspondence with trial authors: March 2014. We received supplemental data from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Medications were administered in random order
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medications were administered in random order, under double-blind conditions; capsules of identical appearance and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At the end of each phase, an investigator blind to pharmacological conditions administered a structured interview to the child's parent concerning emergent side effects in the preceding period
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reports of side effects led to bind reduction of dosages or omission of planned increments for 3 participants under MPH Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	Table with numbers of reported somatic effects not given

Solanto 2009

Study characteristics

Methods	Cross-over trial with 2 interventions: • MPH • placebo Phases: week-long exposure to placebo and to each of 3 different dosage regimens of IR-MPH
Participants	Number of participants screened: not stated

Solanto 2009 *(Continued)*

	Number of participants included: 30 Number of participants followed up: 25 Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (combined (60%), inattentive (40%)) Age: mean 8.53 (combined) and 9.20 (inattentive) IQ: not stated MPH-naive: all but 1 were stimulant-naive Ethnicity: not stated Country: USA Setting: hospital Comorbidity: ODD (combined 13%, predominantly inattentive 20%); learning disability (combined 40%, predominantly inattentive 20%); anxiety (combined 0%, predominantly inattentive 10%) Comedication: no Other sociodemographics: minority representation (combined 53%, predominantly inattentive 20%) **Inclusion criteria** • Between 7 and 12 years of age • Concordant reports: CPRS and CTRS - Combined group T scores ≥ 65 on both DSM-IV Inattentive and DSM-IV Hyperactive-Impulsive Scales • Predominantly Inattentive group T scores ≥ 65 on the DSM-IV Inattentive Scale and < 65 on the DSM-IV Hyperactive-Impulsive scale • Diagnosis of ADHD, combined or predominantly inattentive according to a structured diagnostic interview of the parent: DISC • Expert clinical diagnosis of ADHD based on review of all information collected **Exclusion criteria** • Currently receiving psychotropic medication • WISC-III: < 80 • Mood disorder, Tourette's disorder or psychotic disorder • Sensory impairment or chronic medical or neurological condition including asthma that required systemic medication • Colour blindness
Interventions	Participants were randomly assigned to 1 of 24 possible drug condition orders of LD-, MD- and HD-MPH and placebo Mean MPH dosage (Combined vs predominantly Inattentive): LD 0.50 ± 0.12 vs 0.44 ± 0.13; MD 0.83 ± 0.20 vs 0.73 ±-0.21; HD 1.54 ± 0.31 vs 1.40 ± 0.38 Administration schedule: 3 times daily: morning, midday and 3:00 pm Duration of each medication condition: 1 week Washout before trial initiation: not required Medication-free period between interventions: no Titration period: open-label lead-in week, not specified whether before or after randomisation of treatment

Solanto 2009 *(Continued)*

	Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS, parent and teacher: baseline and end of each medication phase • CTRS, parent and teacher: baseline and end of each medication phase • ADHD-RS-IV: observer, weekly **Non-serious AEs** • Height, weight and vital signs: observer, weekly • Side Effects Rating Scale: observer, weekly
Notes	Sample calculation: no Ethics approval: not stated **Key conclusion of trial authors** • "Results support the clinical utility of MPH in the treatment of predominantly inattentive subtype and provide no evidence of differences in response between subtypes" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: unclear if there was an open-label titration phase before randomisation Any withdrawals due to AEs: yes; 2 Funding source: not declared Email correspondence with trial authors: April 2014. We received supplemental information from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Double-blind, cross-over with week-long exposure to placebo and each of 3 different dosage regimens of IR-MPH in randomly assigned order
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, cross-over with week-long exposure to placebo and each of 3 different dosage regimens of IR-MPH in randomly assigned order. Trial medications were prepared and coded by the hospital pharmacy using identical gelatin capsules for active medication and placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Across the 4 placebo and drug conditions, data points were missing as follows: CPRS 1%, CTRS 6%, Parent SKAMP 1%, Teacher SKAMP 4%, Side Effects 0%. Missing scores were replaced by the mean of scores for that group in that condition Selection bias: titration conducted but unclear whether before or after randomisation. No participants were excluded after the 1-week titration period
Selective reporting (reporting bias)	Low risk	Protocol identified; all outcomes reported

Soleimani 2017

Study characteristics	
Methods	A 4-week cross-over-trial with 4 arms: • 1 week of MPH 0.25 mg/kg/d • 1 week of MPH 0.5 mg/kg/d • 1 week of MPH 1 mg/kg/d • 1 week of placebo Phases: 3 phases (4-week cross-over with focus on ADHD symptoms followed by 1-week washout period and 2-week cross-over with focus on DCD symptoms)
Participants	Number of participants screened: 28 Number of participants included: 17 (12 boys, 5 girls) Number of participants followed-up: 16 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV TR (100% combined type) Age: 7 years 6 months (± 18 months) (range 6-11 years or 6-12 years) IQ: 96.6 (± 12.5, range 80-118) MPH-naive: history of MPH usage, mean 22.9 days (range 0 - 90 days) Ethnicity: not stated Country: Iran Setting: outpatient Comorbidity: all participants had DCD. No other comorbidities allowed Comedication: not stated Additional sociodemographics: number of siblings: 1.3 (SD 0.5, range 1-2) **Inclusion criteria** • 6-11 years old (between 6 and 12 years) (Article and registry) • Diagnosis of ADHD and DCD based on the diagnostic interview according to DSM-IV-TR criteria • Recently diagnosed case (< 3 months), or no prior experience with stimulant medication **Exclusion criteria** • Associated psychiatric disorders (pervasive developmental disorders, anxiety, conduct, mood disorders and schizophrenia) • Evidence of a specific learning or neurological disorder (neurologic problems, seizures, cerebral palsy, sensory deficits including vision and hearing) or IQ score < 70 on Raven's intelligence test • Occurrence of side effects, poor compliance/irregular drug consumption (present in registry, not in article)
Interventions	Participants were randomly assigned to 1 of 4 possible orders of 3 different doses (0.25, 0.5 or 1 mg/kg/d) of MPH (Ritalin) and placebo for 1 week each Number randomised to each group: not stated

Soleimani 2017 *(Continued)*

	Mean medication dosage: not applicable (mean minimal effective dose per day was 17.3 mg (mean 0.85 mg/kg, ± 0.16)) Administration schedule: twice/d, 8:00 and 15:00 Duration (of (each) medication): 3 weeks of MPH with 3 different doses, 1 week of placebo Washout before trial initiation: no Medication-free period between interventions: no Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS-IV Results were only reported for the MPH intervention and no data have been included in our analysis
Notes	Sample calculation: yes. “The sample size was estimated from the previous double-blind study. We estimated that the recruitment of 13 cases would provide 90% power to detect a significant difference between the effects of treatment on motor performance at a significance of P<0.05.” Ethics approval: yes **Comments from trial authors** • "Although the MTA study found that 77 percent of children responded to MPH, we had no non-responder in this study. It is possible that this result is due to the small sample size of the study." • "The present study is the first crossover clinical trial regarding the impact of MPH on ADHD/DCD." • "It should be noted that the usage of minimal effective dosage instead of a fixed MPH dosage as well as the crossover study design are the novelties of this study compared with previous investigations." **Key conclusion of trial authors** • "The present study demonstrated that there was a significant association between ADHD symptoms and motor performance. Overall, MPH improves motor performance only in 26.6% of the children. In addition, this study revealed that the change in BOT-2 [the Bruininks-Oseretsky Test of Motor Proficiency Second Edition] score between the 2 periods was not significantly different (period effect) and the improvement to motor performance in our population was not different to with/without MPH. There is the possibility that this finding is due to a relatively short period (one week) of MPH intervention. Therefore, we recommend a replication of this study with a larger sample size and higher dosage of MPH." Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: no Any withdrawals due to AEs: no Funding source: Guilan University of Medical Sciences Email correspondence with trial authors: August, October and November 2021. We contacted the trial authors for information regarding age of participants and first-period data through personal email in August, October and November 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were randomly allocated into one of the 4 groups using a random number generator.
Allocation concealment (selection bias)	Low risk	**Quote: "**The key to the randomization was kept by the pharmacy and randomization was broken only in case of potential adverse events."

Soleimani 2017 *(Continued)*

		Comment: no adverse events stated, and no statement of code breaking.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	These drugs were prepared by the Shafa Hospital Pharmacy and placed into similar gelatinous capsules. Drugs were labelled by trial participant number according to the randomisation schedule. Parents and the researchers were blinded to child's drug condition and dosage.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents and the researchers were blinded to child's drug condition and dosage.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 withdrawal Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All outcomes from protocol reported

Stein 1996

Study characteristics	
Methods	5-week, triple-blind, placebo-controlled, cross-over trial with 4 interventions: • MPH twice daily • MPH 3 times daily • MPH titration • placebo
Participants	Number of participants screened: not stated Number of participants included: 25 (all boys) Number of participants followed up: 24 Number of withdrawals: 1 Diagnosis of ADHD: DSM-III-R (combined (88%), inattentive (12 %)) Age: mean 8.0 years (range 6-12) IQ: not stated MPH-naive: 44% Ethnicity: white (96%), Hispanic (4%) Country: USA Setting: outpatient clinic Comorbidity: ODD (28%), CD (12%) Comedication: no Other sociodemographics: Hollingshead socioeconomic status category I: 8 (33%), II: 8 (33%), III: 3 (12.5%), IV: 5 (20.8%)

Stein 1996 *(Continued)*

Inclusion criteria

- DSM-III-R ADHD diagnosis from parent interview using Disruptive Behavior Disorders module of the NIMH DISC Parent version
- Clinically significant ratings on CPRS for Impulsivity/Hyperactivity factor (T > 65) or on CBCL (parent form)
- Attention factor (T > 65)
- Teacher ratings < 20th percentile for attention or hyperactivity problems on the ADD-H Teacher Rating Scale (ACTeRS)

Exclusion criteria

- History of significant developmental delay (indicated by IQ testing or special educational services)
- Diagnosis of pervasive developmental disorder
- Unwillingness of parents or school personnel to meet trial requirements

Interventions	Participants were randomly assigned to 1 of 4 possible drug condition orders of MPH and placebo Mean MPH dosage: 8.8 mg, 0.3 mg/kg/dose Administration schedule: twice/3 times daily: 8:00 am, 12:00 pm (and 2:00 pm) Duration of each medication condition: 1 week Washout before trial initiation: ≥ 5 days Medication-free period between interventions: none Titration period: initiated after randomisation Treatment compliance: "there was generally good compliance, with a mean of 1.5 missed doses per child over the 5-week course of the study"
Outcomes	**ADHD symptoms** • CPRS, 48 items; factors include Conduct Problem, Learning Problem, Psychosomatic Problems, Impulsivity/Hyperactivity and Anxiety. Collected on a weekly basis for 5 consecutive weeks, including baseline assessment • ACTeRS: collected on a weekly basis for 5 consecutive weeks, including baseline assessment **Serious AEs** • None observed **Non-serious AEs** • Stimulant Side Effects Rating Scale (SSERS): collected on a weekly basis for 5 consecutive weeks, including baseline assessment • Sleep log: parents completed a sleep log to record the time when the child was sent to bed and fell asleep, as well as total sleep duration • ActiGraph: for 2 consecutive 18-h periods during each week, children wore an ActiGraph wrist monitor from 4:00 pm to 8:00 am to record activity level, latency to sleep onset (time sent to bed to first minute of sleep), duration of sleep and number and duration of awakenings
Notes	Sample calculation: no Ethics approval: approved by the Institutional Review Board of the University of Chicago **Comments from trial authors** • "Analysis revealed no significant effects of order on any of the measures of ADHD symptoms, sleep variables and side effects"

Stein 1996 *(Continued)*

- "Our sample size and resultant statistical power were moderate, limiting our ability to detect mild or subtle effects"

Key conclusions of trial authors

- For many children with ADHD, 3 times/d dosing may be optimal
- Few differences in acute side effects have been noted between twice/d and 3 times/d MPH dosing
- Dosing schedule should be selected according to severity and time course of ADHD symptoms, rather than in anticipation of dosing schedule-related side effects

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: yes; 1

Funding source: the work was supported by the Smart Family Foundation

Email correspondence with trial authors: July 2014. Supplemental information regarding randomisation and whether all planned outcomes were measured and reported was received from trial authors. Unfortunately, trial authors no longer had access to the dataset; therefore it has not been possible to receive supplemental data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to 1 of 4 different orders of drug administration. The research pharmacist used a random numbers table to assign participants to different orders of administration
Allocation concealment (selection bias)	Low risk	"All medication and placebos were prepared by the study pharmacist and placed in opaque gelatin capsules" In addition to the pharmacist, 1 investigator had access to the dosage code in the event of a medical emergency that necessitated breaking the blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blinded: participants always took 3 capsules daily during the trial. "Active drug phase (b.i.d. or three t.i.d. [two or three times/day]) was always preceded by a titration phase. The purpose of the titration phase was to introduce a typical dose of MPH gradually, so that any observation of side effects during the b.i.d. and t.i.d. dosing phases could not be attributed to rapid introduction of MPH"; "All medication and placebos were prepared by the study pharmacist and placed in opaque gelatin capsules"; "In addition to the pharmacist, one investigator had access to the dosage code in the event of a medical emergency that necessitated breaking the blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple-blinded: in addition to the pharmacist, one investigator had access to the dosage code in the event of a medical emergency that necessitated breaking the blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout. Data collected on this participant were used in the descriptive information for baseline, 3 times/d and titration phases Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	All planned outcomes were measured and reported

Stein 2003

Study characteristics	
Methods	4-week, double-blind, placebo-controlled, cross-over trial in which participants were randomly assigned to: • 3 doses of MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 47 (33 boys, 14 girls) Number of participants followed up: 39 Number of withdrawals: 8 Diagnosis of ADHD: DSM-IV (combined (68%), hyperactive-impulsive (0%), inattentive (32%)) Age: mean 9.02 years (range 5 years 11 months-16 years) IQ: mean 106.8 Stimulant-naive: 70% Ethnicity: white (89.4%), African American (4.3%), Hispanic (2.1%), other (4.3%) Country: USA Setting: outpatient clinic Comorbidity: ODD (17%), encopresis/enuresis (10.6%), tic disorder (2.1%) Comedication: no Other sociodemographics: predominantly mid to upper socioeconomic status referral base of the clinic **Inclusion criteria** • DSM-IV criteria for ADHD **Exclusion criteria**: • Intellectual disability • Severe mood disorders (requiring antidepressant or concurrent psychotropic medications) • Tourette's syndrome, seizure disorders or other medical disorders associated with symptoms that may mimic ADHD (e.g. thyroid disorder) • Children taking systemic medications
Interventions	Participants were randomly assigned to different orders of OROS-MPH (18 mg, 36 mg, 54 mg) and placebo. No child could start with the 54-mg dose, and 1 child who weighed < 40 kg did not receive the 54-mg dose to minimise potential side effects in smaller children Administration schedule: once daily Duration of each medication condition: 7 days Washout before trial initiation: 2-week washout period for children who took stimulant medication before trial start Medication-free period between interventions: no Titration period: none

Stein 2003 *(Continued)*

	Treatment compliance: 92% of all trial medications were given
Outcomes	**ADHD symptoms** • ADHD-RS-IV: parent-rated, at baseline and weekly during interventions • ACTeRS: teacher-rated at baseline and weekly during interventions **Non-serious AEs** • Side Effect Rating Scale (SERS; Barkley 1990): parent-rated at baseline and weekly during interventions • Vital signs (weight, height, BP, pulse and temperature): obtained weekly by clinical staff • Children's Sleep Questionnaire
Notes	Sample calculation: no Ethics approval: approved by the Institutional Review Boards of The University of Chicago, Children's National Medical Center and the General Clinical Research Center Advisory Council **Comments from trial authors** • Forced titration procedure deserves some comment • The advantage of this procedure is increased potential to determine optimal response. However, this procedure is likely to result in increased reports of stimulant side effects compared with a more gradual titration procedure In interpreting the results, several limitations should be kept in mind • Potential expectancy biases or placebo effects need to be considered because each medication differed in appearance, size and colour, and, in the case of the 54-mg condition, number of capsules • Other limitations include the short-term nature of the study, the relatively small number of participants with ADHD predominantly inattentive subtype and the measures of ADHD symptoms used that were rating scales rather than behavioural observations or laboratory measures of attention **Key conclusions of trial authors** • In children with ADHD combined subtype - the most common subtype of ADHD - increasing doses of stimulant medication were associated with increased improvement in inattention and hyperactivity symptoms • In children with ADHD predominantly inattentive subtype, symptom improvement occurred at lower doses and less benefit was derived from higher doses • In both ADHD subtypes, higher doses were associated with parent ratings of increased insomnia and decreased appetite • Children who were homozygous for the less common, 9-repeat DAT1 30-UTR genotype displayed a distinct dose–response curve from that of other genotype groups, with absence of typical linear improvement when the dose was increased from 18 mg to 36 mg and 54 mg Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes; 8 Funding source: the NIMH, the General Clinical Research Center Program of the National Center for Research Resources, and the NIH, Department of Health and Human Services Correspondence with trial authors: August 2014. We contacted trial authors to request additional data. Trial authors no longer have access to the data

Risk of bias

Bias	Authors' judgement	Support for judgement

Stein 2003 *(Continued)*

Random sequence generation (selection bias)	Low risk	Dosing schedules were assigned from a randomly ordered list of all dosing schedules
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Each medication differed in appearance, size and colour and, in the case of the 54-mg condition, number of capsules. The placebo capsule was slightly larger than the MPH preparations. Trial authors conducted several analyses to investigate the impact of these differences in appearance on the findings of the trial (almost no impact on the results) but still considered risk of bias to be high. Parents and clinicians who were blinded to genotype and medication status rated ADHD symptoms, impairment and stimulant side effects each week
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents and clinicians who were blinded to genotype and medication status rated ADHD symptoms, impairment and stimulant side effects each week
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Any child who could not complete a treatment phase was classified as a premature discontinuation. Their data were included for all phases that were completed. No description on how many participants the analyses were based on. Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	High risk	Data were included for all phases that were completed. There is no description that reveals how many people the analyses were based on. In the abstract belonging to the trial (Stein et al. 2004), researchers write that they will "prospectively evaluate the effects of different doses of stimulant medication on these and other sleep problems". This is not provided in any of the articles included in the Stein 2003 trial.

Stein 2011

Study characteristics	
Methods	8-week, double-blind, cross-over trial comparing the following: • ER-d-MPH (10 mg, 20 mg, 25-30 mg) • ER-MAS (10 mg, 20 mg, 25-30 mg) with a week of randomly assigned placebo within each drug period
Participants	Number of participants screened: 77 Number of participants included: 65 Number of participants followed up: 56 (41 boys, 15 girls) Number of withdrawals: 9 Demographic data on the 56 participants Diagnosis of ADHD: DSM-IV (combined (67%), hyperactive-impulsive (0%), inattentive (33%)) Age: mean 11.78 years (range 9-17) IQ: > 70

Stein 2011 *(Continued)*

	MPH-naive: 35.7% Ethnicity: white (41.0%), African American (41.0%), Asian (2%), Hispanic (7%), bi-racial/mixed (9%) Country: USA Setting: outpatient clinic Comorbidity: ODD (n = 11, 29.7 %), enuresis (n = 3, 8.1 %), generalised anxiety disorder (n = 1, 2.7 %) and separation anxiety (n = 1, 2.7 %) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-IV diagnosis of ADHD, any subtype • Signed informed consent and assent • CGI-S-ADHD rating ≥ 4 • Findings on physical exam, laboratory studies, vital signs and ECG are judged to be normal for age • Pulse and BP are within 95% of age and sex means • Able to complete trial instruments and swallow capsules • Willing to commit to the entire visit schedule for the trial, including ≥ 1 visit to university Medical Center **Exclusion criteria** • Intellectual disability, autism, severe mood disorders, Tourette's disorder, seizure disorders or other medical disorders that were contraindications of stimulant treatment that mimic ADHD (e.g. thyroid disorder) • Non-responder to either medication at doses offered in the trial in an adequate trial. Must not have experienced disabling adverse effects with either medication • Concomitant psychotropic medications or medications that might have a CNS effect are required • Any other medical condition that represents a contraindication for either treatment • History of alcohol or drug abuse in the past 3 months, or a positive urinary toxic screen on initial evaluation that is not explained by a time-limited medical circumstance • Girls of childbearing age who are sexually active, do not use acceptable birth control (double protection method) and, after counselling, are unwilling to do so • History of allergic reactions to multiple medications • History of psychosis • Diagnosis of bipolar disorder
Interventions	Participants were randomly assigned to 3 dose conditions of ER-d-MPH and ER-MAS administered sequentially from lowest to highest dose with a randomly assigned week of placebo during each period MPH dosage: 10 mg, 20 mg and 25-30 mg. Maximum dose was 25 mg in smaller children (i.e. < 35 kg) to minimise potential side effects Administration schedule: once daily Duration of each medication condition: 1 week Washout before trial initiation: 2-day washout period before beginning of the trial. No washout period between treatment periods Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms**

Stein 2011 *(Continued)*

- ADHD Parent Rating Scale, 4th Edition, rated weekly

Non-serious AEs

- Stimulant Side Effects Rating Scale (Barkley 1990): rated weekly by parents
- Vital signs (weight, height, BP, pulse and temperature): obtained weekly
- ECG before and after trial
- Sleep measured by actigraphy and questionnaires (from abstract)

Notes

Sample calculation: no

Ethics approval: approved by the Institutional Review Board of University of Illinois at Chicago

Comment from trial authors

- Short duration of time children were maintained on each dose and fixed dose titration

Key conclusions of trial authors

- Both ER-d-MPH and ER-MAS were associated with significant, dose-dependent reductions in ADHD symptoms
- Decreased appetite and insomnia were more common and were seen at higher dose levels for both stimulants
- Dose level, rather than stimulant class, was strongly related to medication response
- Although most children responded similarly to both stimulants, 14.3% of total samples were responders to ER-d-MPH only, and 12.5% responded only to ER-MAS
- Future comparative effectiveness studies with multiple informants and larger samples over longer time periods are necessary to develop a data-driven, personalised approach to ADHD treatment

Comment from review authors

- Protocol states that an exclusion criterion was "Non-responder to either medication at the doses offered in the study in an adequate trial". This is not written in the full text of the trial. Asked trial author about this issue, who replied, "Although non response was an exclusion [criterion] a priori, in fact this did not come up and no cases were excluded from participation based upon this". Even though this means that children in the trial were not only responders, we still chose to analyse this trial as part of the studies that included only responders

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; see comments above

Any withdrawals due to AEs: yes; 6

Funding source: investigator-initiated trial sponsored by Novartis Pharmaceuticals, with additional support provided by the University of Illinois at Chicago, Center for Clinical and Translational Science.

Email correspondence with trial authors: November and December 2013. We received supplemental data from trial authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Order of drug was randomly assigned so that 50% started with ER-d-MPH and 50% started with ER-MAS; also a randomly assigned week of placebo during each period
Allocation concealment (selection bias)	Low risk	Weekly blister packs containing capsules of trial drug, which were indistinguishable from each other

Stein 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participant, caregivers, outcome assessors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant, caregivers, outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All trial participants who received ≥ 2 weeks of trial drug to ensure that all participants had been exposed to ≥ 1 week of active drug were analysed Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Outcomes reported according to protocol

Stoner 1994

Study characteristics	
Methods	2 n-of-1, double-blind, placebo-controlled, cross-over, randomised controlled trial. Both cases received 4 levels of the following: • MPH 5 mg, 10 mg and 15 mg • Placebo After the double-blind trial, the code was broken, and the best dose was administered to the participant. Follow-up data on the best dose were also measured. Follow-up data were recorded anecdotally for the first case (Dan) and systematically for the second case (Bill)
Participants	Number of participants screened: 2 boys Number of participants included: 2 Number of participants followed up: 2 Number of withdrawals: none Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: Dan 9 years, Bill 13 years IQ: not stated MPH-naive: 100% Ethnicity: not stated Country: USA Setting: not stated Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria**

Stoner 1994 *(Continued)*

- Not stated

Exclusion criteria

- Not stated

Interventions	Participants were randomly assigned to different orders of 3 doses of MPH and placebo Mean MPH dosage: not relevant Administration schedule: once daily at breakfast Duration of each medication condition: Dan received placebo for 3 days, and 5 days of treatment with 5 mg, 10 mg or 15 mg MPH consecutively. Bill received placebo for 3 days, and 3 days of treatment with 5 mg, 10 mg or 15 mg MPH consecutively Washout before trial initiation: treatment-naive Medication-free period between interventions: 24 h between doses Titration period: none Treatment compliance: parents were instructed to initial a monitoring form each time they gave a dose to their child after breakfast. No further description of this was provided Regarding the follow-up trial: Dan 15 mg; Bill 10 mg (5 mg twice daily)
Outcomes	**General behaviour** • Child Attention Problems Scale (CAP, 12-items; Barkley 1990): teacher-rated, at the end of each medication trial **Non-serious AEs** • Stimulants Drug Side Effect Rating Scale: rated by participants, parents and Bill's teacher at the end of each medication trial
Notes	Sample calculation: not relevant Ethics approval: not stated **Comments from trial authors** • "Although results from both studies are promising, they must be interpreted with great caution because various methodological and design features introduced threats to internal validity. For example, inclusion of a no-medication day between trial phases would be more in keeping with standard practice of clinical research trials of medication" • "Even though methylphenidate has a relative low half-life (4 to 6 hours), it is thought to be completely eliminated from the body within 24 hours of ingestion; a carry-over of effect from one trial to another may have occurred" **Key conclusion of trial authors** • "Curriculum-based measurement data collected during short medication trials can be used to select a dose of MPH that is likely to be beneficial for a student's ongoing academic growth" **Comments from review authors** • As we do not know whether any of the children were intellectually disabled, we can use the trial results only in sensitivity analyses • The article reports some side effects, but we could not obtain more information on this from the trial authors; therefore, these data are not used in the review

Stoner 1994 *(Continued)*

	Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: National Association of School Psychologists Email correspondence with trial author: January 2014. Wrote to trial author to request additional information regarding ethics approval, intellectual disability, etc., but have not received a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The order of medication levels was determined randomly. In packing the envelopes, 1 of the trial authors arranged the coded envelopes according to the randomly determined order of trials
Allocation concealment (selection bias)	Low risk	Each medication level was prepared and packed in separate envelopes by a pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each dose of MPH and placebo was ground into a powder, mixed with an inert compound, and was sealed in a small coloured drug capsule, so that doses were identical in appearance and taste. Thus, the pharmacist, the data collectors, the participants and their families did not know the order of drug administration
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each dose of MPH and placebo was ground into a powder, mixed with an inert compound, and was sealed in a small coloured drug capsule, so that doses were identical in appearance and taste. Thus, the pharmacist, the data collectors, the participants and their families did not know the order of drug administration
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were provided Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol was identified, and no answer was received from the trial author

Sumner 2010

Study characteristics

Methods	3-week, triple-blind, randomised, cross-over trial with 2 interventions: • MPH or atomoxetine • placebo
Participants	Number of participants screened: not stated Number of participants included: 31 Number of participants followed up: not stated Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (subtype not stated)

Sumner 2010 *(Continued)*

	Age: mean not stated (range 6-14 years) IQ: not stated MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: none Comedication: none Other sociodemographics: none **Inclusion criteria** • 6-14 years • ADHD, any subtype, according to DSM-IV criteria • ADHD symptoms of sufficient severity to warrant pharmacotherapy, but patient had never received the active medications evaluated in this trial or had not exhibited significant treatment-limiting adverse effects while using them **Exclusion criteria** • Enrolment in self-contained special education classes • Girls with prior onset of menses: positive urine pregnancy tests at enrolment • Structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias or other serious cardiac abnormalities • Considered by the investigator to be medically inappropriate for inclusion in a trial using placebo • Prior or present use of alcohol or illicit drugs • Major medical or neurological disorders that could affect motor activity, attention, school attendance or ability to follow the trial protocol • Diagnosis of a current anxiety disorder, tics, Tourette's syndrome, major depressive disorder • History of bipolar disorder, dysthymia or psychosis, or a family history of Tourette's syndrome • Treatment with a MAOI within 14 days before screening
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders: placebo, low, medium doses of OROS-MPH; or low, medium doses of OROS-MPH, placebo Doses: low (18 mg), medium (participants < 50 kg: 27 mg; participants > 50 kg: 36 mg) Administration schedule: not stated Duration of each medication condition: 1 week Washout before trial initiation: 1 week Titration period: no Treatment compliance: not stated
Outcomes	**ADHD symptoms** • ADHD-RS: clinician-rated, weekly • CPRS - Revised: short form, parent-rated, weekly
Notes	Sample calculation: no Ethics approval: yes

Sumner 2010 *(Continued)*

Comments from trial authors

- Small participant sample size
- Short medication washout
- Lack of information about prior ADHD medication use
- Absence of a true placebo arm in a parallel design

Key conclusions of trial authors

- Use of an objective measure, coupled with more stringent treatment response thresholds, may better inform treatment decisions by clinicians and may reduce costs and enhance assay sensitivity in ADHD clinical trials
- Longer-term, multi-centre, prospective, parallel-group studies incorporating true placebo arms and more heterogeneous participant populations are warranted to confirm these preliminary findings

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; exclusion of participants who have exhibited significant treatment-limiting AEs while treated with MPH

Any withdrawals due to AEs: not stated

Funding source: it was not clear who sponsored the trial, but someone did (see authors' affiliations)

Email correspondence with trial authors: August-September 2013. We attempted to obtain supplemental information regarding characteristics of participants, withdrawals, funding and efficacy data from trial authors but without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned to 1 of 2 treatment sequence groups
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blinded: trial participants, their parents/guardians and clinicians were blinded to trial assignment in terms of medications and dosing sequences. An unblinded prescribing physician and an unblinded trial co-ordinator did not participate in clinical ratings. Placebo was matched to blinded medication, so that the 2 were indistinguishable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant withdrew before the placebo visit and was not included in these analyses Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol was available

Sunohara 1999

Study characteristics	
Methods	Cross-over trial with 3 arms: • LD-MPH • HD-MPH • placebo Phases: 3
Participants	Number of participants screened: not stated Number of participants included: 20 (16 boys, 4 girls) Number of participants followed up: 20 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 10.5 years (range 10-12) IQ: < 80 MPH-naive: none Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: ODD (n = 4), learning disability (n = 8) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Children 10-12 years of age meeting DSM-II-R criteria for ADHD recruited from Child Development Centre at Hospital for Sick Children, Canada **Exclusion criteria** • CD, externalising disorder, anxiety • IQ < 80
Interventions	Participants were randomly assigned to LD-MPH (mean 0.28 mg/kg) and HD-MPH (mean 0.56 mg/kg) and placebo in the morning and afternoon Duration of each medication condition: 2 days Washout before trial initiation: no Titration period: no Treatment compliance: not stated
Outcomes	**Non-serious AEs** • Reported as adverse effects. There were 0 adverse effects at the higher dose for all children
Notes	Sample calculation: not stated

Sunohara 1999 *(Continued)*

Ethics approval: no information

Key conclusion of trial authors

- No adverse effects of the higher dose were reported for any children

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: unclear

Any withdrawals due to AEs: no

Funding source: RESTRACOM graduate studentship for The Hospital for Sick Children Research Institute and Novartis Pharmaceuticals

Email correspondence with trial authors: April 2014. Wrote to trial authors to ask for additional data but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Swanson 1998

Study characteristics

Methods	Randomised, double-blind, cross-over trial with 6 interventions:
	
	• MPH
	• Placebo
	• MAS (Adderall) in 4 different doses
	  ○ 5 mg
	  ○ 10 mg
	  ○ 15 mg
	  ○ 20 mg

Swanson 1998 *(Continued)*

Participants	Number of participants screened: 36 Number of participants included: 33 (26 boys, 7 girls) Number of participants followed up: 29 Number of withdrawals: 4 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 10.58 years (range 7-14) IQ: > 80 MPH-naive: 0% Ethnicity: not stated Country: USA Setting: outpatient clinic (laboratory classroom) Comorbidity: none Comedication: none Other sociodemographics: none **Inclusion criteria** • Age between 7 and 14 years • Diagnosis of ADHD by DSM-IV • History of clinically significant response to typical doses of MPH (5 mg-20 mg, twice/d or 3 times/d) **Exclusion criteria** • BP outside 95th percentiles for age and sex • WISC-II: score < 80 • Abnormalities noted upon physical examination • Current treatment with a non-stimulant medication for ADHD • Comorbid disorder • History of aggressive behaviour serious enough to preclude participation in regular classroom activities
Interventions	Participants were randomly assigned to 1 of 36 possible drug condition orders of unknown dose of MPH, placebo and 4 doses of MAS (Adderall) Mean MPH dosage: not stated Administration schedule: once, morning Duration of each medication condition: 7 days Washout before trial initiation: not stated Medication-free period between interventions: none Titration period: none Treatment compliance: 30 of 33 participants completed the 7-week trial
Outcomes	**ADHD symptoms**

Swanson 1998 *(Continued)*

- SKAMP Teacher Rating Scale, as modified by Greenhill into 2 domains of Attention and Deportment (i.e. positive behaviour): completed by 1 of the teachers after each 45-min class period (i.e. every 1.5 h on the Saturday of each week, the teacher monitoring behaviour rated each student on each item)

Serious AEs

- No unusual or serious side effects were noted in this trial

Non-serious AEs

- After each classroom period (6 times/d), teachers assessed each student on the MTA 10-Item Stimulant Side Effects (SSE) rating scale
- Parents completed a side effects rating scale that included Stimulant Side Effects items plus an additional item (trouble sleeping) 3 times/d, on Monday, Wednesday and Friday of each week

Notes

Sample calculation: no

Ethics approval: not stated

Comments from trial authors

- Laboratory classroom experience may represent a novel experience for participants, and this could alter response to medication
- Group interactions in a classroom with 16 or 17 students with ADHD may be different from those in the typical classroom of 20-30 students including 1-2 children with ADHD
- Behaviour of 16-17 students with ADHD in a classroom with a student:teacher ratio of about 8:1 may be different from that in a classroom with the typical ratio of 20:1 to 30:1

Key conclusions of trial authors

- "This documentation of efficacy in a controlled study supports the addition of MAS (Adderall) to the armamentarium of psychotropic medications for treatment of ADHD"
- "Differences in time-response patterns of MAS and MPH may help tailor treatment to meet specific clinical needs of different children with ADHD"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; only known MPH responders were included

Any withdrawals due to AEs: no, not in the MPH or placebo group (2 in different MAS groups)

Funding source: grant from Richwood Pharmaceutical Company

Email correspondence with trial authors: January 2014. No reply has been received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Latin-square design (with provisions for 36 participants) was used to determine the within-participant order of administration of the 6 medication conditions, so that for each of the first 6 weeks, approximately one sixth of participants would be assigned to each of the 6 conditions. Separate randomisation was used to determine assignment of conditions across participants for week 7, to provide an opportunity to make up missed weeks
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	Low risk	For each condition, a pharmacist prepared a set of 7 identical capsules, all containing placebo (lactose), 1 of the 4 doses of MAS or MPH

Swanson 1998 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	30 of 33 participants completed the 7-week trial; 98% of data were collected as planned. For each individual, missing data (1.1% for SKAMP, 0% for Stimulant Side Effects) were replaced by the average of values from adjacent time points (or adjacent values for session 1 or 6). Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Swanson 1999

Study characteristics	
Methods	4 week, double-blind, randomised, cross-over trial with 4 interventions of each 1 day duration • MPH twice/d: 2 doses of IR-MPH 4,5 h apart • MPH Flat: morning dose of 80% twice/d morning dose and the rest at 30-minute intervals over 6 h, starting 1.5 h after first dose • MPH Ascending: morning dose of 40% twice/d morning dose and that rest as increasing doses at 30-min intervals over 5 h, starting 1.5 h after 1st dose • Placebo
Participants	Number of participants screened: not stated Number of participants included: 38 (33 boys, 5 girls) 4 withdrew before randomisation and 34 were included in the cross-over trial Number of participants followed up: 31 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 9.2 years (range 7-12) IQ: not stated MPH-naive: 0% Ethnicity: not stated Country: USA Setting: outpatient clinic (laboratory classroom) Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria**

Swanson 1999 *(Continued)*

- Diagnosis of ADHD
- Onset by 7 years of age
- Receiving current treatment with MPH doses of 5-15 mg administered 2 or 3 times/d
- 7 to 12 years of age

Exclusion criteria

- Not stated

Interventions	Participants were randomly assigned to different drug condition orders of 4 different interventions: MPH twice/d, flat and ascending, and placebo Mean MPH dosage: not stated. Nominal dose: 20 mg/d Administration schedule: 30-min intervals from 7:30 am to 3:00 pm Duration of each medication condition: 1 day Washout before trial initiation: none Titration period: none (participants were kept on current standard treatment between trial days) Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP: teacher-rated, 4 times during the day • CLAM: teacher-rated, 4 times during the day
Notes	Sample calculation: no Ethics approval: yes **Comment from trial authors** • Of the 38 children recruited for this trial, only 34 entered **Key conclusion of trial authors** • Acute tolerance to MPH appears to exist **Comment from review authors** • Publication includes 2 studies: in study I, relative efficacy was determined for 3 dosing patterns of MPH vs placebo. In study II, tolerance was assessed by comparison of 3-times-a-day regimens of MPH only. The latter is not part of the data extraction Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, only participants on a stable dose of MPH were included Any withdrawals due to AEs: unclear. No information about withdrawals given Funding: ALZA Corporation, Palo Alto, California Email correspondence with trial authors: May 2014. Emailed trial authors to ask for additional information. No reply has been received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"On subsequent Saturdays, each child received (in random order) 1 of 3 possible drug condition orders of MPH and placebo"

Swanson 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All treatments were administered in identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Only completers were followed up Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): unclear, no information about withdrawals
Selective reporting (reporting bias)	Unclear risk	No protocol was published.

Swanson 2002a

Study characteristics	
Methods	Randomised, double-blind, cross-over design: • IR-MPH 3 times/d or MPH experimental administration • placebo
Participants	Number of participants screened: not stated Number of participants included: 32 (28 boys, 4 girls) Number of participants followed up: 30 Number of withdrawals: 2, due to personal commitments Diagnosis of ADHD: DSM-IV (combined (93.8%), hyperactive-impulsive (6.2%), inattentive (0%)) Age: mean 9.9 years (range 7-13) IQ: not stated MPH-naive: 0%, all children in the trial were undergoing treatment with MPH when they were enrolled Ethnicity: not stated Country: USA Setting: outpatient clinic (laboratory classroom) Comorbidity: 0% Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD

Swanson 2002a *(Continued)*

- Normal BP
- Not physically ill
- Able to understand that they could withdraw from the trial at any time

Exclusion criteria

- ODD
- CD
- Mood disorders
- Anxiety disorders

Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of 5 mg, 10 mg or 15 mg, 3 times/d or 18 mg/d, 36 mg/d or 54 mg/d administered in bolus at 7:30 am and once every 30 min for 8 h of MPH and placebo Mean MPH dosage: not stated Administration schedule: 3 time points Duration of each medication condition: 1 day Washout before trial initiation: not stated Medication-free period between interventions: none Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP **General behaviour** • ActiGraph activity measurements **Non-serious AEs** • Proof of Concept Study (n = 32) • Teachers: appetite loss (3 times/d, n = 6; ascending, n = 7) • Parent reports of somatic complaints (primarily headache or stomachache): 3 times/d MPH (n = 9), ascending (n = 5) • Sleep onset was delayed slightly in the medication conditions (ascending, 0.65 h; 3 times/d, 0.55 h)
Notes	Sample calculation: not stated Ethics approval: yes **Comments from trial authors (limitations)** • Lack of normal control participants • Use of subjective rating measures • Use of different ActiGraph modes of operation • Lack of a systematic evaluation of whether baseline levels of behaviour were predictive of medication effects **Key conclusions of trial authors** • Combination of an initial bolus of MPH and an ascending pattern of small doses significantly decreased hyperactivity and reduced inappropriate behaviour

Swanson 2002a *(Continued)*

- Studies showed acute tolerance to clinical doses of MPH and application of this: creation of an ascending drug delivery pattern (OROS) of rapid onset and with long duration of effect

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, all children in the trial were undergoing treatment with MPH when they were enrolled

Any withdrawals due to AEs: no

Funding source: funding: ALZA Corporation

Email correspondence with trial authors: trial authors were contacted twice by email and were asked for much supplemental information regarding data, but we have received no data; therefore, most of the data from this trial cannot be used in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized, 3-way, crossover trial in which a double-blind, double-dummy procedure was used"
Allocation concealment (selection bias)	Unclear risk	Not enough information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not enough information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 withdrawals, due to personal commitments Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	"Two additional items developed (from SKAMP) for the NIMH Collaborative Multisite Multimodal Treatment Study of Children With ADHD (MTA) (Greenhill et al., 2001) were included in the classroom ratings but were not included in the analyses of this study"

Swanson 2002b

Study characteristics

Methods	Randomised, 3-way, cross-over trial with 2 interventions: • MPH (3 times/d or ER-OROS-MPH) • Placebo Phases: 3
Participants	Number of participants screened: not stated Number of participants included: 64 (81.3% boys)

Swanson 2002b *(Continued)*

	Number of participants followed up: 59 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV (combined (82.8%), hyperactive-impulsive (not stated), inattentive (not stated)) Age: mean 9.2 years (range 6-12) IQ: not stated MPH-naive: none Ethnicity: white (82.8%), African American (not stated), Asian (not stated), Hispanic (not stated) Country: USA Setting: outpatient clinic (laboratory classroom) Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-IV criteria for ADHD diagnosis, treated with IR-MPH 5 mg-15 mg twice/d or 3 times/d **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of 5 mg, 10 mg or 15 mg, 3 times/d, or 18 mg, 36 mg or 54 mg OROS-MPH and placebo Mean MPH dosage: not stated Administration schedule: 3 times/d 7:30 am, 11:30 am and 3:30 pm; OROS-MPH 7:30 am Duration of each medication condition: 1 week Washout before trial initiation: not stated Medication-free period between interventions: not stated Titration period: none Treatment compliance: no measure
Outcomes	**ADHD symptoms** • SKAMP: rated by laboratory school teacher on attendance on Saturdays • CLAM: rated by parent and community teacher on Fridays • SNAP: rated by community teacher and parent at the end of each week **Non-serious AEs** • "In addition to the effectiveness and efficacy measures, adverse effects were actively solicited and assessed and information about sleep, appetite, and tics was collected using a parent questionnaire" • Vital signs (BP, pulse) after each classroom session on Saturdays in the laboratory school setting • Sleep: activity monitoring and parental assessment
Notes	Sample calculation: not stated

Swanson 2002b *(Continued)*

Ethics approval: not stated

Key conclusion of trial authors

- "Pharmacokinetic/Pharmacodynamic modelling provided the target for a novel drug delivery pattern to overcome these shortcomings: an initial bolus to elicit a rapid response and an ascending pattern of drug delivery to maintain constant effects"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; "The children with ADHD in the proof-of-concept and proof-of-product studies were selected based on a history of clinical response to stimulant medication, and this limits the extrapolation of the findings to the drug-naive population"

Any withdrawals due to AEs: no

Funding: ALZA Corporation

Email correspondence with trial authors: March 2014. We contacted trial authors twice by email and asked for supplemental information regarding data, but we have received no data; therefore most of the data from this trial cannot be used in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Double-blind procedures were implemented by administration of MPH or placebo in capsules
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, double-dummy procedure was used to disguise the 3 treatments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 participants not followed up
Selective reporting (reporting bias)	Unclear risk	No protocol

Swanson 2004b

Study characteristics

Methods	Multi-centre, double-blind, double-dummy, placebo-controlled, cross-over trial in an analogue classroom setting comparing 3 treatment conditions • ER-MPH (Metadate CD) • ER-MPH (Concerta) • placebo

Swanson 2004b *(Continued)*

	Each treatment intervention lasted a week
Participants	Number of participants screened: 214 Number of participants included: 184 (131 boys, 48 girls) Number of participants followed up: 157/184 ITT Number of withdrawals: 27 Diagnosis of ADHD: DSM-IV (combined (82.2%), hyperactive-impulsive (4.8%), inattentive (13.0 %)) Age: mean 9.6 years (range 6-12) IQ: > 80 MPH-naive: none Ethnicity: white (70%), African American (11.5%), Asian (1.7%), Hispanic (12.5%), other (5.3%) Country: USA Setting: outpatient clinic Comorbidity: approximately 25% had a comorbid condition; anxiety and ODD were most frequent. Girls had a greater rate of comorbid anxiety disorder (from Sonuga-Barke 2007). Anxiety: 20.8 girls, 5.9 boys. ODD: 12.5 girls, 8.8 boys. Insomnia: 2.1 girls, 5.1 boys Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Children (6-12 years old) who had clinical diagnoses of a DSM-IV subtype of ADHD (inattentive type, hyperactive-impulsive type or combined type) were recruited • Treatment with MPH in doses of 10 mg/d to 60 mg/d (5 mg-20 mg per administration, 1 to 3 times/d) • Children were deemed otherwise healthy by means of a medical history, physical examination, vital signs measurement (BP, heart rate, respiration and temperature) and clinical laboratory assessments (haematology and urinalysis) • In addition, children had to demonstrate the ability to swallow placebo trial treatment capsules whole and without difficulty • Receiving an approved form of MPH with demonstrated clinical improvement during this treatment **Exclusion criteria** • Intelligence quotient < 80 or inability to follow or understand trial instructions • Pregnancy • History of seizure or tic disorder • Family history of seizure or Gilles de La Tourette's syndrome • Congenital cardiac abnormality • History of cardiac disease including myocardial infarction within 3 months of trial entry • Glaucoma • Hyperthyroidism • History of substance abuse or carer with history of substance abuse • Concurrent chronic or acute illness or other condition that might confound trial rating measures • Documented allergy or intolerance to MPH • Use of an investigational drug within 30 days of trial entry • Use of concomitant medication that could interfere with assessment of efficacy and safety of trial treatments

Swanson 2004b *(Continued)*

Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of ER-MPH (Metadate CD), ER-MPH (Concerta), and placebo Dose: children treated with low doses (20 mg/d) of MPH were randomly assigned to receive ER-MPH (Metadate CD) 20 mg, ER-MPH (Concerta) 18 mg, or placebo; those treated with medium doses (20 to 40 mg/d) were randomly assigned to receive ER-MPH (Metadate CD) 40 mg, ER-MPH (Concerta) 36 mg, or placebo; children treated with high doses (40 mg/d) were randomly assigned to receive ER-MPH (Metadate CD) 60 mg, ER-MPH (Concerta) 54 mg, or placebo Administration schedule: once daily in the morning Duration of each medication condition: 7 days Washout before trial initiation: no Medication-free period between interventions: not stated Titration period: none Treatment compliance: regarding the medicine, not stated. 157 received all 3 levels of treatment and participated in all 7 classroom sessions
Outcomes	**ADHD symptoms** • SKAMP: tested on day 7 in the laboratory school by 2 trained observers. Time points for the test (after ingestion of medication/placebo): h = 0, h = 1.5, h = 3.0, h = 4.5, h = 6, h = 7, h = 12.0 • SNAP: parent-rated, administered twice during each treatment week on days 3 and 6 **Non-serious AEs** • AEs reported by participant or parent (guardian). Reported AEs were characterised (by the investigator at each site) as mild, moderate or severe • Barkley Side Effects Rating Scale: rated symptoms during past week and completed weekly by parent (guardian) on day 6 • Heart rate: measured before doses were taken and at the following time points after ingestion: h = 1.5, h = 3.0, h = 4.5, h = 6, h = 7, h = 12.0 • BP: measured before doses were taken and at the following time points after ingestion: h = 1.5, h = 3.0, h = 4.5, h = 6, h = 7, h = 12.0
Notes	Sample calculation: yes Ethics approval: yes **Comments from trial authors** • "In ANOVA of measures of BP and heart rate, only 2 statistically significant differences related to treatment emerged: SBP at h 7.5, and pulse rate at h 1.5" • "Site differences in this trial deserve some comment because this is a common finding in multi-site studies. Site difference was most prominent for subjective outcome measures on the SKAMP Rating Scale, which depends on the training of observers (difficult to equate across sites) and the context of the classroom (controlled but still may vary across sites because of class size, physical space and other factors that may not be standardised)" • "Regarding analysis of sex (Sonuga-Barke 2007): despite the relatively large number of females in the sample, power was insufficient to include dose level as a factor in the analysis" • "Given the manner in which sex effects appeared to vary across the day, present results may be consistent with pharmacokinetic or pharmacodynamic explanations, or a combination of the 2. Early and late sex-related differences in clinical effect may be independent of one another or linked. Several possible explanations seem worth testing. The superior MPH response shown by females in the early part of the day may result from greater sensitivity to MPH or from higher MPH plasma concentrations due to increased rates or efficiency of absorption of IR-components. The steeper decline in MPH re-

Swanson 2004b *(Continued)*

sponse shown by females may be a consequence of earlier but normative clearance of MPH following more rapid absorption, or may be indicative of more rapid clearance in females than in males"

Limitations

- "Laboratory setting lacks many features of the natural environment of the home and school. Thus, it is not certain whether the patterns reported here would be observed in school settings in which an ADHD student would be in a classroom in which most students not affected by this disorder"
- "Trial was designed to contrast total absorbed daily doses that were approximately equal, although this resulted in differences in initial bolus doses of the 2 active treatments (Metadate CD and Concerta). In this trial, doses were not evaluated that were equal to the initial bolus doses of IR-MPH, which would provide another test of the PK/PD model"
- "Effects of both Metadate CD and Concerta in the low-dose subgroup were smaller than in the high-dose subgroup, but we do not know whether a higher dose in the low-dose subgroup would have increased the ES. Lack of tailoring to achieve rigorous experimental control may be another limitation of this trial"
- "This trial included only patients who already were being treated successfully with MPH. This means that severe and marked AEs are unlikely to be seen in this trial, and it is possible that lack of effect on side effects rating scale factors other than sleep/appetite may occur more readily in medication-naive patients. Furthermore, it is important to recognise that this was a secondary analysis of a trial powered to show non-equivalence between the 2 MPH formulations in terms of efficacy, not in terms of AEs"
- Sonuga-Barke 2009 (secondary reference under Swanson 2004b): "this trial included only patients who already were being treated successfully with MPH. This means that severe and marked AEs are unlikely to be seen in this trial"
- "Trial was also underpowered for detecting rare events that could be severe. Measures of AEs were derived only from parent ratings, not from direct observations of behaviour"
- "Significant side effects not measured by the Barkley Side Effects Rating Scale may have occurred"

Key conclusions of trial authors

- "Once-daily doses of Metadate CD and Concerta produced statistically significantly different PD effects on surrogate measures of behaviour and performance among children with attention deficit hyperactivity disorder in the laboratory school setting"
- "As predicted by the PK/PD [pharmacokinetic/pharmacodynamic] model, superiority at any point in time was achieved by the formulation with the highest expected plasma MPH concentration"

Sex differences

- "Dose titration of once-daily formulations of MPH ideally should be based on systematic evidence of response at different periods across the day"
- "Responses of female patients may require additional assessments later in the day to determine optimal dose"

Comment from review authors

- Compared ratings on sex from SKAMP. However only compared the 2 medication conditions vs each other, not medication conditions vs placebo; therefore we cannot use these analyses.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: *yes*

Any withdrawals due to AEs: 3 trial participants discontinued because of AEs that were judged to be unrelated to medications (gastroenteritis: Concerta (n = 1); fever: placebo (n = 1); sunburn: placebo (n = 1))

Funding: Celltech Pharmaceuticals Incorporated

Email correspondence with trial authors: June 2014. We emailed trial authors to obtain supplemental data. Unfortunately, data in the correct format are no longer accessible.

Risk of bias

Swanson 2004b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy. Treatments were packaged according to a double-dummy design. Each treatment pack contained a 1-week supply of trial treatment, with each day's supply consisting of 1 large capsule to accommodate the size of any dose level of Concerta (containing Concerta or placebo) and, depending on dose level, between 1 and 3 smaller Metadate CD-sized capsules (containing Metadate CD or placebo)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data from participants finishing the whole trial (n = 157) and from the ITT population (n = 184) Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Symons 2007

Study characteristics	
Methods	Prospective, randomised, double-blind, placebo-controlled, cross-over, single-case designs were used to evaluate MPH administration for 3 school-aged children with cerebral palsy and comorbid ADHD symptoms • LD-MPH • HD-MPH • placebo Phases: 4 (including baseline)
Participants	Number of participants screened: not stated Number of participants included: 2 (1 boy, 1 girl) Number of participants followed up: 2 Number of withdrawals: none Diagnosis of ADHD: DSM-IV (combined (100%), hyperactive-impulsive (0%), inattentive (0%)) Age: mean 10.4 years (range 9-11) IQ: > 70. Participant 2 = 92 non-verbal and 96 performance non-verbal (range not stated) MPH-naive: not stated Ethnicity: not stated

Symons 2007 *(Continued)*

	Country: USA Setting: outpatient clinic Comorbidity: cerebral palsy (100%), mild cognitive impairment (100%), autism spectrum disorder (50%), physical impairment (50%), learning disability (50%), other health impairment (50%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-IV diagnosis of ADHD • Cerebral palsy • Attending public elementary schools **Exclusion criteria** • None stated
Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of MPH (low or high dose) and placebo Mean MPH dosage: 2 doses of MPH administered: LD-MPH (0.3 mg/kg) and HD-MPH (0.5 mg/kg) Administration schedule: once daily, mornings, before the child's school arrival Duration of each medication condition: order of drug/placebo administration was randomly assigned, and administration was provided for 5 consecutive school days in each condition. Drug treatment was not administered on weekends For participant 2, the order of administration was as follows: baseline, LD, placebo, HD For participant 3, the order of administration was as follows: baseline, placebo, LD, HD Washout before trial initiation: not stated Medication-free period between interventions: weekends Titration period: not stated Treatment compliance: not stated
Outcomes	**General behaviour** • Direct observation protocol based on a 10-s partial interval (1/0) for stereotyped and disruptive behaviours and time sampling for task-related behaviour was used to code data collected directly from each child's classroom for two 30-min sessions on 2 separate days for each week of the trial. Student and teaching staff behaviours were recorded using handheld digital cameras. An observer designated as the primary observer coded all videotaped sessions for that target student. A secondary observer independently coded 20% of randomly selected videotaped sessions for each student **Non-serious AEs** • No parent or teacher reports described significant side effects associated with either dose level (e.g. changes in sleep, eating, etc.)
Notes	Sample calculation: no Ethics approval: not stated **Key conclusions of trial authors**

Symons 2007 *(Continued)*

- LD but not HD-MPH administration resulted in clinically significant reductions in directly observed stereotyped and disruptive behaviours for 3 elementary school–aged children with cerebral palsy
- For 2 of the children, stereotyped behaviour was exacerbated during high-dose administration
- Finally, no change in attending, as measured by direct observation of task-related behaviour, was noted

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: not stated

Any withdrawals due to AEs: no

Funding source: McKnight LandGrant Professorship to the first author

Email correspondence with trial authors: May 2014. Emailed trial author to request additional information but have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Order of drug/placebo administration was randomly assigned
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, school personnel (i.e. teachers, teacher assistants) and research assistants responsible for observational data collection and coding were kept blind to drug/placebo conditions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol

Szobot 2004

Study characteristics

Methods	4-day, double-blind, placebo-controlled, randomised parallel-group trial: • fixed dose-escalating of MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 36 (all boys) Number of participants followed up: 36 (MPH 19, placebo 17)

Szobot 2004 *(Continued)*

	Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV, combined (MPH 84.6%, placebo 76.5%) Age: mean 11.6 years IQ: mean 94.7 MPH-naive: not stated. But no psychiatric medication for the past 6 months Ethnicity: European-Brazilian (89%) Country: Brazil Setting: outpatient clinic Comorbidity: CD and ODD (MPH 58.8%, placebo 68.4%), depressive disorder (MPH 5.2%, placebo 5.9%), multiple anxiety disorder (MPH 5.2%, placebo 0%), tic disorder (MPH 0%, placebo 5.9%) Comedication: not stated Other sociodemographics: low- to middle-income families **Inclusion criteria** • Diagnosis of ADHD according to DSM-IV criteria (American Psychiatric Association, 1994) • Between 8 and 17 years old • Male sex **Exclusion criteria** • Presence of any neurological or significant clinical disease • Presence of bipolar disorder or any substance abuse/dependence disorder • Use of any psychiatric medication in the previous 6 months • Estimated IQ < 70
Interventions	Participants were randomly assigned to MPH or placebo Number of participants randomised to each group: MPH 19, placebo 17 Mean MPH dosage: 0.72 mg/kg/d Administration schedule: twice/d: morning and lunchtime Duration of intervention: 4 days Titration period: first day 0.35 mg/kg Treatment compliance: good
Outcomes	**ADHD symptoms** • Conners' Abbreviated Rating Scale (ABRS) **Quality of life** • Children's Global Assessment Scale (CGAS). CGAS was scored by a child psychiatrist **Non-serious AEs** • A research assistant called each family to check side effects. No participants had to interrupt the protocol because of side effects
Notes	Sample calculation: no

Szobot 2004 *(Continued)*

Ethics approval: approved by the Ethical Committee of the HCPA (approved as an IRB by the Office for Human Research Protections, USA)

Comments from trial authors

- "Our results extend the efficacy of MPH for ADHD core symptoms as extensively demonstrated in clinical trials with samples from developed countries to samples from developing countries, for whom a diverse culture may modulate clinical presentation of the disorder"
- "This study's rate of robust response with methylphenidate might reflect the short duration (4 days) of the clinical trial"
- "Results may not generalise to other different sociocultural groups or to patients from the community"
- "Side effects were not objectively registered"

Key conclusion of trial authors

- "MPH group had a significantly greater decrease in ABRS scores and a significantly greater increase in CGAS scores when compared with the placebo group (P value < 0.01)"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding source: research funds from Hospital de Clínicas de Porto Alegre, FAPERGS and NOVARTIS

Email correspondence with trial authors: October 2013. We received from the trial authors supplemental information regarding blinding and allocation concealment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned on the basis of a computer-derived algorithm (EPIINFO6)
Allocation concealment (selection bias)	Low risk	Only the doctor performing the randomisation knew the allocation, and he had nothing to do with data collection
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind: participants, parents and all research team members who had contact with participants. Both MPH and placebo pills were manufactured by a single pharmaceutical company; they had the same format and colour and were given to participants in 4 different blisters
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All research team members who had contact with participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	None Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo-responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Szobot 2008

Study characteristics	
Methods	6-week cross-over trial with 2 interventions • SODAS MPH • placebo Group A: receiving SODAS MPH dosage: 0.3, 0.7 and 1.2 mg/kg/d for weeks 1, 2 and 3 and placebo for weeks 3, 4, and 6 Group B: receiving placebo for weeks 1, 2, and 3, and SODAS MPH dosage: 0.3, 0.7 and 1.2 mg/kg/d for weeks 4, 5, and 6
Participants	Number of participants screened: 25 from a previous ADHD/substance misuse trial and 15 through advertising Number of participants included: 16 (100% boys) Number of participants followed up: 16 Number of withdrawals: 2 (both from group A; withdrawal rate 12.5%) Diagnosis of ADHD: DSM-IV (combined 12 (75%), hyperactive/impulsive (n = 1), inattentive 3 (18.75%)) Mean age: group A 17.5 years (SD 2.33), group B 17.38 (SD 2.2) IQ: group A 79.43 (SD 16.66), group B 84.75 (SD 21.16) MPH-naive: 100% Ethnicity: European-Brazilian (group A 3 (37.5%), group B 7 (87.5%)) Country: Brazil Setting: outpatient clinic Comorbidity: CD (group A 100%, group B 75%); ODD (group A 25%, group B 37.5%); depression (group A 12.5%, group B 25%) Comedication: yes (marijuana and cocaine); group A: marijuana (100%) and cocaine (50%); group B: marijuana (87.5%) and cocaine (37.5%) Other sociodemographics: divorced parents (group A 37.5%, group B 50%); socioeconomic group A + B + C (group A 50%, group B 87.5%); group D + E (group A 50%, group B 12.5%) **Inclusion criteria** • 15-21 years of age • Male • Current diagnosis of abuse of marijuana or cocaine (K-SADS-E and MINI) • Current diagnosis of ADHD: K-SADS-E • Stimulant-naive **Exclusion criteria** • Absence of responsible adult - to inform on childhood psychopathology and to take responsibility for medication and/or the need for inpatient care for substance misuse or psychiatric comorbidity • Primary psychiatric condition requiring immediate treatment (e.g. moderate/severe depression)
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Mean SODAS MPH dosage: 0.3, 0.7 and 1.2 mg/kg/d for weeks 1, 2 and 3 for group A, and for weeks 4, 5 and 6 for group B

Szobot 2008 *(Continued)*

	Administration schedule: morning dose time points Duration of each medication condition: 3 weeks Washout before trial initiation: no Medication-free period between interventions: 24 h Titration period: none Treatment compliance: "Study compliance was assessed by self-report, mother's report and pill counting"
Outcomes	**ADHD symptoms** • K-SADS-E, for diagnosis • SNAP-IV **Serious AEs** • Barkley Side Effect Rating Scale (SERS) **Non-serious AEs** • Barkley Side Effect Rating Scale (SERS)
Notes	Sample calculation: not stated Ethics approval: "The project was approved by the Institutional Review Board (IRB) of Hospital de Clinicas de Porto Alegre (approved as an IRB by the Office for Human Research Protections, United States of America, IRB 00000921" **Comments from trial authors** • "In the present trial, SODAS MPH was significantly superior to placebo in reducing ADHD symptoms and improving global functioning for all main outcome measures (SNAP-IV and CGI scores)" • "No treatment effect on illicit substance use disorders was noted, and MPH-SODAS was well tolerated, despite causing greater appetite reduction than was seen with placebo" **Key conclusions of trial authors** • SODAS MPH was more effective than placebo in reducing ADHD symptoms in a non-abstinent outpatient sample of adolescents with comorbid substance use disorders • RCTs, with larger samples and substance use disorder interventions, are recommended Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: 1 withdrawal resulted from a participant feeling "worse", "more restless" Funding source: "The ADHD outpatient program receives research support from Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag and Novartis" Email correspondence with trial authors: May 2014. We received supplemental information from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"One of the investigators (LAR) randomized the 16 subjects into groups A or B and prepared weekly blisters of medications for each participant"

Szobot 2008 *(Continued)*

Allocation concealment (selection bias)	High risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A pharmacist packaged mPH-SODAS and matching placebo in capsules so that the MPH-SODAS and placebo could not be visually differentiated"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	From author correspondence: "all persons who evaluated outcome measures were blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): unclear
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Tannock 1989

Study characteristics	
Methods	Within-participant, cross-over trial with 3 interventions: • MPH 0.3 mg/kg • MPH 1 mg/kg • Placebo 2 different drug conditions each day
Participants	Number of participants screened: 16 Number of participants included: 12 Number of participants followed up: 12 (10 boys, 2 girls) Number of withdrawals: none Diagnosis of ADHD: DSM-III ADD-H (equivalent to 'combined' in later classifications) Age: mean 8.4 years (range 6-11) IQ: mean 105 MPH-naive: 5 received MPH previously. 3 were taking MPH at the time of referral and had a 48-h pre-trial washout Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: ODD (n = 4), learning difficulties (n = 8; according to school record and defined as < 25th percentile on ≥ 1 subtests within the Wide Range Achievement Test (WRAT-R)) Comedication: not stated

Tannock 1989 *(Continued)*

	Other sociodemographics: none **Inclusion criteria** • Thought by referring physician to have ADHD • Confirmed through assessment by 2 child psychiatrists using the PICS Questionnaire • Confirmed by teacher information on Conners' Teacher Questionnaire, Rutter B Questionnaire and the Swanson, Nolan and Pelham Questionnaire **Exclusion criteria** • Full-scale WISC-R < 80 • Exclusive diagnosis of emotional or CD; major neurological, physical or sensory impairment; and/or any contraindication for use of MPH (e.g. tics, seizures, heart disease)
Interventions	Participants were randomly assigned to 1 of 3 possible drug condition orders of 0.3 mg/kg or 1.0 mg/kg MPH and placebo Mean MPH dosage: not stated. Administration schedule: interval of 4 h separated morning and afternoon doses Duration of each medication condition: not stated Washout before trial initiation: 4 h Titration period: none Treatment compliance: not stated
Outcomes	**Non-serious AEs** • Treatment-emergent side effects (e.g. stomach distress, pallor, mood swings, tics) • Pulse and BP readings taken in sitting position immediately before medication and again 1 h after administration of dose
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusions of trial authors** • Behavioural and academic improvements produced by a dose of 0.3 mg/kg in the morning were no longer evident in the afternoon • 1 mg/kg MPH produced behavioural improvements that were clinically and statistically discernible in the afternoon, although academic improvements had dissipated • Carryover effects of MPH into the afternoon were discernible with 1.0 mg/kg but not with 0.3 mg/kg **Comment from review authors** • Outcomes for ADHD symptoms were not appropriate for this trial, so only adverse effects were examined Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: Jointly funded by Ontario Mental Health Foundation (Grant Number 963-86/88) and Health and Welfare Canada (Grant Number 6606-3166-42) Email correspondence with trial authors: sent email to trial authors to ask for additional information but have not received a reply.

Tannock 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The order of medication condition was randomized with the restrictions that each child receive two different medication conditions each day (e.g. high, low) occur with equal frequency in the morning and afternoon" "The order of these six combinations was randomized for each child"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The methylphenidate and placebo were packaged in coloured gelatin capsules by the hospital pharmacist to avoid detection of dose and taste, packaged in individual envelopes and dispensed by project staff 1 hour before testing"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Tannock 1992

Study characteristics

Methods	Cross-over trial with 3 interventions: • LD-MPH • HD-MPH • placebo Phases: 3 separate drug conditions: placebo, LD (0.3 mg/kg) and HD (1.0 mg/kg) medication, with 2 test sessions each. Drug conditions changed on a daily basis: 6 test sessions plus baseline practice session
Participants	Number of participants included: 26 (24 boys, 2 girls) Number of participants followed up: 23 Number of withdrawals: 3 Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 9.2 years (range not stated) IQ: mean 105.9 (SD 10.5) MPH-naive (not clear; "9 children receiving stimulant medication prior to the present study") Ethnicity: not stated Country: Canada

Tannock 1992 *(Continued)*

	Setting: hospital/outpatient department Comorbidity: n = 12, oppositional disorder: 5, oppositional and CD: 3, oppositional and separation anxiety disorder: 1, oppositional and CD and major depression: 2, oppositional and CD and avoidant disorder: 1. Comedication: not clear Other sociodemographics: none **Inclusion criteria** • Diagnosis of ADHD confirmed • Child had to be scheduled to receive a trial with MPH independent of the present investigation **Exclusion criteria** • WISC-R: < 80 • Exclusive DSM-III diagnosis of CD or an emotional disorder • Major neurological, physical or sensory impairment
Interventions	Participants were randomly assigned to different drug condition orders of 3 possible interventions: LD-MPH, or HD-MPH, and placebo Mean MPH dosage: N/A (modal dose at 0.3 mg/kg = 7.5 mg (range 5.0 mg-15 mg), modal dose at 1.0 mg/kg = 27.5 mg (range 17.5 mg-47.5 mg)) Administration schedule: daily single dose Duration of each medication condition: 1 day Washout before trial initiation: 48 h before trial initiation Medication-free periods between interventions: no Titration period: none Treatment compliance: capsules administered by project staff
Outcomes	**General behaviour** • Wisconsin Card Sorting Test: observer, daily, 90 minutes after treatment **Non-serious AEs** • Decreased cognitive flexibility (repetitive actions with obsessive quality) • Movement stereotypes • Facial motor tics • Topic perseveration • Excessive pre-occupation with the task at hand and persistent talkativeness: observer, during test session • Treatment-emergent side effects conducted routinely during medication trial in our laboratory • Monitored throughout sessions 3 children exhibited unusual side effects leading to trial termination. One exhibited hypersensitivity (skin rash, urticaria and throat clearing), and 2 became somewhat disoriented and confused and complained of odd sensations in their limbs
Notes	Sample calculation: no Ethics approval: not stated **Key conclusion of trial authors**

Tannock 1992 *(Continued)*

- Results indicate that MPH increased perseverative errors on the first assessment but decreased them on the second; clinical symptoms of perseveration occurred at both assessments. Findings suggest that MPH may reduce cognitive flexibility temporarily in some children with ADHD

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, child had to be scheduled to receive a trial with MPH independent of the present investigation

Any withdrawals due to AEs: yes; 3

Funding source: grant from the Canadian Psychiatric Research Foundation and a Post-Doctoral Fellowship by the Ontario Mental Health Foundation.

Email correspondence with trial authors: April 2014. We emailed trial authors twice to ask for supplemental information/data but have not received a response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear
Allocation concealment (selection bias)	Low risk	Double-blind, placebo-controlled design. Drug order for the first 3 test sessions was randomly assigned, and each child retained the same order for the remaining 3 sessions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled design. Medication packaged in coloured gelatin capsules to avoid detection of dose and taste. Each child followed the same routine for every test session
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data for 3 respondents with unusual side effects Selection bias (e.g. titration after randomisation → exclusion): exclusion due to AEs
Selective reporting (reporting bias)	Unclear risk	No information presented on numbers of participants with side effects or outcomes for data on nausea, BP, etc.

Tannock 1993

Study characteristics

Methods

Cross-over trial with 3 interventions:

- LD-MPH
- HD-MPH
- placebo

Phases

- Each child in ADHD group participated in a 6-day medication trial, consisting of six 3-h test sessions

Tannock 1993 *(Continued)*

- Each child was tested on 2 separate occasions when given placebo, LD-MPH (0.3 mg/kg) and HD-MPH (1.0 mg/kg) in a randomly assigned counterbalanced sequence

Participants	Number of participants screened: not stated Number of participants included: 22 (and 16 healthy controls) Number of participants followed up: 22 (21 boys, 1 girl) Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 9.4 years (range not stated) IQ: mean 105.5 (SD 11.3) MPH-naive: not clear: "Thus all these children would have received a trial with psychostimulants independently of this study"; "8 children had been receiving stimulant medication prior to this study") Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: 55%; oppositional disorder (n = 5), CD (n = 3), emotional disorder as well as oppositional or CD (n = 4), major depression (n = 2), avoidant disorder (n = 1), separation anxiety disorder (n = 1) and learning disorder (n = 6) Comedication: not clear Other sociodemographics: none **Inclusion criteria** • Confirmed diagnosis of ADHD: child demonstrated ≥ 3 symptoms of inattentiveness, 3 of impulsiveness and 2 of hyperactivity, with a history of these symptoms before 6 years of age, based on diagnostic interview • Diagnosis was made if the child received a Rutter B total score ≥ 9 and fulfilled any 2 of the following criteria: score ≥ 15 on the Conners' Abbreviated Teacher Questionnaire; ≥ 4 inattentive, 4 impulsive and 3 hyperactivity symptoms on the SNAP; or score of 5 or 6 on the Rutter-B hyperactivity factor **Exclusion criteria** • WISC-R: score < 80 with psychosis, or with any major neurological, physical or sensory impairment
Interventions	Participants were randomly assigned to 1 of 6 possible drug condition orders of (dose not stated) MPH and placebo Mean MPH dosage: not stated Administration schedule: 6 separate medication administrations: 2 placebo, 2 LD (0.3 mg/kg) and 2 HD (1.0 mg/kg). First 3 test sessions were ordered randomly, then were ordered repeatedly for last 3 sessions: daily for 6 days Duration of each medication condition: 3 h Washout before trial initiation: 48 h Medication-free period between interventions: not clear Titration period: none Treatment compliance: "Medication was administered by project staff"

Tannock 1993 *(Continued)*

Outcomes	**Non-serious AEs** • BP and pulse readings: before and 1 h after ingestion • Reduced social responsivity: during each test session, observer • Intense concentration: during each test session, observer • Stereotypy: during each test session, observer
Notes	Sample calculation: no Ethics approval: not stated **Key conclusions of trial authors** • Results indicate that only high-dose treatment had a specific effect on focused attention, and this effect was delayed relative to the more salient but non-specific effects on overall efficiency of information processing • Task performance at high dose was related to concurrent clinical manifestations of intense concentration, but no evidence suggested that MPH produced overfocusing Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: unclear Withdrawals due to AEs: no Funding source: Canadian Psychiatric Research Foundation and the Medical Research Council of Canada. Email correspondence with trial authors: April 2014. Emailed trial authors twice for supplemental information/data but have received no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Double-blind, placebo-controlled, within-participant design was used ...randomly assigned, counterbalanced sequence. Medications were prepared individually for each child and were packaged in coloured gelatin capsules to avoid detection of dose and taste
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled, within-participant design was used ...randomly assigned, counterbalanced sequence. Medications were prepared individually for each child and were packaged in coloured gelatin capsules to avoid detection of dose and taste
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals were noted Selection bias (e.g. titration before randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting, all outcomes reported

Tannock 1995a

Study characteristics	
Methods	4-day, randomised, double-blind, placebo-controlled, cross-over trial with: • 3 doses of MPH (0.3 mg/kg, 0.6 mg/kg and 0.9 mg/kg) • placebo With initial 1-day open-label trial
Participants	Number of participants screened: 28 Number of participants included: 28 (25 boys, 3 girls) Number of participants followed up: 28 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 8.9 years (range 7-11) IQ: mean 106.5 (15.6) MPH-naive: 80% Ethnicity: white (90%), other (10%) Country: Canada Setting: outpatient clinic Comorbidity: ODD or CD (35%), learning disabilities (39%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD, DSM-III-R **Exclusion criteria** • IQ: WISC-R: score < 80 • Anxiety disorder (DSM-III-R) • Major neurological, physical or sensory impairment
Interventions	Participants were randomly assigned to 3 doses of MPH (0.3 mg/kg, 0.6 mg/kg, 0.9 mg/kg) and placebo Mean MPH dosage: not stated Administration schedule: once daily Duration of each medication condition: 1 day Washout before trial initiation: for children receiving MPH before trial, washout period ≥ 48 h before trial, with no washout between periods Titration period: no, but all children participated in an initial 1-day open trial with a 0.3 mg/kg dose of MPH to ascertain tolerance, before proceeding with the double-blind, placebo-controlled trial Treatment compliance: not stated
Outcomes	**Non-serious AEs**

Tannock 1995a *(Continued)*

- Cardiovascular function (heart rate). Radial pulse, taken for 1 min with the child seated, was measured 3 times during each session: immediately before medication (time 0) and again at 1 h (time 1) and 2 h (time 2) following administration of the oral dose. From time 0 to time 1, children were seated at a table, colouring or playing quietly with puzzles or board games: children completed the cognitive task from time 1 to time 2

Notes	Sample calculation: yes Ethics approval: yes; Institutional Research Ethics Board **Key conclusions of trial authors** • "Results indicate that MPH enhanced cognitive flexibility, although the high dose was less effective than lower doses in enhancing response inhibition" • "Dissociations of dose effects on cognitive function and behaviour were demonstrated: dose-response functions for changes in behaviour were linear, whereas the function for response inhibition was U-shaped" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; 1-day open-label trial to ascertain tolerance towards medication, but all participants were analysed Any withdrawals due to AEs: no Funding source: Medical Research Council of Canada and Health and Welfare Canada Email correspondence with trial authors: August 2013. We received from the first trial authors supplemental information regarding dropouts, screening and ethics approval

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Low risk	All medication was prepared by the hospital pharmacy and was packaged in opaque gelatin capsules to avoid detection of dose and taste
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Children, parents, teachers and research staff were all blinded to medication conditions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Children, parents, teachers and research staff were all blinded to medication conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data from all 28 participants were analysed Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Tannock 1995b

Study characteristics

Tannock 1995b *(Continued)*

Methods	Cross-over trial with 4 interventions: • MPH (0.3 mg/kg, 0.6 mg/kg, 0.9 mg/kg) • placebo Phases: washout, baseline, trial 2 groups, ADHD and ADHD + anxiety - were subjected to the same trial

Participants	Number of participants screened: 50
	Number of participants included: 40 (34 boys, 6 girls)
	Number of participants followed up: 40
	Number of withdrawals: none
	Diagnosis of ADHD: DSM-III-R (no subtype)
	Age: ADHD mean 9.4; ADHD + anxiety mean 9.1 (range 7-11 years);
	IQ: > 80
	MPH-naive: not stated
	Ethnicity: white (90%), African American or Asian (10%)
	Country: Canada
	Setting: outpatient clinic
	Comorbidity (type: overanxious 27.5%, separation anxiety 5%, over anxiety and separation anxiety 10%, avoidant disorder with overanxious traits 2.5%, ODD 55%, CD 10%)
	Comedication: not stated
	Other sociodemographics: predominantly from middle-class families
	Inclusion criteria
	• Meeting DSM-III-R criteria
	• At least 2 of the following
	  ◦ ≥ 15 on the Conners' Abbreviated Symptom Questionnaire
	  ◦ ≥ 4 inattentive, 4 impulsive and 3 hyperactive symptoms rated as "pretty much" or "very much" on SNAP Questionnaire
	  ◦ Score of 5 or 6 on the Hyperactivity factor of the Rutter Child Scales
	Exclusion criteria
	• Full scale IQ < 80
	• Evidence of major neurological, physical or sensory impairment
	• Medical or neurological contraindications for stimulant medication
	• Not knowing the number facts of 10. Needing to use concrete materials (i.e. fingers) to add numbers
	Inclusion criteria for the ADHD + anxiety group
	≥ 1 of the following
	• DSM-III-R criteria for overanxious, separation anxiety or avoidant disorder based on parent interview
	• Score > 1 SD above the mean for age and sex on the Revised Children's Manifest Anxiety Scale
	• Score > 1 SD for age and sex on the Trait Scale-C2 of the State-Trait Anxiety Inventory for Children
	Children in the ADHD group did not meet any of these criteria for anxiety

Tannock 1995b *(Continued)*

Interventions	Participants were randomly assigned to 1 of 12 possible drug condition orders of 0.3 mg/kg, 0.6 mg/kg or 0.9 mg/kg MPH and placebo Mean MPH dosage: 0.3 mg/kg = 8.75 (± 2.2); 0.6 mg/kg = 17.75 (± 4.2); 0.9 mg/kg = 27.25 (± 5.6) Administration schedule: once/d Duration of each medication condition: 1 day Washout before trial initiation: 48 h when applicable Medication-free period between interventions: not stated Titration period: no, but there was a 1-day open trial on 0.3 mg/kg before proceeding to ascertain tolerance Treatment compliance: medication was administered at the laboratory
Outcomes	**Non-serious AEs** • Heart rate and radial pulse, once at baseline and 3 times during each session
Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusion of trial authors** • "High levels of trait anxiety in children with ADHD predict poor (but not adverse) response to methylphenidate in terms of working memory, and add to growing evidence that ADHD with anxiety constitutes a distinct and clinically meaningful subtype of ADHD." **Comment from review authors** • Main trial was preceded by a 1-day trial of the lowest dose to assess tolerance to MPH Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; see above Any withdrawals due to AEs: no Funding: in part by the Ontario Mental Health Foundation and the National Health Research and Development Program, Health Canada Email correspondence with trial authors: June 2014. Emailed trial authors twice to request supplemental information/data but have received no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drug order was counterbalanced and determined by random assignment, such that an approximately equal number of children were assigned to each of 12 possible orders
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active medication and placebo were prepared by the hospital pharmacy, packaged in identical opaque gelatin capsules and administered in a double-blind manner

Tannock 1995b *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): 1-day open trial to assess tolerance before main trial, but no children were excluded
Selective reporting (reporting bias)	Low risk	All outcomes are reported

Tannock 2018

Study characteristics	
Methods	A 10-week to 4 months parallel-trial with 2 arms, which were further parted into 3 trial arms of different reading therapy: • IR-MPH • placebo Phases: 2 phases (open-label titration and double-blind intervention)
Participants	Number of participants screened: 221 Number of participants included: 65 (49 boys, 16 girls) Number of participants followed-up: 49 (15 teacher ratings and 1 parent rating not completed) Number of withdrawals: 16 (15 teacher ratings and 1 parent rating not completed) 13 participants changed their allocated intervention (8 from MPH group, 5 from placebo group) Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 8.5 years (SD 1.4, range 7-11) IQ: 91.5 (SD 10.6) MPH-naive: not stated Ethnicity: white (90%), African-American (4%), Hispanic (1%), and Asian (5%) Country: Canada Setting: classroom laboratory in a clinical setting Comorbidity: all participants had a reading disorder. 29.3% had ODD 8.6% had CD Comedication: not stated Additional sociodemographics: socioeconomic status: 6.4 (SD 1.7) **Inclusion criteria** • DSM-IV diagnosis of ADHD and Reading Disorder (based on a clinical diagnostic assessment) • Aged between 7 and 11 years old • IQ > 80 (confirmed with WISC-III)

Tannock 2018 *(Continued)*

- A diagnosis of RD based on low achievement criteria, namely, a score of at least 1.5 standard deviations below age-level expectations on at least 2 of the standardised reading tests, or 1 standard deviation below age-level expectation on 3 tests
- Full-time attendance in a local school and consent for the child to be withdrawn from class to participate in the intervention trial
- English as the primary language spoken by parent and child
- Parental consent for the child to participate in the randomised controlled trial

Exclusion criteria

- Receiving pharmacological treatment for ADHD at the start of the trial
- Children attending full-time French immersion programmes
- Chronic medical or neurological conditions or history of head injury/loss of consciousness requiring hospitalisation
- Children with a history of adverse or poor response to stimulant medication

Interventions	Participants were randomly assigned to receive either MPH at optimal dosage or placebo twice/d, while also receiving one of 3 reading interventions. Number randomised to each group: 39 to MPH, 26 to placebo. 13 participants changed their allocated intervention (8 from MPH group, 5 from placebo group) Mean medication dosage: not stated. Maximum oral dose of 0.7 mg/kg twice/d or 20 mg twice/d Administration schedule: twice/d, in the morning and before lunch Duration of each medication: 12-13 weeks or 4-5 months of MPH or placebo Washout before trial initiation: no information Titration period: 2-3 week titration phase in which the dose of MPH or placebo was increased in 5 mg steps. Identical, scored, 10 mg pills of MPH and placebo were used Treatment compliance: research staff recorded the number of pills returned at trial completion (average of about 90%).
Outcomes	**ADHD symptoms** • Parent and teacher versions of the CRS-R **Serious AEs** • None stated **General behaviour** • Oppositional Behavior subscale of the parent and teacher CRS-R • IOWA-CRS (during blinded titration phase - results are not available and therefore not included in our analysis) **Non-serious AEs** • Side Effect Rating Scale (during blinded titration phase - results are not available and therefore not included in our analysis)
Notes	Sample calculation: no Ethics approval: no **Comments from trial authors**

Tannock 2018 *(Continued)*

- "The main limitations of our study included the small sample sizes and attrition from the assigned medication condition prior to commencing the academic programs both of which threaten the study's internal validity."

Key conclusion of trial authors

- "Active medication treatment, while improving the behavioral symptoms of ADHD, does not result in gains in reading ability in this comorbid group of children in the absence of concurrent reading remediation treatment."

Comments from review authors

- Review authors are uncertain if trial duration (besides titration period) is 4 months (amount of pills given to parents) or 10 weeks (length of reading intervention).

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: not stated

Funding source: an operating grant from the Canadian Institutes of Health Research (Grant #MT 13366), and by the donation of placebo medication from Novartis Pharmaceuticals.

Email correspondence with the trial authors: September 2021. We sought supplemental information regarding details of the medical intervention through personal email correspondence with the authors in September 2021. Unfortunately the data are no longer available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	20% of parents (n = 13) requested a change in their child's assigned medication condition (8 from placebo to MPH; 5 from MPH to placebo)
Allocation concealment (selection bias)	Low risk	Parents were then provided with a 4-month supply of pills, each month packaged separately.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The MPH and placebo pills were identical in color, shape and size and were administered in a double-blind manner twice daily (once in the morning before school and once at lunch)" **Comment**: 1 participant was unblinded during requested change of medication assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"We analysed behavioral data when both parent and teacher reports were present to ensure that results from these 2 sources could be compared"
Incomplete outcome data (attrition bias) All outcomes	High risk	"Within the initial 2-week dose-adjustment phase and prior to starting the academic programs, 20% of parents (n= 13) requested a change in their child's assigned medication condition (8 from placebo to MPH; 5 from MPH to placebo)." **Comment**: an ITT analysis as well as an as-treated analysis was made Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): there was a titration phase after randomisation
Selective reporting (reporting bias)	Unclear risk	No trial protocol identified

Taylor 1987

Study characteristics	
Methods	Double-blind, randomised, placebo-controlled, cross-over trial with 2 arms • MPH • placebo Each treatment period lasted for 3 weeks with a washout period of 1 week planned between treatments and up-titration to optimum dosage during the 3 weeks
Participants	Number of participants screened: 64 Number of participants included: 39 (all boys). Of these, 26 had an ADHD diagnosis according to DSM-III Number of participants followed up: 38 Number of withdrawals: 1 Diagnosis of ADHD: DSM-III (n = 26; type not stated) The following data reflect the whole trial (n = 38) Age: mean 8.6 years (range 6-10) IQ: all > 65; mean 93.4 MPH-naive: 100% Ethnicity: not stated Country: UK Setting: outpatient clinic Comorbidity: no attentive or restless behaviour, but antisocial, disruptive or aggressive in conduct (n = 6), hyperactive but not antisocial or aggressive (n = 9), with both hyperactive and disruptive behaviour (n = 23), CD (n = 7), relationship problems (n = 2) and disturbance of emotions specific to childhood (n = 3) Comedication: not stated Other sociodemographics: 40% from broken homes **Inclusion criteria** • IQ > 65 • Free of autistic features • Lives in a family home, not an institution • Attending primary school • Problems assessed at the clinic as severe enough to warrant psychiatric treatment • Free of contraindications to stimulant medication • No treatment with stimulant drugs • No psychotropic drugs given for ≥ 6 months previously **Exclusion criteria** • Children with severe intellectual disability or neurological disease • Autistic and psychotic children

Taylor 1987 *(Continued)*

- Pre-school children
- Adolescents
- Female

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo Mean MPH dosage: 9 received doses from 0.2 mg/kg to 0.5 mg/kg, 21 from 0.5 mg/kg to 0.9 mg/kg and 8 from 0.9 mg/kg to 1.4 mg/kg Administration schedule: time points not stated Duration of each medication condition: 3 weeks Washout before trial initiation: all were stimulant-naive Medication-free period between interventions: 1 week Titration period: a flexible dosage regimen was used after randomisation. Each child began with 5 mg daily, with dosage adjustments made at 2- to 3-day intervals. The optimum dosage was assessed for each child, in the light of clinical response and the occurrence of side effects, to a maximum of 30 mg daily Treatment compliance: compliance with medication was rated as good or very good in 89%
Outcomes	**ADHD symptoms** • CTRS: rated at the end of each treatment period, that is, day 21 • Parental Account of Childhood symptoms (PACS), hyperactivity scale: rated at the end of each treatment period, that is, day 21 **Serious AEs** • No serious physical effects of medication were encountered **Non-serious AEs** • Unwanted effects of medication were assessed by using the physician's ratings of 26 possible symptoms with full physical examination, rated at the end of each treatment period, that is, day 21
Notes	Sample calculation: no Ethics approval: not stated **Comment from trial authors** • Long-term treatment with stimulant drugs could not be assessed in this short-term trial **Key conclusion of trial authors** • A good response to MPH was predicted by higher levels of inattentive and restless behaviour, impaired performance on tests of attention, clumsiness, younger age and absence of symptoms of overt emotional disorder. DSM-III and ICD-9 diagnoses of "hyperactivity" were not good predictors **Comments from review authors** • Long-term treatment with stimulant drugs could not be assessed in this short-term trial • Children with tics or cardiovascular disease were excluded • Demographic characteristics and mean dose include the whole sample (n = 38). However, upon receipt of correspondence from the trial author, outcomes measured included the 26 individuals diagnosed with ADHD (DSM-III) • Investigators tested both for MPH vs placebo (effects of treatment) and for end of first treatment period vs end of second treatment period (effects of occasion), as well as the interaction between treatment and occasion. "The two order groups were combined together for those measures that had

Taylor 1987 *(Continued)*

shown no significant effects of test occasion or interaction of occasion with treatment. For measures th did show main or interactive effects of occasion, the two order groups were considered separately"

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no; all MPH treatment-naive

Any withdrawals due to AEs: yes; 1 in the placebo group

Funding source: partially funded by grant from CIBA Ltd., which provided medicine and placebo

Email correspondence with trial authors: October 2013. We received from trial authors no supplemental information regarding data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were randomly allocated to receive drug first or placebo first. This was carried out by pharmacy staff, who knew only the name and identifying number of each case
Allocation concealment (selection bias)	Low risk	Allocation was carried out by pharmacy staff, who knew only the name and identifying number of each case
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets were dispensed to a trial member, who did not know what they contained and handed them to parents
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Psychiatrist supervising treatment also assessed and recorded side effects, physical findings and parents' general impressions at the end of each treatment; other assessors of outcomes were blinded to the treatment given but also to possible clues arising from physical effects of the drug. Behavioural measures were carried out independently of one another by investigators blind to results of the other tests and to teacher ratings
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were missing for 3 children: 1 child had missing data on the Parental Account of Childhood Symptoms because he had been taken into care, and 2 children had missing data on the CTRS hyperactivity factor because they had been excluded from school. Method of imputation not described Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Taylor 1993

Study characteristics

Methods	4-week, double-blind, cross-over trial with 3 interventions: • MPH 5-10 mg • MPH 10-15 mg • placebo Each medication dose/placebo was given for 1 week

Taylor 1993 *(Continued)*

Participants	Number of participants screened: 57 Number of participants included: 57 (27 boys, 5 girls) Number of participants followed up: all 57 completed the trial but only 32 were included in the final analysis Number of withdrawals: 0, but 25 were not reported (due to non-response and not enough data) Diagnosis of ADHD: DSM-III-R Age: mean 10.26 years (range 7.0-12.9) IQ: mean 107 (SD 16.2; range 78-139) MPH-naive: 12 (37.5%) Ethnicity: not stated Country: Canada Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • 7-12 years of age • Verbal or performance IQ ≥ 85 **Exclusion criteria** • No information
Interventions	Participants were randomly assigned to possible drug condition orders of, respectively, mean 6.72 mg (5 mg-10 mg) and mean 11.88 mg (10 mg-15 mg) MPH and placebo Administration schedule: morning and noon Duration of each medication condition: 1 week Washout before trial initiation: none Titration period: none Treatment compliance: no information
Outcomes	**Non-serious AEs** • Decreased appetite, trouble falling asleep, stomachache, headache, dysphoria; withdrawn, tearful, anxious, licking lips, picking at skin; facial grimacing, repetitive movements
Notes	Sample calculation: no information Ethics approval: no information **Key conclusion of trial authors** • Only ERPs (event-related potentials) reflected slowed processing in children with ADHD that normalised with appropriate medication

Taylor 1993 *(Continued)*

	Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: not declared Email correspondence with trial authors: January 2014. No supplemental information was received. We therefore have no more information on numbers of participants with non-serious AEs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised. All medication and placebo testing was conducted under double-blind conditions with randomly assigned testing order
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active medication and placebo substances were placed in identical red and white capsules in powder form. Matched on both taste and appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All medication and placebo testing was conducted under double-blind conditions with randomly assigned testing order, but how blinding was done was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Selection bias (e.g. titration after randomisation → exclusion): this series of 32 children with ADHD does not include an additional group of 12 children with ADHD, who after drug trials were deemed "non-responders" as well as 13 participants on whom adequate Event-Related Potentials data were not obtained
Selective reporting (reporting bias)	High risk	Did not report AE data

Tervo 2002

Study characteristics

Methods	Triple-blind, 3-way, cross-over trial with 2 interventions: • LD-MPH and HD-MPH • placebo Phases • HD-MPH: 0.3 mg/kg twice/d • LD-MPH: 0.05 mg/kg twice/d
Participants	Number of participants screened: not stated Number of participants included: 63 (49 boys, 14 girls) Number of participants followed up: 49 Number of withdrawals: 14

Tervo 2002 *(Continued)*

	Diagnosis of ADHD: DSM-IV (combined (70%), hyperactive-impulsive (16%), inattentive (5%), other (9%)) Age: mean 9 years 10 months (SD 2 years 10 months; range not stated) IQ: not stated MPH-naive: not stated Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: motor dysfunction (35%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Not stated **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 2 possible dose levels of IR-MPH and placebo Mean MPH dosage: not stated Administration schedule: twice daily; time points not stated Duration of each medication condition: 6 days Washout before trial initiation: 1 day Titration period: none Treatment compliance: not stated
Outcomes	**ADHD symptoms** • CPRS: parent-rated at baseline and at end of period • CTRS: teacher-rated at baseline and at end of period **General behaviour** • CBCL: parent-rated at baseline and at end of period • Home Situations Questionnaire: parent-rated at baseline and at end of period • Teacher report form (similar to CBCL): teacher-rated at baseline and at end of period • School Situations Questionnaire: teacher-rated at baseline and at end of period **Non-serious AEs** • Side Effects Rating Scale: parent, at baseline and at end of period
Notes	Sample calculation: no Ethics approval: no **Comments from trial authors**

Tervo 2002 *(Continued)*

- A limitation of this study is that neuropsychological functioning (e.g. intellect, ability, memory, visual perceptual functioning) was not measured in all children
- All children with MD had substantially impaired motor skills and "soft neurological signs" such as mixed laterality, mirror or overflow movements or choreiform movements

Key conclusions of trial authors

- Children with ADHD-MD were more likely to have severe ADHD combined type and other neurodevelopmental and behavioural problems
- Both groups of children had a linear dose response to medication (placebo, low, high), and no evidence was found of a group-by-dose interaction or an overall group effect at home or at school

Comments from review authors

- IQ not reported
- 4 children withdrew from the trial as the result of adverse reactions - all taking HD-MPH

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: yes

Funding source: not declared

Email correspondence with trial authors: April 2013. We received from trial authors the full dataset in Statistical Package for the Social Sciences(SPSS)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned
Allocation concealment (selection bias)	Low risk	Only the clinical pharmacist knew the sequence of phases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules of medication and placebo were made and dispensed as described by Barkley (1988). Tablets were crushed and placed within orange opaque gelatin capsules. Capsules disguised the taste of MPH and lactose placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	14 of the 63 trials were excluded from the analysis because of inadequately completed outcome measures. 4 of the 14 children did not complete the trial because of adverse reactions to medication (e.g. irritability, headache, stomachache). These children received HD medication in the first trial interval Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol was published

Tirosh 1993a

Study characteristics	
Methods	16-day, double-blind, cross-over, counterbalanced trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: not stated Number of participants included: 20 (16 boys, 4 girls) Number of participants followed up: 20 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (ADD 30%, ADHD 70%) Age: mean 9.3 years (range 7-12) IQ: mean 102 (SD 11) MPH-naive: 100% Ethnicity: not stated Country: Israel Setting: outpatient clinic Comorbidity: no Comedication: no Other sociodemographics: middle (12), upper-middle (5) and low (3) socioeconomic status of parents **Inclusion criteria** • DSM-III diagnosis of ADHD • 7-12 years old **Exclusion criteria** • MPH before trial • Neurological, sensory or physical health problems
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo MPH dose range: 0.3 mg/kg -0.5 mg/kg Administration schedule: twice daily Duration of each medication condition: 8 days Washout before trial initiation: no (participants were MPH-naive) Titration period: no Treatment compliance: parents were asked to bring their packages of tablets back for pill count; no data
Outcomes	**ADHD symptoms** • Abbreviated Parent Rating Scale (APRS), weekly • Teacher Rating Scale (TRS), weekly

Tirosh 1993a *(Continued)*

Notes	Sample calculation: no Ethics approval: yes **Key conclusions of trial authors** • Teacher Rating Scale: placebo-drug difference correlated more significantly with outcome measures than did the baseline drug difference • Trial underlines the validity of a multi-measure placebo/drug trial in evaluating the efficacy of MPH for children with attention deficit disorder Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: none Email correspondence with trial authors: August 2013. Trial author stated that data were discarded (Ramstad 2013d [pers comm]).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation with a table of random numbers
Allocation concealment (selection bias)	Low risk	Look-alike placebo tablets were supplied by the hospital pharmacy and were similarly administered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Tirosh 1993b

Study characteristics

Methods	Double-blind, controlled, cross-over trial with 2 interventions: • MPH • placebo
Participants	Number of participants screened: unknown

Tirosh 1993b *(Continued)*

	Number of participants included: 11 (8 boys, 3 girls) Number of participants followed up: 10 Number of withdrawals: 1 Diagnosis of ADHD: DSM-III (subtype not stated) Age: median 9 years 8 months (range 6.9-12.3 years) IQ: median 106 (range 92-118) MPH-naive: 100% Ethnicity: not stated Country: Israel Setting: outpatient clinic Comorbidity: none Comedication: none Other sociodemographics: low middle class (n = 2), middle class (n = 8) **Inclusion criteria** • Healthy; no neurological deficit • Living with their natural parents • Medication-naive **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg to 0.4 mg/kg MPH (total dose 10 mg-15 mg) and placebo Mean MPH dosage: 0.3 mg/kg-0.4 mg/kg Administration schedule: once daily at 7:30 am on 6 of the 8 days. During the other 2 days, a second dose was administered at 2:00 pm Duration of each medication condition: 8 days Washout before trial initiation: not stated Medication-free period between interventions: 3 days Titration period: none Treatment compliance: as measured by returned package pill counts, this was rated as full compliance for the 10 children remaining in the trial
Outcomes	**ADHD symptoms** • CTRS and CPRS: before therapy and after each intervention **Non-serious AEs** • Sleep measurements, 10 min before "lights out" until morning awakening for 4 successive nights during each of the 3 respective periods
Notes	Sample calculation: no

Tirosh 1993b *(Continued)*

Ethics approval: not stated

Key conclusions of trial authors

- Results support the notion that ADHD is a centrally generated disorder attributable to hypoarousal, which subsequently stimulates motor overactivity
- MPH does not appear to affect sleep patterns adversely and possibly normalises them in individuals with ADHD

Comment from review authors

- No useful data

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: yes; 1

Funding source: not declared

Email correspondence with trial authors: December 2013. We were unable to receive supplemental data from trial authors because the trial is 20 years old (Ramstad 2013d [pers comm]).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	A drug-placebo sequence was used for children assigned odd numbers in the trial and vice versa
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Look-alike placebo tablets were supplied
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator who analysed the data was unaware of the drug-placebo sequence
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol available

Tourette's Syndrome Study Group 2002

Study characteristics

Methods	16-week, multi-centre, randomised, double-blind, placebo-controlled, parallel trial with 4 arms: • MPH • clonidine • MPH + clonidine

Tourette's Syndrome Study Group 2002 *(Continued)*

- placebo

Phases: 3

- Weeks 1-4: clonidine/placebo dose titration
- Week 5-8: addition of MPH/placebo dose titration
- Weeks 9-16: maintenance therapy

Participants	Number of participants screened: not stated Number of participants included: 136 Number of participants followed up: 121 (MPH 33, placebo 25, clonidine 30, MPH + clonidine 33) Number of withdrawals: 19 (MPH 4, placebo 7, clonidine 4, clonidine + MPH 4) Diagnosis of ADHD: DSM-IV: MPH: combined 32%, hyperactive-impulsive 3%, inattentive 65%; placebo: combined 19%, hyperactive-impulsive 0%, inattentive 81%; clonidine: combined 21%, hyperactive-impulsive 3%, inattentive 76%; clonidine + MPH: combined 33%, hyperactive-impulsive 3%, inattentive 64% Mean age: MPH 10.7 years (SD 2.0); placebo 9.7 years (SD 1.8); clonidine 9.7 years (SD 1.8); clonidine + MPH 10.6 years (SD 1.9). Total age range 7-14 Sex: MPH 34 boys, 3 girls; placebo 29 boys, 3 girls; clonidine 29 boys, 5 girls; clonidine + MPH 24 boys, 9 girls Stimulant-naive: 42% Ethnicity: MPH 81% white; placebo 94% white; clonidine 94% white; clonidine + MPH 85% white Country: USA Setting: outpatient clinic Comorbidity: tic disorder diagnosis 100%; primarily OCD and ODD. Furthermore, CD, generalised anxiety disorder and major depressive disorder. MPH: OCD (11%), ODD (33%). Placebo: OCD (22%), ODD (41%). Clonidine: OCD (15%), ODD (48%). Clonidine + MPH: OCD (16%), ODD (31%) Comedication: not stated IQ: > 70 Other sociodemographics: participant groups were similar, except that participants assigned to MPH (alone or in combination with clonidine) are approximately 1 year older, present a higher proportion of pubertal cases, show underrepresentation of the inattentive subtype of ADHD (and overrepresentation of the combined subtype) and have lower baseline Conners' Abbreviated Symptom Questionnaire (ASQ)-Teacher scores. A higher proportion of girls was found in the combined treatment group **Inclusion criteria** • DSM-IV for ADHD • Designated teacher in daily direct contact with the participant had to indicate the presence of a sufficient number of ADHD symptoms (rated as "pretty much" or "very much") in the classroom setting using the Disruptive Behavior Disorders Rating Scale (updated to DSM-IV) to meet DSM-IV criteria; and had to rate the severity of ADHD symptoms above specified cut-off scores (boys: grade 2 to 3 = 10, grade ≥ 4 = 9; girls: grade 2 to 3 = 7, grade ≥ 4 = 6) on the IOWA CTRS • Investigator's rating of global functioning on the CGAS had to be 70 (indicating difficulty in ≥ 1 area, such as school) • DSM-IV for Tourette's disorder, chronic motor tic disorder or chronic vocal tic disorder **Exclusion criteria** • Secondary tic disorder (tardive tics, neuroacanthocytosis, Huntington disease)

Tourette's Syndrome Study Group 2002 *(Continued)*

- Major depression, pervasive developmental disorder, autism, psychosis, anorexia nervosa, bulimia, serious cardiovascular or other medical disorder that would preclude the safe use of MPH or clonidine, impaired renal function, pregnancy
- Mental disability
- The following cardiac conditions: prolonged QTc interval (> 440 milliseconds), high-grade ventricular ectopy, atrioventricular block > 1 degree, bundle branch block, intraventricular conduction block (100 milliseconds), pacemaker rhythm or heart rate < 60 on the ECG, cardiomyopathy, complex heart disease, aortic or pulmonary stenosis, family history of long QT syndrome, cardiomyopathy or premature sudden death (age 45 years), history of syncope and BP < 2 SD from age- and sex-adjusted mean
- Other medications for treatment of ADHD, tics or other associated behavioural symptoms. Any such treatment had to be discontinued ≥ 6 weeks (2 weeks for MPH) before enrolment

Interventions	Participants were randomly assigned to MPH (Ritalin; Novartis) alone, clonidine alone, clonidine + MPH or placebo Number randomised to each group: MPH 37, placebo 32, clonidine 34, MPH + clonidine 33 MPH dosage: MPH alone 25.7 mg/d, MPH + clonidine 26.1 mg/d Administration schedule: 2-3 times daily Duration of intervention: 12 weeks (4-week titration of MPH, 8-week maintenance phase) Titration period: 4-week initial dose titration period for clonidine, after which came 4-week dose titration for MPH. Both titration periods took place after randomisation Treatment compliance: pill count monitored compliance
Outcomes	**ADHD symptoms** • ADHD Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher): rated at baseline and at week 16 • IOWA CTRS: rated at baseline and at week 16 • Conners' Abbreviated Symptom Questionnaire for Parents (ASQ-Parent): rated at baseline and at weeks 8, 12 and 16 **General behaviour** • IOWA CTRS: rated at baseline and at week 16 **Quality of life** • CGAS: rated by site investigator at baseline and at weeks 8, 12 and 16 **Non-serious AEs** • YGTSS: rated by site investigator at weeks 8, 12 and 16 • TSSR: parent/participant- and teacher-rated at weeks 8, 12 and 16 (teacher ratings only at week 16) • Global Tic Rating Scale: parent/participant- and teacher-rated at weeks 8, 12 and 16 (teacher ratings only at week 16) • Vital signs, ECG: rated at weeks 8, 12 and 16 • Side Effects Rating Scale: rated at weeks 8, 12 and 16 (teacher ratings only at week 16) • Independent safety monitoring committee, consisting of child psychiatrist, paediatric cardiologist, paediatrician and statistician; reviewed data regarding AEs throughout the trial
Notes	Sample calculation: yes; 120 participants Ethics approval: yes; the protocol was approved by the institutional review board at each site **Comment from trial authors**

Tourette's Syndrome Study Group 2002 *(Continued)*

- "Our study did exclude participants with known cardiac problems, so the safety of combined clonidine and MPH in this group was not addressed."

Key conclusions of trial authors

- "Our study indicates that prior concerns that MPH worsens tics and that the drug should be avoided in patients with tics may be unwarranted"
- "The most effective treatment for ADHD in our trial was the combination of clonidine and MPH, although the incremental benefit of adding clonidine to MPH came at the expense of additional side effects, particularly sedation"

Comments from review authors

- Data extracted from week 4 to week 16 (from when MPH was introduced to participants)
- Not able to use trial data in our analyses

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: not stated

Funding: the National Institute of Neurological Disorders and Stroke, the General Clinical Research Center, the National Center for Research Resources, the Tourette Syndrome Association Boeringer Ingelheim Inc. (particularly Dr. Virgil Dias), for supplying clonidine and matching placebo; Bausch and Lomb, Inc., for supplying small gifts for our study participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation. Stratification by centre (investigator) and sexual maturity status (prepubertal: Tanner stage I to II; pubertal: Tanner stage III to V). Blocking was used to ensure approximate balance among treatment groups within each stratum
Allocation concealment (selection bias)	Low risk	Sealed envelopes that contained participants' treatment assignments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded: participants, clinicians, data collectors, outcome assessors, data analysts, data safety and monitoring committee, manuscript writers
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only the programmer in the Biostatistics Center who generated the plan and the pharmacist in the Pharmacy Center who packaged and labelled the drug were aware of treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary statistical analyses were performed according to the ITT principle and were based on all randomly assigned participants, as randomised. For analysis of outcome variables for efficacy, if a participant was missing a response at a particular visit, the last available observation for that participant was carried forward and imputed for that visit Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Tucker 2009

Study characteristics	
Methods	Multi-centre, open-label RCT including behaviour treatment as co-intervention with 2 arms • ER-MPH and behavioural treatment • Behavioural treatment
Participants	Number of participants screened: 142 Number of participants included: 109 Number of participants followed up: 104 (66 boys, 38 girls) Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (subtypes not described) Age: mean 8.4 years (range 6-12) IQ: not stated; all age-appropriate cognitive functioning MPH-naive: 100% Ethnicity: white (73.1%), African American (24.0%), other (2.9%) Country: USA Setting: outpatient clinic Comorbidity: none Comedication: no Other sociodemographics: none **Inclusion criteria** • DSM-IV diagnosis of ADHD • Age-appropriate cognitive functioning **Exclusion criteria** • Previous exposure to MPH or any amphetamine-based medication • Positive urine drug screen • Clinically significant abnormality in the screening assessment (physical exam, vital signs, laboratory tests) • Cardiac abnormality • History of seizures or schizophrenia; current diagnosis of mood disorder or anxiety disorder
Interventions	Participants were randomly assigned to ER-MPH plus behavioural treatment or to behavioural treatment alone. We considered this as ER-MPH versus no intervention. Mean MPH dosage: not stated Administration schedule: once daily Duration of intervention: 3 months Titration period: initiated after randomisation. MPH was started at 10 mg/d and could be increased weekly in intervals of 10 mg/d to a maximum of 60 mg/d. MPH was administered to achieve the desired clinical effect with minimum or no side effects

Tucker 2009 *(Continued)*

	Treatment compliance: not stated
Outcomes	**ADHD symptoms** • Conners' ADHD/DSM-IV Scales for Parents: measured at baseline and at end of treatment **Non-serious AEs** • Investigating for potential genotoxic effects: no significant differences were found • Chromosomal aberrations (CAs), including micronuclei (MN) and sister chromatid exchanges (SCEs), in cultured peripheral blood lymphocytes. Blood samples were obtained from all participating patients for evaluation of cytogenetic status at baseline and after 3 months of treatment. These data are not used in the review
Notes	Sample calculation: yes Ethics approval: yes; approved by the ethics committees for all 17 trial centres **Key conclusion of trial authors** • These findings support the notion that MPH does not induce chromosomal alterations nor other types of genetic damage in children treated for ADHD Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no; all participants were MPH-naive Any withdrawals due to AEs: no Funding source: Novartis Pharmaceuticals Corporation Email correspondence with trial authors: December 2013 and January 2014. Not able to contact trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised; no further description
Allocation concealment (selection bias)	Unclear risk	Randomisation was stratified by age group (6-8 years and 9-12 years) and by centre
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluation of cytogenetic damage by blinded slide readers
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome data reported for 68 of 109 randomly assigned participants Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Ullmann 1985

Study characteristics	
Methods	8-week, cross-over trial: • 3 doses of MPH (0.3 mg/kg, 0.5 mg/kg, 0.8 mg/kg) • placebo Phases: 2 • Phase 1: 4-week fixed increase in MPH dose • Phase 2: 4-week randomised, cross-over trial The trial was conducted over 3 years
Participants	Number of participants screened: not stated Number of participants included: 86 Number of participants followed up: 86 (67 boys, 19 girls) Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (ADD (15.1%), ADD-H (70.9%), other (14.0%)) Age: mean 8.6 years (SD 1.8; range not stated) IQ: > 70 MPH-naive: not stated Ethnicity: African American (17.4%), other (82.6%) Country: USA Setting: not stated Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • ADHD diagnosis according to DSM-III **Exclusion criteria** • Not described
Interventions	Participants were randomly assigned to 3 different doses of MPH (0.3 mg/kg, 0.5 mg/kg and 0.8 mg/kg) and placebo Administration schedule: once daily, before school Duration of each medication condition: 1 week Washout before trial initiation: dose taken in the morning to the next day's dose Titration period: 4 weeks Treatment compliance: "compliance were probably high"
Outcomes	**ADHD symptoms**

Ullmann 1985 *(Continued)*

- ADD/H Comprehensive Teacher Rating Scale: completed by teachers on a weekly basis, on the last day before treatment switching

Notes	Sample calculation: no information Ethics approval: no information **Comment from trial authors** • Order effects were non-significant, that is, ratings were similar for the first and second weeks on each dose, regardless of the order in which doses were given **Key conclusion of trial authors** • Results from the study show that MPH has a major effect in improving attention and is helpful in decreasing activity levels but often has only a minor effect on deficient social skills and oppositional (aggressive) behaviour Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: NIMH. Ciba-Geigy provided medication and placebo Email correspondence with trial authors: not able to find first or second trial author's contact information; therefore not able to request supplemental data necessary for meta-analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random assignment
Allocation concealment (selection bias)	High risk	No description; only "methylphenidate in opaque capsules"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Teacher rating under blinded conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were pooled for a total of 86 participants Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	Unable to obtain protocol

Ullmann 1986

Study characteristics

Ullmann 1986 *(Continued)*

Methods	Double-blind, cross-over trial in which participants were randomly assigned to the following conditions: • 3 different doses of MPH (0.3 mg/kg, 0.5 mg/kg and 0.8 mg/kg) • placebo
Participants	Number of participants screened: not stated Number of participants included: 118. Number of participants followed up: 118 (92 boys, 26 girls) Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 8.6 years (range 6-14) IQ: > 70 MPH-naive: not stated Ethnicity: white (81.4%), African American (18.6%) Country: USA Setting: school setting and outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Diagnosis of ADHD **Exclusion criteria** • None mentioned
Interventions	Participants were randomly assigned to 3 different doses of MPH (0.3 mg/kg, 0.5 mg/kg and 0.8 mg/kg) and placebo Mean MPH dosage: not stated Administration schedule: not stated Duration of each medication condition: 1 week Washout before trial initiation: no information Titration period: none Treatment compliance: excellent compliance in all but a few children
Outcomes	**ADHD symptoms** • ADD/H Comprehensive Teacher Rating Scale: rated by teachers at the end of each school week **Non-serious AEs** • Teacher Checklist: rated by teachers at the end of each school week

Ullmann 1986 *(Continued)*

	Unable to obtain data on AEs, as could not locate contact details of the first or second trial author (see notes)
Notes	Sample calculation: no Ethics approval: no information **Key conclusion of trial authors** • "Double-blind placebo evaluation of children with ADD can and should be done by practitioners to avoid medicating children who are responding to non-specific effects of drugs" **Comment from trial authors** • Very few children were reported completely free of adverse effects; however, these were, on the whole, mild effects. In fact, a slightly higher proportion of children were reported to show adverse psychological effects at baseline (0.60) and on baseline (0.53) than on medication (0.46), but these differences were not significant **Comment from review authors** • Used data from MPH responders in our analyses, which yielded a highly biased result Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: in part by a NIMH grant. Ciba-Geigy provided medication and placebo. Email correspondence with trial authors: not able to find first or second trial author's contact information; therefore not able to obtain additional data (e.g. data (table) on adverse effects) from trial authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Daily doses of MPH or placebo were placed in gelatin capsules to disguise taste and dose differences; medication for each week was packaged in a dated envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Children, parents and teachers were blinded to dose order, as was the assistant who recorded data sent in by the teachers
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Children, parents and teachers were blinded to dose order, as was the assistant who recorded data sent in by the teachers
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol

Urman 1995

Study characteristics	
Methods	Double-blind, placebo-controlled, within-participant (cross-over) trial looking at cardiovascular effects of MPH (0.3 mg/kg, 0.6 mg/kg and 0.9 mg/kg) doses at baseline and after 60 and 120 min post-MPH challenge in 2 groups of participants with ADHD • ADHD without anxiety • ADHD with anxiety
Participants	Number of participants screened: not stated Number of participants included: 63 (58 boys, 5 girls) Number of participants followed up: 63 (ADHD without anxiety 34, ADHD with anxiety 29) Number of withdrawals: not stated Diagnosis of ADHD: DSM-III-R (but "82% of the ADHD and 93% of the ADHD/ANX [ADHD + anxiety] group" would meet the DSM-IV criteria for a diagnosis of ADHD combined type) Age: ADHD without anxiety, mean 9.1 years (SD 1.3; range 6-12); ADHD with anxiety, mean 8.7 years (SD 1.4) (overall range 6-12) IQ: not stated MPH-naive: 63 (100%) Ethnicity: white (90%), "African or Asian descent" (10%) Country: Canada Setting: not stated Comorbidity: ADHD group: ODD (14; 42%), CD (5; 15%); ADHD with anxiety group: ODD (11; 38%), CD (8; 28%). Also, in the ADHD with anxiety group, 3 met the DSM-III criteria for overanxious disorder, 2 met criteria for separation anxiety disorder and 5 met criteria for both overanxious and separation anxiety disorders) Other sociodemographics: "The children tended to come from middle-class families" **Inclusion criteria** ADHD with anxiety group • T score ≤ 1 SD above the mean for age and sex on both the RCMAS and the Trait Scale of the State-Trait Anxiety Inventory for Children (STAIC) ADHD without anxiety group • T score > 1 SD above the mean for age and sex on the Revised Children's Manifest Anxiety Scale (RC-MAS) and/or the Trait Scale of the STAIC • "The children could also meet diagnostic criteria for any anxiety disorder based on the parent interview" **Exclusion criteria** ADHD without anxiety group • "Any child who scored within this range but met diagnostic criteria for any anxiety disorder on the basis of parent diagnostic interview was excluded from the analysis"

Urman 1995 *(Continued)*

Interventions	Participants were randomly assigned to 1 of 4 possible drug condition orders of placebo and MPH (0.3 mg/kg, 0.6 mg/kg or 0.9 mg/kg), given once daily over a 4-day period. Dosage was based on a child's body weight to the nearest 2.5 mg. Children followed the same routine for every test session with pre-MPH measurements and with measurements at 60 min and again at 120 min after taking MPH Mean MPH dosage: not stated Duration of each medication condition: once daily, administered over a 4-day period - each medication condition given once to each child Washout before trial initiation: all were MPH-naive Medication-free period between interventions: not stated Treatment compliance: "Any child with missing data for a particular measure was excluded from the analysis of that measure", but trial authors did not indicate the overall quantity of missing data. "Medication was administered by a research nurse"
Outcomes	**Non-serious AEs** • SBP and DBP • Heart rate (radial pulse measured for 60 seconds)
Notes	Sample calculation: no information Ethics approval: no information **Comment from trial authors** • From a clinical perspective, stimulant-related increases in heart rate and BP in both groups of children with ADHD were modest and generally of little clinical concern. Nonetheless, the present findings of an exaggerated cardiovascular response to MPH in the ADHD with anxiety group should alert clinicians to the possibility of a differential medication response in anxious ADHD children **Key conclusions of trial authors** • This trial yielded 2 major findings. First, it demonstrated that baseline cardiovascular function did not differ between children with ADHD and children with ADHD and anxiety. Second, it revealed the presence of an exaggerated DBP response to MPH in children with ADHD and anxiety • Data from the present trial add to growing evidence that children with ADHD and anxiety constitute a distinct subgroup of children with ADHD. Moreover, the exaggerated response of children with ADHD and anxiety to MPH suggests the presence of abnormal regulation of norepinephrine (NE) function in this group, compared with that observed in the anxiety disorder population **Comments from review authors** • Inadequate description of method for BP and heart rate measurement • Measurement of heart rate was presumably carried out by palpating radial pulse - pulse oximetry or ECG would produce more reliable results Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: in part by funds from the Medical Research Council of Canada and the Research Institute of the Hospital for Sick Children

Risk of bias

Bias	Authors' judgement	Support for judgement

Urman 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"The order of medications was counterbalanced and determined by random assignment such that an approximately equal number of children received each dose on a given day in the trial"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All medication was prepared by the hospital pharmacy and packaged in opaque gelatin capsules, to avoid detection of dose and taste"; "Children, parents and research staff were blind to the medication conditions"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Medication was administered by a research nurse who was blind to children's medication condition and classification of anxiety"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol identified

Van der Meere 1999a

Study characteristics	
Methods	7-week, randomised, double-blind, placebo-controlled, parallel-group trial with 3 arms • MPH • placebo • clonidine
Participants	Number of participants screened: not stated Number of participants included: 48 (+24 in the clonidine group not used in this review) (62 boys, 10 girls) Number of participants followed up: 47 (MPH 23, placebo 24) Number of withdrawals: 1 (from the MPH group) Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 8.8 years (range 7-12) IQ: > 70 MPH-naive: 100% Ethnicity: mainly white Country: the Netherlands Setting: outpatient clinic Comorbidity: CD (11%), ODD (33%), depressive disorder (3%), overanxious disorder (1%), dysthymia (3%), generalised tonic-clonic seizures (1%), ventricular septal defect (1%), congenital hypothyroidism (1%), precocious puberty (1%), deaf in right ear (1%), atresia in 1 ear (1%)

Van der Meere 1999a *(Continued)*

	Comedication: yes; for participants who had diseases that required it, for example, hypothyroidism Other sociodemographics: 44% from lower socioeconomic families Differences between groups No significant differences in age and IQ were noted between the 2 groups **Inclusion criteria** • Boys and girls • 6-15 years of age • IQ > 70 • Living in a family home and attending school • DSM-III-R diagnosis of ADHD, ADHD symptoms impeding development and psychological/educational treatments with insufficient effect • No earlier use of stimulant drugs or clonidine and no psychoactive medications of any kind in the last 6 months • No medical contraindications • No important changes expected for the course of the trial • It was considered clinically meaningful by both parents and the attending physician to try "hyperactivity medication" **Exclusion criteria** • Additional psychoactive drugs during the trial • Pervasive developmental disorder or tic disorder. These participants were included in other trial groups.
Interventions	Participants were randomly assigned to MPH, placebo or clonidine Number of participants randomised to each group: MPH 24, placebo 24, clonidine 24 Total oral daily MPH dosage: 0.06 mg/kg Mean of the absolute MPH dose: 9.85 mg (2.26) Administration schedule: breakfast and lunchtime Duration of intervention: 7 weeks Titration: no, but dosage adjustments were made/allowed during first weeks Titration period: none Treatment compliance: maintained and checked by instructions (both oral and written) to both parents and child, and by counting tablets remaining at the end of treatment. Only 1 participant in the MPH group showed poor compliance
Outcomes	**ADHD symptoms** • CTRS: baseline and at week 7 **General behaviour** • Parent and Teacher Versions of the abbreviated Groninger Behaviour Observation Scale (GOO and GBO, respectively): baseline and at weeks 3, 5 and 7 • Parent and Teacher Versions of the abbreviated Groninger Behaviour Checklists (GGGS and GGBS, respectively): baseline and at week 7 • GPO rating: baseline and at week 7 **Non-serious AEs**

Van der Meere 1999a *(Continued)*

- Parent ratings of drowsiness, insomnia, decreased appetite, nausea, headache, nervousness, motor restlessness, feelings of dizziness, dry mouth, nightmares, apathy, irritability and "other complaints"
- Child and parents were asked about all kinds of physical and behavioural complaints or changes at trial visits

Notes	Sample calculation: yes (≥ 15 participants in each group) Ethics approval: yes **Key conclusion of trial authors** • "We concluded that the state regulation problem in ADHD is resistant to MPH and clonidine" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: grants from the Sophia Foundation for Medical Research and Boehringer Ingelheim BV, the Netherlands Email correspondence with trial authors: September 2013. We obtained supplemental information regarding a publication with information about randomisation and supplemental data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The statistician sent the randomisation list to the pharmacist. Participants were then randomly assigned by a research pharmacist. To ensure blinding, pharmacists applied randomisation blocks at random at a length of 2 or 4 participants. MPH and matching placebos were used
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Teacher, parent, clinician, child and experimenter were blind to treatment conditions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Teacher, parent, clinician, child and experimenter were blind to treatment conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT Selection bias: no, but dosage adjustments were made for several participants because of annoying AEs
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Wallace 1994

Study characteristics

Methods	Double-blind, single-participant, randomised, cross-over trial:

Wallace 1994 *(Continued)*

	• MPH • placebo Conducted in 11 hospitalised children with ADHD
Participants	Number of participants screened: not stated Number of participants included: 11 Number followed up: 11 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype not described) Age: mean 9 years 5 months (range 4-13 years) IQ: not stated MPH-naive: not stated Ethnicity: not stated Country: USA Setting: inpatient Comorbidity type: not stated Other sociodemographics: none **Inclusion criteria** • Children diagnosed with ADHD who were hospitalised at a psychiatric hospital **Exclusion criteria** • Not stated
Interventions	Participants were randomly assigned to 1 of 2 conditions: MPH and placebo on a daily basis Mean MPH dosage: not stated Administration schedule: daily Duration of each medication condition: MPH 2-7 days, placebo 3-6 days Washout before trial initiation: not described Medication-free period between interventions: none Titration period: "Prior to trial commencement, all participants were treated with MPH for a period long enough to determine the dose believed to have optimal effectiveness and minimal side effects" Treatment compliance: not described
Outcomes	**ADHD symptoms** • Abbreviated CTRS (15-item): rated by teachers and by day and night nursing staff **Serious AEs** • Side effects mentioned but not reported **Non-serious AEs**

Wallace 1994 *(Continued)*

- Side effects mentioned but not reported

Notes	Sample calculation: not stated Ethics approval: not stated **Comment from trial authors** • Assigning highly consistent rates would reduce variance in measurements **Key conclusions of trial authors** • n-of-1 trial is useful for evaluating the effectiveness of MPH in individual patients with ADHD • Short duration of MPH action allows for multiple cross-over trials over a brief time **Comment from review authors** • Data are not reported in a suitable form for meta-analysis; therefore we could use no data from this trial Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, see titration before randomisation Any withdrawals due to AEs: no Funding source: The Veterans Administration Medical Center, Vermont Email correspondence with trial authors: we could find no contact information; therefore, we could not get additional data through personal email correspondence with trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence was determined by "coin toss method"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"After completion of each trial, the treatment code was broken" Method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data appear to have been reported. Selection bias (e.g. titration after randomisation → exclusion): no, but trial length was changed according to MPH response
Selective reporting (reporting bias)	High risk	Protocol not identified "Also trial length increased as effect size decreased, implying that if clinical effects were unconvincing, the trial was extended. The trials examined here did have trial length designated at commencement by the treating psychiatrist (generally 10 days). However, trials were extended, if after the predetermined number of days, the graphed data appeared equivocal."

Wallander 1987

Study characteristics	
Methods	Double-blind, placebo-controlled, cross-over trial with 3 interventions: • MPH 0.3 mg/kg • MPH 0.6 mg/kg • placebo
Participants	Number of participants screened: 28 (20 boys, 8 girls) Number of participants included: unclear Number of participants followed up: unclear Number of withdrawals: unclear Diagnosis of ADHD: DSM-III (subtype not stated) Age: mean 8.4 years (range 6-12) IQ: mean 79.64 MPH-naive: 28 (100%) Ethnicity: not stated Country: USA Setting: outpatient clinic and inpatient ward Comorbidity: not stated Comedication: not stated Other sociodemographics: 3.52 (Hollingshead-Redlich Index) **Inclusion criteria** • Meeting DSM-III criteria for the diagnosis of ADHD, as assessed by an experienced psychiatrist and paediatrician • Scoring 2 SD above the mean for age and sex on both hyperactivity and distractibility factors of the CTRS • Naive to stimulant medication **Exclusion criteria** • No information
Interventions	Participants were randomly assigned to 1 of the possible drug condition orders of MPH (0.3 mg/kg and 0.6 mg/kg) and placebo Mean MPH dosage: no information Administration schedule: twice/d, 8:30 am and noon Duration of each medication condition: 12 days for inpatients and 19 days for outpatients (mean 15.25 days) Washout before trial initiation: none Medication-free period between interventions: 68 h

Wallander 1987 *(Continued)*

	Titration period: none Treatment compliance: no information
Outcomes	**General behaviour** • Oppositional behaviour
Notes	Sample calculation: none Ethics approval: no information **Key conclusions of trial authors** • Results indicate no change in social behaviours, as participants decreased their display of problem behaviours as a function of stimulants • "Peers and teachers responded and attendees less to them, however, when they received stimulants as compared with placebo" **Comment from review authors** • Data could not be used in meta-analyses because some were missing Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: no Funding source: in part by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) grants and the University of Southern California Faculty Research and Innovation Fund. Email correspondence with trial authors: December 2013. No supplemental information available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Receiving interventions in counterbalanced orders
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Agreement of 90% across all categories had to be reached with this validity observer Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	Protocol not identified

Waxmonsky 2008

Study characteristics	
Methods	9-week therapeutic summer camp consisting of a cross-over trial with 4 interventions: • Placebo • MPH 0.15 mg/kg 3 times/d • MPH 0.3 mg/kg 3 times/d • MPH 0.6 mg/kg 3 times/d Varied daily within a cross-over design of 3 intensities of behaviour modification therapy • No • Low • High Each lasted 3 weeks
Participants	Number of participants screened: 106 participants in the 2003 and 2004 Summer Treatment Program (University of Buffalo) Number of participants included: 101 (82 boys, 19 girls) (ADHD subgroup 33, ADHD + severe mood dysregulation (SMD) subgroup 68) Number of participants followed up: 99 Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV (combined (92%), hyperactive-impulsive (not stated), inattentive (not stated)) Age: mean 8.5 years (range 5-12) IQ: mean: 105 MPH-naive: not stated Ethnicity: predominantly white Country: USA Setting: outpatient clinic (Summer Treatment Program) Comorbidity: ODD (54%), CD (12%) Comedication: not stated Other sociodemographics: predominantly middle class **Inclusion criteria** • 5-12 years of age • Participants were required to stop all psychotropic medication 1 week before intake • DSM-IV diagnosis of ADHD • ADHD-related impairment in ≥ 2 realms according to Parent and Teacher Versions of the Impairment Rating Scale (IRS) • IQ > 80 • Subgroups ○ ADHD: not meeting NIMH criteria for severe mood dysregulation

Waxmonsky 2008 *(Continued)*

- ADHD plus severe mood dysregulation: meeting NIMH criteria for severe mood dysregulation, and having Young Mania Rating Scale (YMRS) score ≥ 12 based on the last month's behaviour and CGI mania severity score ≥ 3

Exclusion criteria

- History of seizures or other neurological problems
- Medical history that would involve considerable risk in taking stimulant medication
- History or concurrent diagnosis of any of the following disorders: pervasive developmental disorder, schizophrenia or other psychotic disorders, sexual disorder, organic mental disorder or eating disorder
- Documented serious adverse reaction to MPH
- Significant developmental delays or autistic spectrum illness
- Active use of psychotropic medication for disorders besides ADHD, including use of antidepressants or mood-stabilising medications
- Meeting full criteria for the narrow-phenotype criteria of bipolar disorder or in need of urgent psychiatric treatment (active suicidal ideation). Participants newly identified with major depressive disorder or bipolar disorder on the DISC were directly assessed by an M.D.- or Ph.D.-level clinician

Interventions	Participants attended a Summer Treatment Program each Monday through Friday for 9 weeks. Participants were randomly assigned possible drug condition orders of 0.15 mg/kg 3 times/d, 0.3 mg/kg 3 times/d and 0.6 mg/kg 3 times/d and placebo Average MPH dosages: 5 mg, 10 mg and 18 mg for 0.15 mg/kg, 0.3 mg/kg and 0.6 mg/kg doses, respectively Administration schedule: 7:45 am, 11:45 am and 3:45 pm Duration of each medication condition: each dose varied daily and was repeated 3 or 4 times within each behavioural treatment condition Trial duration: Monday through Friday for 9 weeks, totaling 45 days Washout before trial initiation: 1 week Medication-free period between interventions: 0-2 days Titration period: none Treatment compliance: not stated Cointervention: 3 behavioural conditions (no behaviour modification, low-intensity behaviour modification and high-intensity behaviour modification) are delivered in random order, with each condition lasting 3 weeks. Parents attended training sessions and implemented behaviour programmes at home
Outcomes	**Non-serious AEs** • Pittsburgh Side Effects Rating Scale: completed daily by camp staff and parents
Notes	Sample calculation: not stated Ethics approval: yes; by the Health Sciences Institutional Review Board (IRB) of the University of Buffalo **Comment from trial authors** • Limitations: trial duration of only 9 weeks, lack of daily completion of mood assessments and limited generalisation potential due to a population of predominantly white and middle-class participants. **Key conclusion of trial authors** • MPH and behaviour modification therapy are tolerable and effective treatments for children with ADHD and severe mood dysregulation, but additional treatments may be needed to optimise their functioning.

Waxmonsky 2008 *(Continued)*

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; excluded patients with prior serious reactions to MPH

Any withdrawals due to AEs*:* 1 withdrew because of tic-like movements

Funding source: NIMH Grant MH62946 and a Klingenstein Third Generation Foundation Fellowship in Child and Adolescent Depression Research

Email correspondence with trial authors: August 2014. Obtained supplemental information regarding randomisation, allocation concealment and handling of missing data. Not possible to retrieve safety data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random orders were generated by computer with the restrictions that each condition occurred at least once in each week. Children were assigned to previously generated codes at enrolment
Allocation concealment (selection bias)	Low risk	Because this was a cross-over trial in which all children received all conditions multiple times, each child's entire 9-week schedule was assigned at once. Treatment orders were concealed in an opaque envelope and were stored in a locked cabinet in the medication lab. Only authorised staff members had access to this cabinet.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Children, parents and staff were blinded to medication conditions. Placebo and MPH were packaged in identical opaque capsules to maintain blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Parents and staff were blinded to medication conditions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Outcomes reported according to protocol

Weiss 2021

Study characteristics

Methods

A 4-week parallel trial with 5 arms:

- MPH-ER (PRC-063) 25 mg/d
- MPH-ER (PRC-063) 45 mg/d
- MPH-ER (PRC-063) 70 mg/d
- MPH-ER (PRC-063) 85 mg/d
- placebo

Phases: 4 (1 week washout, 2 weeks forced titration, 2 weeks stable dose, 6-month open-label, follow-up trial)

Weiss 2021 *(Continued)*

Participants	Number of participants screened: 450 Number of participants included: 367; after exclusion of 1 trial site, 354 remained randomised (239 boys, 115 girls) Number of participants followed-up: 323 Number of withdrawals: 31 (+ 13 from excluded trial site) Diagnosis of ADHD: DSM-5 (255 combined, 5 hyperactive/impulsive, 94 inattentive) Age: placebo 14.1 mean years, MPH 14.2 mean years (range 12 to ≤ 17) IQ: > 80 MPH-naive: 66% Ethnicity: not stated Country: Canada and USA Setting: outpatient Comorbidity: no allowed comorbidity specified. Many somatic and psychiatric disorders were exclusion criteria Comedication: a stable dose of melatonin was permitted (5.1% of participants); 1 participant in a MPH group received a hypnotic/sedative medicament Additional sociodemographics: none **Inclusion criteria** • Participant must be male or non-pregnant female at least 12 years of age and < 18 years of age • Must have an ADHD diagnosis, in attentive, hyperactive/impulsive or combined, as defined by the DSM-5 based on clinician assessment using multiple informants and a structured interview • Must be unsatisfied with his or her current pharmacological therapy for treatment of ADHD or not currently receiving pharmacological therapy for ADHD. Inclusion of participants naïve to pharmacological therapy for ADHD is permitted • Female participants must be one of the following: a. surgically sterile prior to screening; b. if of childbearing potential, abstinent or willing to use a reliable method of contraception, such as oral contraceptive, 2 barrier methods, a barrier method plus a spermicidal agent • Female participants of childbearing potential must be a negative serum β-hCG pregnancy test at screening • Must have a minimum level of intellectual functioning, as determined by an IQ score of ≥ 80 based on the WASI or the KBIT • Mentally and physically competent to sign an informed assent document, in the case of the participant, and an informed consent document, in the case of the parent/guardian, indicating that they understand the purpose of and procedures required for the trial and are willing to participate in the trial • Able and willing to comply with the trial procedures for the entire length of the trial, including a successful swallow test of an empty 85 mg capsule • Total score of ≥ 24 on the clinician-rated ADHA-5-RS, as assessed at Visit 2 **Exclusion criteria** • Having an allergy to MPH or amphetamines or a history of serious adverse reactions to MPH • Known to be non-responsive to MPH treatment. Non-response is defined as MPH use at various doses for a phase of at least 4 weeks at each dose with little or no clinical benefit • Being diagnosed with or having a history of strokes, epilepsy, migraine headaches (> 1 instance every 2 months), glaucoma, thyrotoxicosis, tachyarrhythmias or severe angina pectoris or have serious or unstable medical illness. Participants with controlled or stable asthma or diabetes permitted • Elevated BP, defined as any values > 89 DBP or 139 SBP, as assessed at Visit 1

Weiss 2021 *(Continued)*

- Clinically significant ECG abnormalities, as assessed at Visit 1
- Clinically significant laboratory abnormalities, as assessed at Visit 1
- Currently receiving guanethidine, pressor agents, MAOIs, coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), phenylbutazone, tricyclic antidepressants (e.g. imipramine, desipramine), SSRIs or herbal remedies (unless on a stable dose for 4 weeks)
- Participant has known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary heart disease, transient ischemics attack or stroke or other serious cardiac problems that may place the participant at increased vulnerability to the sympathomimetic effects of a stimulant drug
- Participant has a known family history of sudden cardiac death or ventricular arrhythmia
- Participants who are currently considered a suicide risk by the investigator
- Having a primary diagnosis of schizophrenia, schizoaffective disorder, primary affective disorder, schizotypal personality, major depression, bipolar disorder, generalised anxiety, borderline personality disorder, antisocial personality or another unstable psychiatric condition requiring treatment, as assessed by the structured interview conducted at Visit 1
- Having a history or suspected physiological dependence (excluding nicotine) on narcotic analgesics or other psychoactive drugs (including barbiturates, opiates, cocaine, cannabinoids, amphetamines and benzodiazepines)
- Excessive consumption of alcohol (consumes alcohol in quantities > 15 drinks/week; 1 drink is defined as 360 mL/12 oz. of beer, 120 mL/4 oz. of wine, or 30 mL/1 oz. of hard liquor), or history (within previous 6 months) of alcohol abuse
- Currently (or within 30 days before the planned start of treatment) receiving an investigational drug or using an experimental medical device
- Homeless

Interventions	Participants were randomly assigned to either MPH PRC-063 (25, 45, 70 or 85 mg) or placebo once/d. Number randomised to each group: first 367 were randomised (293 to MPH PRC-063 groups and 74 to placebo). Due to major protocol violations, 13 participants from 1 site were excluded from the analysis, leaving 71 randomised to placebo and 283 randomised to MPH PRC-063 groups (25 mg/d: n = 71, 45 mg/d: n = 69, 70 mg/d: n = 73, 85 mg/d: n = 70) Mean medication dosage: participants were evenly distributed to a forced dose of 25, 45, 70 or 85 mg/d. Administration schedule: once daily Duration (of (each) medication): 4 weeks Washout before trial initiation: 1 week Titration period: 2 weeks (blinded forced-titration) Treatment compliance: compliance was evaluated by counting and recording the number of dispensed capsules and the number of returned capsules. Noncompliance was defined as missing ‡2 doses from a single bottle of trial medication. 83.7% compliance
Outcomes	**ADHD symptom severity** • ADHD-5-Rating Scale: clinician rated • ADHD-5-Rating Scale: parent rated **Serious AEs** • C-SSRS **General behaviour** • BRIEF **Non-serious AEs**

Weiss 2021 *(Continued)*

- Pittsburg Sleep Quality Inventory (PSQI)
- Spontaneous reporting

As no SD was reported in the trial articles, we have not been able to use the ADHD Symptom or General Behavior data for the analysis.

Notes

Sample calculation: yes, 360 participants

Ethics approval: yes. "For each study site, the study protocols were approved by an independent ethics committee or institutional review board, as appropriate. The studies were conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice (GCP), and all applicable local, state, and federal regulations." (Weiss 2021a, p 2)

Comments from trial authors

- The double-blind study was only powered to determine the overall effect of PRC-063 relative to placebo, and individual dose groups were too small to evaluate dose effectiveness.
- The fixed-dose design of the double-blind study may have resulted in some participants (most of whom were treatment naïve) being titrated too rapidly to an 85 mg dose.
- Overall, 77% of participants were randomised to a dose that was either too low or too high, potentially leading to the treatment response being underestimated and AE rates being overestimated.

Key conclusion of trial authors

- Significant improvements in ADHD symptomatology were observed based on the primary and secondary outcome measures and across 3 different sets of informants: clinicians, parents, and adolescents themselves. PRC-063 was generally well tolerated, with an AE profile consistent with other long-acting stimulants.
- Significant improvements in executive function and patient satisfaction were also observed with no negative impact on sleep quality or unexpected safety findings.

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: yes, 10 participants all from the MPH PRC-063 groups

Funding source: Rhodes Pharmaceuticals, LP

Email correspondence with trial authors: no correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization schedules were generated by Y-Prime, Inc., using an integrated web response system"
Allocation concealment (selection bias)	Low risk	Central allocation through Y-Prime, Inc. and identically appearing drug containers and capsules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**"**PRC-063 and placebo were supplied in bottles, each containing 10 capsules. To maintain blinding, placebo and PRC-063 at each dose were identical in appearance. No emergency unblinding occurred during the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**"**No emergency unblinding occurred during the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Due to multiple protocol violations and Good Clinical Practices (GCP) issues, it was necessary to exclude efficacy data for the 13 participants enrolled at one trial site from the primary efficacy analysis. A sensitivity analysis including da-

Weiss 2021 *(Continued)*

		ta from this trial site was performed. As a further sensitivity analysis to assess the impact of missing data, the primary efficacy analysis for the full analysis population was repeated using Markov Chain Monte Carlo (MCMC) multiple imputation. Missing data were imputed 20 times. Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All protocol outcomes reported

Whalen 1990

Study characteristics	
Methods	2-day cross-over trial with 2 interventions • MPH 0.3 mg/kg • Placeb In a connected trial 25 children were randomised to the same interventions. The outcome of this trial included the social judgement processes during the different drug conditions. Outcomes from the trial included in this review were reported in this connected trial.
Participants	Number of participants screened: unknown Number of participants included: 24 Number of participants followed up: 24 (22 boys, 2 girls) Number of withdrawals: 0 ADHD diagnosis: trial 1 DSM-III-R Age: trial one mean 9 years 8 months (range 6.4-13.2 years) IQ: no mental disability MPH-naive: 0% Ethnicity: white (92%), African American (4%), Hispanic (4%) Country: USA Setting: outpatient clinic (Summer Treatment Program) Comorbidity: not stated Comedication: not stated Other sociodemographics: all were from middle- or low middle-income backgrounds **Inclusion criteria** • Primary diagnosis of ADDH • Taking MPH on a regular basis before the programme • Conners' ADHD Stigma Questionnaire: ratings from parents > 15 **Exclusion criteria** • No information

Whalen 1990 *(Continued)*

Interventions	Participants were randomly assigned to 1 of the possible drug condition orders of 0.3 mg/kg MPH or placebo. Mean MPH dosage: 8.75 mg Administration schedule: twice/d, morning and lunchtime Duration of each medication condition: 1 day Washout before trial initiation: unknown Medication-free period between interventions: medication and placebo were given on 2 consecutive days Titration period: none Treatment compliance: good (2 staff dispensed the medication for ingestion)
Outcomes	**General behaviour** • Evaluations of Social Behaviors in Medicated and Unmedicated Peers (Negative detections): rated by healthy controls (children)
Notes	Sample calculation: no Ethics approval: no information **Key conclusions of trial authors** • In both studies, double-blind ratings done by naive and staff observers demonstrated nearly identical medication effects, that is, placebo-related increases in behaviour problems and MPH-related increases in dysphoria • Ratings of medication effects proved remarkably resilient, showing an invulnerability to biasing influences introduced by general knowledge about research design, diagnostic status or treatment effects; or by specific knowledge about and experience with participating children Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; only participants taking maintenance dosage of MPH or well titrated Any withdrawals due to AEs: no Funding source: not stated Email correspondence with trial authors: January 2014. No supplemental information has been received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both active medication and placebo were placed in opaque gelatin capsules. 2 staff, blinded to medication status, dispensed medication

Whalen 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessments were made by independent healthy controls through video tapes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Wigal 2003

Study characteristics	
Methods	Double-blind, 2-stage, cross-over, pharmacokinetic and pharmacodynamic trial with 4 interventions • IR-MPH (Ritalin) 10 mg • IR-or ER-MPH 40:60 (treatment C) • IR-or ER-MPH 30:70 (treatment D) • Placebo Phases: initial screening week, stage 1 cross-over of IR-MPH (Ritalin) vs placebo, stage 2 cross-over of treatment C and treatment D. 4 weeks, with each trial period lasting 1 week
Participants	Number of participants screened: not stated Number of participants included: 27 Number of participants followed up: 25 (21 boys, 4 girls) Number of withdrawals: 4 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 10 ± 1.4 years (range 7-12) IQ: not stated MPH-naive: not stated Ethnicity: white (88%), African American (8%), Asian (4%), Hispanic (0%), other (0%) Country: USA Setting: outpatient clinic (laboratory classroom and community) Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • 1 of 3 DSM-IV ADHD diagnostic criteria as specified in the DISC or the SNAP, or both • 7-12 years of age • In need of MPH treatment • Positive MPH response

Wigal 2003 *(Continued)*

- Prior successful treatment of ADHD symptoms with a MPH product without AEs
- MPH products restricted to IR-MPH twice daily, with the first daily dose required to be between 7.5 mg and 15 mg, and the second daily dose required to be between 5 mg and 15 mg, yielding a total daily dose of between 12.5 mg and 30 mg; or a ER-MPH product taken once daily, with the single daily dose required to be 20 mg
- Oral or written consent by both children and parents
- Normal BP, pulse rate and temperature
- Girls had to be premenarchal

Exclusion criteria

- Participation in another drug trial during the preceding 30 days
- Concurrent illness or condition with symptoms that could affect performance of any of the tests performed
- Family history of drug abuse
- Unable to follow instructions given in the trial
- Individuals who were severely depressed, psychotic, anxious, tense or agitated; or who had seizures or a family history of Tourette's syndrome, with primary diagnosis of ODD or CD
- Participants taking a medication in addition to MPH for ADHD
- Documented allergy or intolerance to MPH
- Individuals who were diagnosed with hyperthyroidism, were lactose-intolerant or had glaucoma
- Participants unable to comply with blood drawing procedures during initial screening
- Use of any of the following medications: amphetamines, pemoline, tricyclic antidepressants, MAOIs, SSRIs, neuroleptics, benzodiazepines or benzodiazepine derivatives, clonidine, anticonvulsant medications, cough/cold preparations containing stimulants or sedatives

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH and placebo in each of the 2 stages, 1 and 2, with each treatment period lasting 1 week.
	
	Stage 1
	
	• Treatment A
	  ◦ Participants were given 1 encapsulated tablet of IR-MPH (Ritalin) (10 mg) and 1 capsule of placebo after breakfast, and 1 encapsulated tablet of IR-MPH (Ritalin) (10 mg) after lunch for 7 days
	• Treatment B
	  ◦ Participants were given 2 placebo capsules after breakfast and 1 placebo capsule after lunch for 7 days
	
	Stage 2
	
	Half of the participants in each treatment group were randomly assigned to 20 mg/d dosage of MPH, the other half to 40 mg/d dosage
	
	• Treatment C
	  ◦ Participants were given a daily morning dose (after breakfast) of 2 20 mg capsules of the 40:60 prototype formulation or one 20 mg capsule of the 40:60 prototype formulation and 1 capsule of placebo; and a midday dose (after lunch) of 1 capsule of placebo for 7 days
	• Treatment D
	  ◦ Participants were given a daily morning dose (after breakfast) of 2 20 mg capsules of the 30:70 prototype formulation or one 20 mg capsule of the 30:70 prototype formulation and 1 capsule of placebo; and a midday dose (after lunch) of 1 capsule of placebo for 7 days
	  ◦ Blood samples (3 mL) were collected pre-dose and at 0.5, 1.5, 2, 3, 4.5, 6, 7.5 and 9 h after the morning dose on the last day (Saturday) of each treatment week
	
	Mean MPH dosage: 20 mg/d or 40 mg/d
	
	Administration schedule: once daily or twice daily
	
	Time points: mornings and after lunch

Wigal 2003 *(Continued)*

Duration of each medication condition: 1 week

Washout before trial initiation: not stated

Medication-free period between interventions: 1 day (Sundays)

Titration period: none

Treatment compliance: not stated

Outcomes

ADHD symptoms

- SKAMP (10-item) Scale: deportment and attention ratings performed every 1.5 h (0 to 9 h) at the end of each treatment week, by laboratory classroom teachers
- SKAMP (10-item) Scale: rated on weekdays by community classroom teachers
- CLAM (16-item): rated Monday, Wednesday and Friday by community classroom teachers and parents

General behaviour

- CLAM (16-item) Scale: ratings performed once every Monday, Wednesday and Friday of each treatment week by the regular community classroom teacher and the parents

Non-serious AEs

- Side Effects Rating form completed during all treatments by the children's regular community classroom teacher on Monday, Wednesday and Friday of each treatment week, daily by parents and each Saturday by the University of California at Irvine Child Developmental School (UCI-CDC) classroom teacher
- All AEs occurring during the trial were reviewed by the investigator to assess their relationship to drug treatment (unrelated, unlikely, possibly, probably, almost certainly)
- In addition, each sign or symptom reported was graded on a 3-point scale (mild, moderate or severe), and date and time of onset, time relationship to drug dosing, duration and outcome were noted
- Clinical laboratory tests were performed at the local laboratory at baseline and at the end of the trial, and included blood count with differential, biochemistry (Na (sodium), K (potassium), Ca (calcium), PO4 (phosphate), total protein, glucose, alkaline phosphatase, AST, ALT, total bilirubin, creatinine, albumin) and urinalysis (osmolality, pH (power of hydrogen) level, glucose, protein, white blood cells and casts)
- Vital signs, including BP and heart rate, were measured at each visit to the laboratory classroom
- Body weight: 36.9 ± 7.6 kg
- Height: 142 ± 8.4 cm

Notes

Sample calculation: not stated

Ethics approval: yes; trial protocol and participant's informed consent form were approved by the Institutional Review Board (Office of the Vice Chancellor for Research, University of California at Irvine)

Key conclusion of trial authors

- "Both MPH formulations, given once in the morning, were superior to placebo and comparable with Ritalin b.i.d. [twice/d] treatment on all primary efficacy measures."

Comments from review authors

- Prototype formulation used - this may not be bioequivalent to the marketed formulation
- Selective reporting of safety findings - omission of data obtained by AEs rating form. Pre-specified primary outcome measure for efficacy (of prototype formulations versus placebo) - regular community classroom teacher. CGI scores from Collegiate Learning Assessment (CLA) results presented only in Figure 4; no mean (SD) values provided in publication

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; positive MPH response was an inclusion criterion. Serious AEs were an exclusion criterion.

Wigal 2003 *(Continued)*

Any withdrawals due to AEs: no

Funding source: Celltech Americas Incorporated

Email correspondence with trial authors: July 2014. Emailed trial authors twice for supplemental information but have received no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Qualified participants were randomly assigned to a 2-stage, double-blind trial sequence consisting of 4 trial treatments, each lasting for a period of 1 week
Allocation concealment (selection bias)	Low risk	MPH (Ritalin) (10 mg) tablets were placed into capsule shells by Eurand Americas Incorporated. Resulting capsules were tested according to US Pharmacopeial Convention (USP) dissolution conditions for MPH tablets and showed a dissolution profile comparable with intact Ritalin tablets. All medications were supplied in white, opaque, size 3, hard gelatin capsule shells, and were packaged in blister cards to enhance compliance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Ritalin (10 mg) tablets were placed into capsule shells by Eurand Americas Incorporated. Resulting capsules were tested according to US Pharmacopeial Convention (USP) dissolution conditions for MPH tablets and showed a dissolution profile comparable with intact Ritalin tablets. All medications were supplied in white, opaque, size 3, hard gelatin capsule shells, and were packaged in blister cards to enhance compliance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): yes
Selective reporting (reporting bias)	Unclear risk	"Because the administration of the Side Effects Rating Form involved queries about specific adverse events, the frequency of adverse events reported in the parents' and teachers' Side Effect Rating Form was higher than that obtained from the reports elicited by general inquire (data not shown)"

Wigal 2004

Study characteristics

Methods	4-week, randomised, double-blind, placebo-controlled, ITT, parallel multicentre trial with 3 arms: • d-MPH • Dex,l-MPH • placebo
Participants	Number of participants screened: 174 Number of participants included: 132 (116 boys, 16 girls) Number of participants followed up: 119 (d-MPH 42, dex,l-MPH 40, placebo 37) Number of withdrawals: 13 (d-MPH 2, dex,l-MPH 6, placebo 5)

Wigal 2004 *(Continued)*

	Diagnosis of ADHD: DSM-IV (combined (64%), hyperactive-impulsive (1%), inattentive (35%)) Age: mean 9.8 years (range 6-17) IQ: not stated. No mental disability MPH-naive: 95 (72%) Ethnicity: white (78%), African American (14%), other (8%) Country: USA Setting: outpatient clinic Comorbidity: no Comedication: no Other sociodemographics: no significant differences in baseline demographics were noted between the 2 groups **Inclusion criteria** • Enrolled in elementary school • Within 30% of normal body weight • Anticipated as available for the entire length of the trial • Female participants were required to be pre-menarche **Exclusion criteria** • History or evidence of cardiovascular, renal, respiratory (other than asthma/allergy), endocrine or immune system disease • History of substance abuse • Hypersensitivity to dex,l-MPH or other stimulants • Treatment with any investigational drug within 30 days of screening • Any other significant CNS disorders such as mental disability, Tourette's or chronic tic disorder, psychosis, pervasive developmental disorder, eating disorders, OCD, impulse control disorder or sleep disorders requiring medication, major depressive disorder or generalised anxiety disorder • Treatment with antidepressants (tricyclic antidepressants, SSRIs and MAOIs), sedative/hypnotics (e.g. barbiturates, benzodiazepine), neuroleptic/antipsychotics, mood stabilisers; anticonvulsants, beta-blockers, α2-agonists, thyroid medications and long-term oral steroids
Interventions	Participants were randomly assigned to IR-MPH (dex-MPH, dex,l- MPH) or placebo No of participants randomised to each group: d-MPH 44, dex,l-MPH 46, placebo 42 Mean MPH dosage: d-MPH 18.25 mg/d, dex, l-MPH 32.14 mg/d Administration schedule: twice daily in the morning (7:00 am-8:00 am) and at noon (11:30 am-2:30 pm) Duration of intervention: 4 weeks Titration period: maximum 3 weeks initiated after randomisation, included in the 4 weeks of intervention Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SNAP ADHD-RS - Teacher Version: teacher-rated, at baseline and twice weekly for 4 weeks, in the afternoon • SNAP ADHD-RS - Parent Version: parent-rated, at baseline and daily on the weekend for 4 weeks, at 3:00 pm and 6:00 pm

Wigal 2004 *(Continued)*

Non-serious AEs

- Occurrence and severity, monitored by investigator, at weekly visits
- Laboratory tests, physical examination findings and vital signs

Notes

Sample calculation: yes

Ethics approval: yes; approved by the institutional review board at each centre

Comments from trial authors

- Post hoc contrasts of small differences between d-MPH and dex,l-MPH conditions were not statistically significant in this between-participant design
- 3 participants who did not meet the criteria set for a placebo response during the lead-in period were inadvertently entered into the double-blind phase (2 randomly assigned to dex,l-MPH, 1 to placebo), which was a violation of the protocol

Key conclusions of trial authors

- For treatment of ADHD, an average titrated dose of 18.25 mg/d of d-MPH is as efficacious and safe as an average titrated dose of 32.14 mg/d of dex,l-MPH
- Both active treatments have large effect sizes. Thus, d-MPH and dex,l-MPH appear to provide similar efficacy

Comment from review authors

- We have not used these data, as reported data could not be used in our meta-analyses

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, see exclusion criteria

Any withdrawals due to AEs: yes. “parental consent was withdrawn for one patient due to deterioration of behavior on placebo”, and “AEs (two patients each in the d,l-MPH and placebo groups)”

Funding source: Celgene Corporation

Email correspondence with trial authors: January 2014. Not possible to obtain data from trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drug (d-MPH and dex,l-MPH) and placebo were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Sample size calculations were based on a clinically meaningful effect size of 0.75 in the change in score over 4 weeks on the teacher-rated SNAP between d-MPH and placebo groups. Efficacy parameters were performed on the ITT sample, which included participants who received medication, had a baseline efficacy evaluation and had ≥ 1 post-baseline efficacy evaluation

Wigal 2004 *(Continued)*

		Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Unclear risk	No protocol published

Wigal 2011

Study characteristics	

Methods	Double-blind, randomised, cross-over, analogue classroom trial with 2 interventions:
	• OROS-MPH
	• placebo
	Phases
	• Screening/washout phase: up to 28 days
	• Titration: up to 6 weeks
	• Double-blind assessment period, with the following subperiods
	  ○ Open-label OROS-MPH
	  ○ School day 1: OROS-MPH or placebo
	  ○ Open-label OROS-MPH: ≥ 7 days
	  ○ School day 2: OROS-MPH or placebo

Participants	Number of participants screened: not stated Number of participants included: 78 (55 boys, 23 girls) Number of participants followed up: 71 Number of withdrawals after randomisation: 0 Diagnosis of ADHD: DSM-IV-TR (81% combined, 0% hyperactive-impulsive, 19% inattentive) Age: mean 10.1 years (range 9-12 years) IQ: > 80 MPH-naive: not stated Ethnicity: white (58%), African American (28%), other (14%) Country: USA Setting: outpatient clinic, laboratory classroom Comorbidity: anxiety (0%), depressive disorders (0%), learning disability (32%) Comedication: not stated Additional sociodemographics: none **Inclusion criteria** • 9-12 years of age • DSM-IV-TR diagnosis of ADHD • Baseline score on ADHD-RS-IV, in the ≥ 90th percentile relative to the general population of children of the same age and sex

Wigal 2011 *(Continued)*

- Participants receiving medication for ADHD at the time of trial enrolment exhibited an inadequate response to their then-current stimulant dose and completed a washout equivalent to 5 half-lives of the given medication before completing baseline assessments
- Attendance at regular school
- Ability to read and understand English
- To be eligible for the double-blind, randomised assessment period, participants had to reach their individualised dose of OROS-MPH, defined as
  - score on the ADHD-RS, 4th Editiion (as scored by parent or guardian): ≤ 75th percentile for age and sex
  - score on the ADHD-RS, 4th Edition (as scored by parent or guardian): between 75th and 85th percentiles for age and sex after (1) dose decrease for tolerability (1 dose decrease by 18 mg to a minimum of 18 mg/d was allowed) or (2) having reached dosage of 54 mg/d

Exclusion criteria

- History or current diagnosis of epilepsy, severe anxiety or conduct or psychotic disorders
- Pervasive developmental, eating, OCD, sleep, major depressive, bipolar or chronic tic disorder, substance use disorder
- Personal or family history of Tourette's syndrome
- Known cardiac abnormalities: clinically significant abnormalities in ECG results; family history of sudden death or ventricular arrhythmia
- Inability to take or tolerate OROS-MPH
- Allergies to MPH or other ingredients of OROS-MPH
- Known gastrointestinal narrowing or significant gastrointestinal problems
- Glaucoma
- Use of medication with CNS effects (excluding bronchodilators)
- Clinically significant laboratory and ECG abnormalities and BP in ≥ 95th percentile for age, sex and height
- Trial participants were prohibited from using any caffeine-containing products on trial visit days or laboratory assessment days, and were limited to 1 (12-ounce) caffeinated beverage/d during trial participation
- Estimated full-scale IQ 80, as measured by WASI
- Scores of ≥ 2 SD less than mean scores for age on the Gray Oral Reading Test (GORT), the Comprehensive Test of Phonological Processing (CTOPP), or the Wechsler Individual Achievement Test - Second Edition (WIAT-II AB13)
- Weight < 3rd percentile for age
- History of hospitalisation for treatment of a mood, anxiety or psychotic disorder
- History of failed response to MPH

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of OROS-MPH and placebo Mean OROS-MPH daily dosage: 40.5 mg Administration schedule: once daily (morning) Average duration of OROS-MPH treatment: 40 days; only a single blinded day Duration of placebo intervention: 1 day Washout before trial initiation: up to 28 days Medication-free period between interventions: no Titration period: before randomisation, up to 6 weeks Treatment compliance: not stated
Outcomes	**ADHD symptoms**

Wigal 2011 *(Continued)*

- SKAMP, observer-rated, 4 h post dose (on the 2 laboratory days)

Serious AEs

- Serious adverse effects assessed on the 2 laboratory days and during the open-label period

Non-serious AEs

- Adverse effects, vital signs and body weight, assessed on the 2 laboratory days

Notes

Sample calculation: yes

Ethics approval: yes

Key conclusions of trial authors

- Wigal 2011: "OROS-MPH dose to reduce core symptoms of ADHD to within the normal range also improved performance on a variety of academic tasks in school-aged children compared with placebo. Reported adverse effects were consistent with those of prior studies"
- Armstrong 2012 (Wigal 2011): "robust treatment effect occurred with OROS-MPH; onset was at 1 h post treatment and persisted for ≥ 12.5 h after dosing"

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; a history of failed response to MPH was an exclusion criterion. Only children demonstrating the required decrease in ADHD symptoms with OROS-MPH within the labelled dosing range were included in the randomised phase of the study. Children who may have required a dose > 54 mg to achieve full therapeutic effect may also have been excluded.

Any withdrawals due to AEs: no

Funding source: supported by Ortho-McNeil-Janssen Scientific Affairs, LLC. Phase IV trial

Email correspondence with trial authors: June 2013-June 2014. We obtained supplemental efficacy data (SKAMP) and safety data. Awaiting data through the Yale Open Data Access Project

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Wigal 2011: "computer-generated randomisation schedule"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Wigal 2011: "blinding of investigators and participants maintained throughout the trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Wigal 2011: "blinding of investigators and participants maintained throughout the trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on incomplete outcome data Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All outcomes reported according to protocol

Wigal 2013

Study characteristics	
Methods	4- to 6-week, open-label treatment (dose optimisation), cross-over, 2-week double-blind trial with 2 interventions: • MPH (NWP06 - liquid formulation of ER-MPH) • placebo Phases: 2
Participants	Number of participants screened: 45 (32 boys, 12 girls) entered the open-label phase and were randomised at baseline visit Number of participants included: 39 entered the double-blind cross-over trial Number of participants followed up: 39 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (combined (70.5%), hyperactive-impulsive (2.3%), inattentive (27.3%)) Age: mean 8.8 years (range 6-12) IQ: not stated MPH-naive: 0 (0%) Ethnicity: white 35 (79.5%), black/African American 4 (9.1%), Asian 3 (6.8%), other 2 (4.5%) Country: USA Setting: outpatient clinic Comorbidity: elimination disorder (4; 9.1%), ODD (8; 18.2%), specific phobias (2; 4.5%) Comedication: no Other sociodemographics: none **Inclusion criteria** • ADHD diagnosis by psychiatrist, psychologist, developmental paediatrician or paediatrician • Pharmacological treatment for ADHD and has experienced suboptimal efficacy or a safety or tolerability issue with current regimen, or has been in need of a long-acting liquid formulation • CGI Scale score > 3 • ADHD-RS score (Hyperactive-Impulsive or Inattentive subscale) > 90th percentile for age and sex **Exclusion criteria** • Comorbidity (DSM-IV Axis I), with the exceptions of specific phobia, motor skills disorders, ODD, sleep disorders, elimination disorders, adjustment disorders, learning disorders or communication disorders • IQ < 80 • Chronic disease: seizure disorder, thyroid disease, Tourette's disorder or family history of Tourette's disorder or tics, serious cardiac conditions, cardiomyopathy, serious arrhythmias, structural cardiac disorders, glaucoma or severe hypertension • Any investigational medication 15 days before screening • Atomeoxetine inhibitor 30 days before screening
Interventions	Participants were randomly assigned to different sequences of MPH and placebo

Wigal 2013 *(Continued)*

	Mean MPH dosage: 32.8 mg/d Administration schedule: 4 times/d Duration of each medication condition: 1 week Washout before trial initiation: yes (1 day for stimulants) Medication-free period between interventions: no Titration period: 3 weeks before randomisation Treatment compliance: 2 withdrawals of assent/consent, 2 AEs, 1 lack of efficacy, 1 LTFU, all during the open-label phase
Outcomes	**ADHD symptoms** • SKAKMP, ADHD-RS (open-label phase) **Non-serious AEs** 42 participants (93.3%) experienced a TEAE. 3 (6.7%) participants experienced severe adverse effects (affect lability, aggression and initial insomnia), and 2 (4.4%) participants had to discontinue medication (affect lability and aggression) • Open-label phase: participants experienced decreased appetite (55.6%), abdominal pain upper (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%) and headache (17.8%). Other AEs reported in > 5% of participants included vomiting, diarrhoea, logorrhoea, aggression, dizziness, irritability, fatigue, upper respiratory tract infection, cough and flushing • Double-blind phase: 11 (24.4%) participants had an AE while receiving NWP06, and 5 (11.1%) participants had an AE while receiving placebo
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • "This study of NWP06 allowed inclusion of patients who were either treatment naive or had previously been treated with stimulants (...)"; "Subjects were required to have been in need of pharmacological treatment for ADHD (...)" • "Our population more closely reflects a real-world population and provides a more rigorous test of the study drug" **Key conclusion of trial authors** • "NWP06 resulted in significant improvement in the Swanson, Kotkin, Agler, M-Flynn and Pelham-combined score at 4 h post dose as compared with placebo among completers. This study shows that NWP06 significantly improved ADHD symptoms in school-aged children and was well tolerated" **Comments from review authors** • Laboratory school environment and lack of the ADHD-RS • Race/ethnicity does not reflect a real-world population Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, there was an open-label titration phase before randomisation, during which 2 participants discontinued due to AEs and 1 due to lack of efficacy. Also participants had to be in treatment with suboptimal efficacy (no inclusion of placebo responders). Any withdrawals due to AEs: no Funding source: trial received funds from NextWave Pharmaceutics (Belden and Berry are with NextWave)

Wigal 2013 *(Continued)*

	Email correspondence with trial authors: emailed trial authors to request additional information but have not received a response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Results from open-label phase
Blinding of outcome assessment (detection bias) All outcomes	High risk	Results from open-label phase
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants in the double blind phase followed up Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	ADHD-RS not reported (used only in the open phase)

Wigal 2014

Study characteristics

Methods	Cross-over trial with 2 interventions: • MPH-MLR • placebo Phases: 4 • Screening/washout period (< 4 weeks) • Open-label dose-optimisation period • Randomised, double-blind, placebo-controlled, cross-over design • 30-day safety follow-up period
Participants	Number of participants screened: 32 Number of participants included: 26 (in open-label phase; 12 boys, 10 girls) Number of participants followed up: 20 Number of withdrawals: 6 Diagnosis of ADHD: DSM-IV-TR (combined (n = 11), hyperactive-impulsive (n = 3), inattentive (n = 12)) Age: mean 8.7 years (range 6-12)

Wigal 2014 *(Continued)*

	IQ: mean not stated (range 86-133) MPH-naive: none Ethnicity: white (82%), black (9%), Asian (5%), Hispanic or Latino (23%), other (5%) Country: USA Setting: outpatient clinic, laboratory classroom setting Comorbidity: 11; generalised anxiety disorder, enuresis, ODD, chronic motor or vocal tic disorder, transient tic disorder Comedication: no Other sociodemographics: none **Inclusion criteria** • Children (male or female) 6-12 years of age • Any of the 3 subtypes of ADHD as defined by DSM-IV-TR, ADHD-RS-IV total or subscale score > 90th percentile relative to the general population of children by age and sex • Naive to treatment for ADHD or inadequately managed on current treatment regimen • Negative illicit drug and alcohol test results at screening and at each visit to the research site **Exclusion criteria** • IQ > 80 • Any severe psychiatric or significant comorbid condition • Use of a MAOI or any psychotropic medication with CNS effects < 14 days of screening, or any experimental drug or medical device > 30 days of screening • Clinically significant ECG, or any laboratory abnormality • Any participant unable or unwilling to follow directions and complete trial assessments or take oral capsules
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH (15 mg, 20 mg, 30 mg or 40 mg) and placebo Mean MPH dosage: 32 mg Administration schedule: once/d Time points: in the morning Duration of each medication condition: 1 week Washout before trial initiation: 2 days Medication-free period between interventions: not stated Titration period: yes; 2-4 weeks before randomisation Treatment compliance: yes; verified at scheduled trial visits by trial personnel who examined documentation of drug dispensed, drug consumed and remaining drug, and recorded the information on the drug reconciliation form Compliance was calculated to be > 82% throughout the trial
Outcomes	**ADHD symptoms** • SKAMP: total scores, trained observers, post-dose over time points 1.0, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 h • SKAMP: attention and deportment scores averaged over all post-dose time points

Wigal 2014 *(Continued)*

- ADHD-RS-IV: clinician-rated, 3.0 h post-dose each laboratory day

Non-serious AEs

- Safety and tolerability assessments
- CSHQ

There is not enough data on the CSHQ available for us to include it in the analysis.

Notes

Sample calculation: yes

Ethics approval: yes

Comment from trial authors

- Limitations of this study: study was slightly underpowered and produced a study population that may not be reflective of the general population of children and adolescents with ADHD

Key conclusions of trial authors

- "In this study, methylphenidate-MLR administered to children 6 to 12 years of age demonstrated a significant decrease in scores on the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale compared with placebo."
- "Onset of action in this population is 1 hour, and duration of efficacy is sustained to 12 hours post dose."
- "Future studies that include measurement of efficacy earlier than hour 1.0 and extend beyond hour 12.0 would add clarity to the precise onset and duration of clinical efficacy."

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; 2 withdrew during the open-label phase as the result of lack of efficacy

Any withdrawals due to AEs: yes (n = 1)

Funding source: Rhodes Pharmaceuticals L.P.

Email correspondence with trial authors: April 2015. Obtained supplemental information from trial authors.

Trial authors were contacted regarding CSHQ data in November 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation was determined by using a table of random numbers. Randomisation tables were provided to the randomisation monitor, who created unblinding envelopes and packaged the drug with blinded labels.
Allocation concealment (selection bias)	High risk	One participant received placebo at 2 periods - the method was not efficacious
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All sponsor representatives, investigators, participants and independent raters remained blinded until after data were locked
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Yes; this has been done

Wigal 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT were used Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo-responders): no; no exclusion of MPH non-responders after randomisation
Selective reporting (reporting bias)	Low risk	No indication of selective reporting

Wigal 2015

Study characteristics	
Methods	A 1-week parallel trial with 5 arms: • MPH-MLR 10 mg • MPH-MLR 15 mg • MPH-MLR 20 mg • MPH-MLR 40 mg • Placebo Phases: 4 (screening, double-blind, open-label, and safety follow-up)
Participants	Number of participants screened: 280 Number of participants included: 230 (154 (67%) boys, 76 (33%) girls) Number of participants followed up: 221 Number of withdrawals: 9 Diagnosis of ADHD: DSM-IV-TR (140 combined, 6 hyperactive-impulsive, 75 inattentive, 9 not reported) Age: mean 10.8 years (SD 3.0, range 6-18) IQ: IQ < 80 was an exclusion criterion MPH-naive: 146 of 221 (66%); "Two-thirds of the sample were stimulant naïve, and one-third of the sample (75/221) had a medication washout" Ethnicity: race was measured: white (n = 158, 68.7%), black (n = 53, 23%), Asian (n = 3, 1.3%), other (n = 16, 7%) Country: USA Setting: outpatient Comorbidity: many comorbidities were exclusion criteria (see exclusion criteria). Most common comorbidities were ODD (n = 22) and enuresis (n = 14) Comedication: CNS medication was an exclusion criterion, many illnesses were exclusion criteria, no further information Sociodemographics: none **Inclusion criteria** • Age 6-18 years

Wigal 2015 *(Continued)*

- ADHD diagnosis with ADHD-RS-IV scores ≥ 90th percentile relative to the general population of children by age and sex at screening or baseline (diagnosis of all subtypes (except "not otherwise specified") as defined in the DSM-IV-TR
- In need of treatment for ADHD and able to have 2-day washout from previous medication
- Patients had to require pharmacological treatment for ADHD
- Female participants of child-bearing potential not pregnant and practice birth control
- Participant and parent/guardian willing to comply with protocol
- Signed consent and assent

Exclusion criteria

- IQ < 80 WASI
- Current primary psychiatric diagnosis of other listed disorders - severe anxiety disorder, CD, psychotic disorder, pervasive developmental disorder, eating disorder, OCD, major depressive disorder, bipolar disorder, substance use disorder, chronic tic disorder, or a personal or family history of Tourette's syndrome as defined by the DSM-IV-TR criteria and supported by the K-SADS-PL
- Chronic medical illnesses: seizure, hypertension, thyroid disease, cardiac, family history of sudden death, glaucoma
- Use of MAOIs or psychotropic CNS medications having effect exceeding 14 days from screening
- Planned use of prohibited drugs
- Is pregnant or breast-feeding
- Significant ECG or laboratory abnormalities
- Experimental drug or medical device within 30 days prior to screening
- Hypersensitivity to MPH
- Inability or unwillingness to comply with protocol
- Well controlled on current ADHD treatment
- Inability to take oral capsules

Interventions

4 phases

- Screening (≤ 28 days) and washout (≥ 48 h)
- Double-blind fixed-dose phase (1 week)
- Open-label dose-optimisation phase (11 weeks)
- Follow-up call after 30 days/21 month open-label compassionate use extension

Participants were randomly assigned to: 5 different groups, 4 receiving MPH-MLR (biphentin MPH extended release capsules) of either 10 mg, 15 mg, 20 mg or 40 mg, or placebo capsules

Number randomised to each group: MPH-MLR 10 mg: 49, MPH-MLR 15 mg: 44, MPH-MLR 20 mg: 45, MPH-MLR 40 mg: 45, placebo: 47

Patients weighing < 25 kg were not assigned to receive the 40 mg dose

Mean medication dosage: forced-dose: 10 mg, 15 mg, 20 mg or 40 mg

Administration schedule: once daily at 10.00 am

Duration (of (each) medication): 1 week

Washout before trial initiation: minimum 48 h

Treatment compliance: no information

Outcomes

ADHD symptoms

- ADHD-RS-IV. We do not have enough data to include this outcome in our analysis.

Serious AEs

- Spontaneous reporting

Wigal 2015 *(Continued)*

Non-serious AEs

- Spontaneous reporting at each visit
- Vital signs
- Physical examination
- ECG
- Clinical laboratory evaluations
- CSHQ. There is not enough data on the CSHQ available for us to include it in the analysis.

Notes

Sample calculation: yes; "It was estimated that a total sample size of 225 would have 80 % power to detect a mean difference […]"

Ethics approval: yes; "The study protocol, amendments, and informed consent form were reviewed and approved by an Institutional Review Board for each study site."

Comments from trial authors

- "fixed dosing used during the double-blind phase might have resulted in study patients who were over or under-treated with MPH-MLR"
- "The double-blind period was short and, overall, the study duration was only 12 weeks, thus limiting a clear understanding of long-term efficacy"
- "The brief washout period (2 days), while equaling or exceeding at least 5 half-lives for ADHD medications patients may have been using prior to study entry, may have resulted in inflated baseline scores for some patients[…]"

Key conclusion of trial authors

- "Methylphenidate (MPH) multilayer bead extended release (ER) capsules (MPH-MLR; Aptensio XRTM) administered once daily demonstrated significant dose-related improvements in Attention-Deficit/Hyperactivity Disorder Rating Scale, 4th Edition(ADHD-RS-IV) scores compared with placebo in children and adolescents with ADHD"
- "The safety profile of MPH-MLR is consistent with other ER MPH formulations"
- "The results of this phase III study indicate that MPH-MLR, with a novel release profile, offers a valuable option for the treatment of ADHD in children and adolescents"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes, known hypersensitivity to MPH was an exclusion criteria

Any withdrawals due to AEs: yes, 3

Funding source: Rhodes Pharmaceuticals […]. Medical writing assistance was provided by Linda Wagner, PharmD, from Excel Scientific Solutions and funded by Rhodes Pharmaceuticals LP

Email correspondence with trial authors: September and November 2021. We contacted the trial authors for information regarding risk of bias and CSHQ data through personal email in September and November 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised (1:1:1:1:1) to receive MPH-MLR 10 mg, 15, 20, or 40 mg or placebo following a computer-generated randomisation schedule with patients assigned the next random number arranged in an ABCDE block design with each letter representing one of the 5 treatment groups. There was no site stratification in randomization. Patients weighing <25 kg were not assigned to receive the 40 mg dose"
Allocation concealment (selection bias)	Unclear risk	Not stated

Wigal 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All trial treatments (MPH-MLR 10, 15, 20, 30, 40, 50, 60 mg, placebo) were given orally once daily in the morning, no later than 10 a.m. and were packaged in bottles of ten capsules for a 1-week dispensing interval and bottles of 30 for 4- and 8-week dispensing intervals. Lot numbers used during the double-blind phase were A07983-2. 002L01 (10 mg), A07983-002L02 (15 mg), A07983-3. 002L03 (20 mg), A07983-002L04 (40 mg), and A07983-001L02 (placebo)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The model had class terms for treatment (5 levels), site (sites with less than ten patients were combined into a pseudo site), and a covariate term for baseline ADHD-RS-IV total score. The same model was applied to the ITT population as a sensitivity analysis. Subjects not completing the double-blind phase had the decrease in total score set to zero for the sensitivity analysis." Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	High risk	"Incidence of adverse findings using various measures of safety, tolerability, and quality of life assessments following administration of once daily Biphentin" (NCT01239030) Quality of life is mentioned as an outcome in the protocol but not in the full report. It is described that the C-SSRS is assessed at screening and at the end of the double-blind phase, but the results are not included.

Wigal 2017

Study characteristics	
Methods	A 1-week parallel-trial with 2 arms: • ER-MPH chewable tablets • placebo Phases: 3 (open-label phase (6 weeks), double blind-phase (1 week), follow-up 1-2 weeks after)
Participants	Number of participants screened: 90 entered the open-label phase Number of participants included: 86 randomised in the double-blind trial Number of participants followed up: 85 (ITT population, 53 (62.4%) boys, 32 (37.6%) girls) Number of withdrawals: 1 during double-blind (lost to follow-up) Diagnosis of ADHD: confirmed at screening (23 (27.1%) inattentive, 0 hyperactive/impulsive, 62 (72.9%) combined) Age: 9.6 years (SD 1.69, range 6-12) IQ: not measured MPH-naive: not stated Ethnicity: Hispanic/Latino (n = 13, 15.3%), non-Hispanic/-Latino (n = 72, 84.7%) Country: USA

Wigal 2017 *(Continued)*

	Setting: multi-site, outpatient Comorbidity: not allowed Comedication: not allowed Additional sociodemographics: white (n = 49, 57.6%), black/African American (n = 30, 35.3%), Asian (n = 1, 1.2%), other (n = 5, 5.9%) **Inclusion criteria** • Children aged 6-12 years with ADHD who require pharmacologic treatment for this condition • Investigator administered CGI-S score of at least 3 (mildly ill) • Investigator administered ADHD-RS (ADHD-RS-IV) Home Version score in the 90th percentile or greater for gender and age on the hyperactive–impulsive subscale, inattentive subscale, and/or total score at screening or baseline **Exclusion criteria** • Current primary psychiatric diagnosis of severe anxiety disorder, CD, pervasive developmental disorder, eating disorder, OCD, major depressive disorder, bipolar disorder, or other psychiatric disorder, substance abuse disorder, or a personal or family history of Tourette's syndrome • Clinically significant or severe medical illness or condition, including seizure disorder, cardiac disorders or conditions (including severe hypertension), untreated thyroid disease, or a history of HIV or hepatitis B or C infections • Clinically significant abnormal laboratory results or a positive test for illicit drug use at screening • History of hypersensitivity or lack of efficacy to MPH • Other serious illnesses or conditions that would put the patient at particular risk for safety events or would interfere with treatment/assessment of ADHD • Psychotropic agents were prohibited. Sedative hypnotics were prohibited within 24 h before screening, except sedative hypnotics that had been prescribed as sleep aids (at bedtime only) for at least 30 days before the baseline visit. (Promethazine (1 ER-MPH chewable tablet-treated patient, for viral infection) was the only sedative hypnotic reported in this trial.) • Pharmacologic treatments for ADHD, including non-investigational stimulant medications for the control of ADHD, were allowed until 24 h before the baseline visit for the open-label, dose-optimisation period
Interventions	Participants were randomly assigned to 2 different groups, either placebo or ER-MPH chewable tablet at optimised dose (between 20-60 mg/d) Number randomised to each group: 44 placebo, 42 ER-MPH chewable tablet Mean medication dosage: not stated Administration schedule: daily Duration (of (each) medication): 7 weeks of MPH for MPH group, 6 weeks MPH + 1 week placebo for placebo group Washout before trial initiation: a minimum of 24-h before open-label phase. No information on washout period before double-blind trial initiation Titration period: 6 weeks before double-blind week. Starting at a dose of 20 mg, participants could either be increased or decreased by 10-20 mg/d once a week to a maximum of 60 mg/d and a minimum of 20 mg/d, depending on a clinical judgement by the investigators Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP Rating Scale

Wigal 2017 *(Continued)*

Serious AEs

- C-SSRS
- Spontaneous reporting

Non-serious AEs

- Vital sign measurements
- AE queries

Notes

Sample calculation: no

Ethics approval: yes; “The protocol, consent and assent forms, and the investigator’s brochure received institutional review board approval before initiation of the study”

Comments from trial authors

- "The exclusion of participants with significant co-occurring psychiatric or medical illness may limit the generalisability of these findings to a wider patient population."
- "Although comparable bioavailability has been demonstrated for 40 mg MPH ERCT [ER-MPH chewable tablet] and 40 mg IR MPH in a chewable tablet formulation given as 2 20 mg doses 6 h apart, no comparative data on the pharmacokinetics of the 20 and 60 mg MPH ERCT [ER-MPH chewable tablet] doses are available."
- "[…] no data were collected for analysis of patient socioeconomic status or intelligence, so effects of those factors could not be assessed in the current study"
- "[…] the study did not include an active comparator. Efficacy for MPH ERCT [ER-MPH chewable tablet] was demonstrated versus placebo, but direct comparison with other effective ADHD medications would require additional study"

Key conclusion of trial authors

- "Safety and tolerability findings from this study are consistent with those of other MPH ER formulations, including oral tablets and capsules, transdermal patch, and oral suspension."
- “The potential availability of a safe and effective chewable MPH ER tablet would provide a new valuable formulation option, addressing an unmet need for patients with ADHD who dislike the other available formulations, cannot swallow tablets or capsules, or would prefer the convenience of a chewable tablet.”

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH: yes

Any withdrawals due to AEs: not stated for double-blind period (1 during open-label phase)

Funding: this research was sponsored by NextWave Pharmaceuticals, a wholly owned subsidiary of Pfizer, Inc

Email correspondence with trial authors: September and November 2021. We contacted the trial authors for information regarding risk of bias through personal email in September and November 2021, but no answer was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted according to a fixed schedule using a permuted block design stratified by clinical site.
Allocation concealment (selection bias)	Low risk	The randomisation code was maintained centrally by the clinical supply group, and the trial team and investigator site personnel were blinded throughout the trial.

Wigal 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mention of double-blind, method not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators who recorded the AEs did not conduct the efficacy evaluations, and the classroom raters collecting efficacy data had no duties outside the classroom and were not aware of AEs collected by the investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analyses were based on the ITT population, which included all participants who received at least 1 dose of the trial drug and had at least 1 post-baseline assessment of the primary efficacy variable. Safety assessments were based on the enrolled safety population Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	All protocol outcomes are reported

Wilens 2006b

Study characteristics	
Methods	2-week, randomised, double-blind, 15-centre, parallel trial with 2 arms: • OROS-MPH • placebo Phases: preceded by a 4-week, open-label, dose-titration phase, and followed by an 8-week, open-label, follow-up phase
Participants	Number of participants screened: 220 in the 4-week dose-titration phase Number of participants included: 177 (142 boys, 35 girls) Number of withdrawals: 44. MPH 16, placebo 28 Number of participants followed up: 171; number completing follow-up: 135 Diagnosis of ADHD: DSM-IV (subtype not stated) Age: mean 14.6 years (range 13-18) IQ: not stated ADHD treatment-naive: 24 Ethnicity: white (75.1%), African American (13.6%), other (11.3%) Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: the 2 groups were similar demographically, but the placebo group had a greater ratio of boys (P value < 0.04)

Wilens 2006b *(Continued)*

	Inclusion criteria • Diagnosis of ADHD, as defined by DSM-IV • CGAS rating of 41-70 at baseline (screening phase) • Between 13 and 18 years of age **Exclusion criteria** • Participants who are known to not respond to MPH • Adverse experiences from MPH or hypersensitivity to Concerta or its components • Marked anxiety, tension or agitation • Psychiatric comorbidity requiring additional or different medication • Glaucoma, ongoing seizure disorder, psychotic disorder, Tourette's disorder or family history of Tourette's disorder, bipolar disorder, an eating disorder • Treatment with theophylline, coumarin, anticonvulsants • Severe gastrointestinal narrowing • SBP or DBP at ≥ 95th percentile for age, sex and height at screening
Interventions	Participants were randomly assigned to OROS-MPH or placebo Number of participants randomised to each group: MPH 87, placebo 90 Mean MPH dosage: 0.84 mg/kg Administration schedule: once daily Duration of intervention: 2 weeks Titration period: 4 weeks initiated before randomisation. All participants initiated therapy at 18 mg/d, and clinical response was measured after 1 week. If response to treatment was inadequate, as per the a priori trial definition, the dose was titrated upward (in 18-mg increments) at 1-week intervals for up to 4 weeks, with maximum dose of 72 mg/d Treatment compliance: not stated; 8-week, open-label follow-up on individualised dosage
Outcomes	**ADHD symptoms** • ADHD-RS, clinician- and parent-rated: completed at baseline and weekly during double-blind phase **Serious AEs** • Reported in only 1 participant during the open-label dose-titration phase of the trial. While being treated with OROS-MPH 18 mg/d, a 16-year-old female participant with a history of depression and suicidal ideation threatened suicide on the **3**rd day of medication use after an argument with her mother. Decision was made to discontinue trial medication, and symptoms resolved • No serious AEs were reported during the double-blind phase **Non-serious AEs** • Heart rate and BP, recorded by a clinician weekly throughout the whole trial • ECG at screening and at end of double-blind phase of the trial • Spontaneous reports to the investigator of AEs recorded at weekly visits • Safety assessments made at monthly visit and every 2 weeks between monthly visits during follow-up • Height and weight assessed at baseline and at weeks 4 and 8 in the follow-up trial No participants experienced clinically important effects on ECG indexes, heart rate or BP during the trial
Notes	Sample calculation: yes

Wilens 2006b *(Continued)*

Ethics approval: yes; trial was approved by the institutional review boards for all participating centres before the start of the trial

Comments from trial authors

- "Exclusion criteria were significant and possibly limited the generalisability of results."
- "Participants may have had improved ADHD symptoms or psychosocial carry-over effects as a consequence of participation in the study, medication titration and regular meeting with study personnel."
- "Our study was conducted partially during the summer, and this may have resulted in less stress on adolescents and overall improvement in both study groups. More sensitive measures of attention may be needed for adolescents with ADHD than for children."
- "Participants were titrated to their individualised dosage before the double-blind phase of the study. This may have biased the results toward a positive response in the double-blind phase."
- "The short duration of the double-blind phase may have decreased the likelihood of detecting potential rare AEs." Rates of AEs reported for OROS-MPH have been underestimated because participants entering this study phase were already stabilised on an affective tolerated dosage of medication.

Key conclusions of trial authors

- In adolescents, once-daily OROS-MPH significantly reduced ADHD symptoms and was well tolerated at dosages up to 72 mg/d
- Adolescents required, on average, a higher absolute dose but a lower weight-adjusted dose (mg/kg) of OROS-MPH than was previously reported in children
- The incidence of AEs was not related to dose

Inclusion of MPH responders only/exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; criteria of response, defined as ≥ 30% improvement from baseline on the investigator-scored ADHD-RS. Participants who successfully completed the open-label, dose-titration phase were assigned a randomisation number

Any withdrawals due to AEs: yes; 1 in the placebo group

Funding source: McNeil Consumer and Specialty Pharmaceuticals

Email correspondence with trial authors: December 2013 and Janurary 2014. Not able to make contact with trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but method was not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators were supplied with packages containing medication for each participant, as identified by randomisation number. Therefore, investigators and participants were blinded to whether a participant was receiving active medication or placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were supplied with packages containing medication for each participant, as identified by randomisation number. Therefore, investigators and participants were blinded to whether a participant was receiving active medication or placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	Non-responders not included. LOCF technique was used for all assessments in the double-blind phase. Of 182 (83%) participants who successfully achieved the criteria for improvement at the dose-titration phase, only 177 were ran-

Wilens 2006b *(Continued)*

		domly assigned to the double-blind phase, because 5 reached the criteria after the double-blind phase was closed. Of 177 randomly assigned participants, 1 did not enter the double-blind phase, and efficacy data were not collected for another participant. Therefore, 175 participants were included in the efficacy analysis of the double-blind phase, but 177 were included in the dosage and safety analysis. Selection bias: yes, participants were excluded due to lack of efficacy during the double blind phase
Selective reporting (reporting bias)	Low risk	No indication of selective reporting, outcomes according to protocol

Wilens 2008

Study characteristics	
Methods	Open-label, 5-week, dose-optimisation period. This dose was maintained during the subsequent 3 weeks of the trial, except for 1 d/week of 3-way cross-over assessment. Randomised, double-blind, 8-centre, 3-way, 3-week, cross-over trial with 3 interventions: • MPH transdermal patch (4 h) • MPH transdermal patch (6 h) • placebo
Participants	Number of participants screened: 148 Number of participants included: 128 in open-label, dose-titration; 117 entered the blinded, randomised trial Number followed up: 127 for safety and 117 for efficacy Number of withdrawals: 2 (both withdrew from the analogue classroom phase but were included in the ITT efficacy analysis) **Characteristics of the 127 followed up for safety** Sex: 84 boys, 42 girls Diagnosis of ADHD: DSM-IV (combined or hyperactive-impulsive (92.1%) inattentive (not stated)) Age: mean 8.8 years (SD 1.84; range 6-12) IQ: > 80 MPH-naive: not stated Ethnicity: white (63.2%), African American (15.4%), Asian (not stated) Country: USA Comorbidity: not allowed Comedication: not stated Other sociodemographics: none **Characteristics of the 117 followed up for efficacy** Sex: 75 boys, 42 girls

Wilens 2008 *(Continued)*

	Diagnosis of ADHD: DSM-IV (type not stated) Age: mean 8.8 years (range 6- 12) IQ: > 80 MPH-naive: not stated Ethnicity: white (63.2%), African American (15.4%), Asian (0%), other (21.4%) Country: USA Setting: outpatient clinic (analogue class room) Comorbidity: not allowed Comedication: not stated Sociodemographics: not stated **Inclusion criteria** • Diagnosed with ADHD according to DSM-IV-T • Minimum IQ score of 80 **Exclusion criteria** • CD or comorbid illnesses that contraindicated or could confound MPH transdermal system treatment • History of failing to respond to psychostimulant treatment • Taken another investigational product within 30 days of screening or participated in other research trials involving drug treatment during the course of the trial • Safety population consisted of 127 participants, who received ≥ 1 dose of trial medication 11 participants discontinued before the double-blind randomisation phase, resulting in an ITT population of 117 participants 7 participants discontinued before the double-blind randomisation phase, 3 were randomly assigned but did not undergo MPH transdermal system treatment 2 participants did not complete the analogue classroom phase of the trial: 1 because of an application site reaction, and 1 because of an AE (conjunctivitis), resulting in a total of 115 trial completers
Interventions	Participants were randomly assigned to 1 of 3 possible drug orders of MPH (4 and 6 h) and placebo Mean MPH dosage: 10 mg patch (n = 15), 15 mg patch (n = 34), 20 mg patch (n = 32) and 30 mg patch (n = 36) Administration schedule: once daily in the morning; patch worn for 9 h daily, and for 4 or 6 h for cross-over assessments Duration of each medication condition: 1 day Participants were kept on their optimised dose between classroom sessions Washout before trial initiation: none; in-between treatment with optimal dose of MPH Titration period: 5 weeks before randomisation Treatment compliance: not stated
Outcomes	**ADHD symptoms** • SKAMP: teacher-rated at randomisation (week 5) and 2 h after patch application at end of treatment (week 6, 7, 8)

Wilens 2008 *(Continued)*

Quality of life

- ADHD Impact Module-Child - Child Impact Scale and Family Impact Scale: rated at baseline, at randomisation (week 5) and at end of trial (week 8)

Non-serious AEs

- Vital signs were evaluated at screening, at baseline and at weeks 1-8
- Erythema, oedema, papules and vesicles, discomfort, haematology, urinalysis and ECG measures were completed at screening, at baseline and at weeks 5 and 8

No clinically meaningful changes from baseline were observed in vital signs, ECG, urinalysis and haematological results or physical examinations. AEs were recorded from the time informed consent was signed until 30 days (week 12) after the last drug treatment

Notes

Sample calculation: yes; assuming a mean difference in SKAMP deportment score of 2.0 between active treatment and placebo, an SD of 5.0, a between correlation of 0.2, 90% power and a probability level of.05 (2-sided), it was estimated that approximately 102 participants were needed to complete the double-blind, cross-over phase of the trial

Ethics approval: yes; institutional review board at each site approved the trial

Comments from trial authors

- Important to note that participants who failed to respond to psychostimulants in the past and those with CD were excluded from the study. Therefore, results of this study should not be extrapolated to these patient populations
- From Manos in Wilens 2008: "Lack of placebo comparison has the potential to confound the findings of this study. The relatively short study duration (about 2 months) may not be sufficient to capture some emerging changes in health-related quality of life"

Key conclusion of trial authors

- All efficacy measures indicated that 4- and 6-h wear times improved ADHD symptoms

Comments from review authors

- Treatment period is 1 day, 1 week apart for the 3 phases, and all participants are treated with MPH at optimal titrated dose in-between
- Quality-of-life assessments are aggregated for all (not possible to assess MPH vs placebo)

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; participants with a history of failing to respond to psychostimulant treatment were also excluded

Any withdrawals due to AEs: yes; 1 (conjunctivitis)

Funding: Shire Development Incorporated

Email correspondence with trial authors in April-June 2014. Emailed trial authors twice to ask for additional data but never received a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Single randomisation schedule prepared by an independent statistician using computer software that generated random numbers
Allocation concealment (selection bias)	Unclear risk	No information

Wilens 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each participant wore 2 patches prepared by an unblinded pharmacist to maintain treatment blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were only 2 withdrawals during the double blind phase Selection bias (e.g. titration after randomisation → exclusion of MPH non-responders or placebo responders): no
Selective reporting (reporting bias)	Low risk	No indication of selective reporting, outcomes according to protocol

Wilens 2010

Study characteristics	
Methods	Blind, randomised, 4-week, cross-over trial with 2 interventions: • MPH (transdermal patch) • placebo
Participants	Number of participants screened: unknown Number of participants included: 36 Number of participants followed up: 30 (25 boys, 5 girls) Number of withdrawals: 4 Diagnosis of ADHD: DSM-IV (combined (53%), hyperactive-impulsive (3%), inattentive (43%)) Age: mean 9.17 years (SD 1.84; range 6-12) IQ: > 70 MPH-naive: 14 (47%) Ethnicity: white (90%), African American (not stated), Asian (3%), Hispanic (not stated), other (7%) Country: USA Setting: outpatient clinic Comorbidity: oppositional disorder (70%), CD (7%), major depressive disorder (3%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Male and female outpatients • 6-12 years of age • Diagnosis of ADHD by DSM-IV, as manifested in clinical evaluation and confirmed by structured interview

Wilens 2010 *(Continued)*

- Participation in structured morning routine (e.g. school, camp, other organised activities)

Exclusion criteria

- Mental disability (IQ < 75)
- Participants with a medical condition, or treatment that will jeopardise participant safety or affect the scientific merit of the trial
- Participants with moderate to severe dermatological atopy
- Participants with known structural cardiac abnormalities
- Organic brain disorders
- Seizure disorder
- Participants with Tourette's syndrome or a history of psychosis or bipolar disorder
- Participants with current comorbid psychopathology that, in the investigator's opinion, will warrant immediate treatment or will interfere with safe execution of the protocol (i.e. anxiety or major depressive disorder rated as moderate on CGI)
- Participants with a history of intolerable adverse effects or non-response to MPH
- Pregnant or nursing females

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH (20 mg) and placebo Mean MPH dosage: not stated Administration schedule: patch applied in morning and worn for 9 h Duration of each medication condition: 2 weeks Washout before trial initiation: none Titration period: 1 week after randomisation Treatment compliance: > 80% for all participants
Outcomes	**ADHD symptoms** • ADHD-RS: clinician-rated at baseline and weekly for 4 weeks • CGI: parent-rated at baseline and weekly for 4 weeks (no data) **Non-serious AEs** • AEs and vital signs: clinician-rated at baseline and weekly for 4 weeks • ECG: clinician-rated at baseline and at end of trial
Notes	Sample calculation: no Ethics approval: not stated **Comment from trial authors** • "Doses used are lower than US FDA-approved dose of 30 mg. It is unclear whether results of this study represent optimal response" **Key conclusion of trial authors** • "Early administration of MPH transdermal system was associated with improved ADHD symptoms and before-school functioning in children with ADHD" Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; participants with a history of no response or intolerability to MPH were excluded for ethical reasons Any withdrawals due to AEs: yes; 2

Wilens 2010 *(Continued)*

Funding source: trial and medication/placebo were funded by a grant through Shire Pharmaceuticals. Shire had no role in design, collection, analysis, interpretation, writing or decision to submit

Email correspondence with trial authors: March/April 2014. We contacted the first trial author twice to ask for supplemental data but have not received a response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned
Allocation concealment (selection bias)	Low risk	Prescriptions filled by hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No additional information from trial author
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind (participant, caregiver, investigator)
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT: participants who completed 1 week of treatment; LOCF Selection bias: yes. Excluded participants not following 1 week of treatment
Selective reporting (reporting bias)	Low risk	No indication of selective reporting, outcomes according to protocol

Wilkison 1995

Study characteristics

Methods	Double-blind, placebo-controlled, cross-over trial with 2 interventions: • MPH • Placebo Phases: 2
Participants	Number of participants screened: not stated Number of participants included: 16 Number of participants followed up: 16 implied (16 boys, 0 girls) Number of withdrawals: not stated Diagnosis of ADHD: DSM-III-R (subtype not stated) Age: mean 10.2 years (range 8-13) IQ: mean 112.6 MPH-naive: 0%

Wilkison 1995 *(Continued)*

	Ethnicity: not stated Country: USA Setting: outpatient clinic Comorbidity: no Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Boys • 8-13 years of age • ADHD • Recruited from an outpatient clinic at a large metropolitan children's hospital in the USA • Conners' Hyperactivity Index score 1.5 SD above the norm on parent ratings • ≥ 6 months of treatment with MPH • Confirmed DSM-III-R diagnosis • History of > 6 months of MPH treatment **Exclusion criteria** • No physical or psychiatric diagnosis other than ADHD • Evidence of learning disability • "Each parent and prescribing physician reported that the subject responded positively to MPH"
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH (normal dose) and placebo Mean MPH dosage: 0.030 mg/kg (range 0.08 to 1.10 mg/kg/d) Administration schedule: not stated Duration of each medication condition: 36 h Washout before trial initiation: not stated Titration period: not stated Treatment compliance: not stated
Outcomes	**General behaviour** • Behaviour problems - CBCL, parent ratings. Data not reported
Notes	Sample calculation: not described Ethics approval: not described **Key conclusion of trial authors** • Stimulant effects on child's motivation to perform a task may compensate for deficits in other areas **Comment from review authors** • All participants had been treated previously with MPH for longer than 6 months; each parent and physician reported good response Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes, only participants who responded positively to MPH included

Wilkison 1995 *(Continued)*

	Any withdrawals due to AEs: unclear Funding source: a University of Utah Biomedical Sciences Research Grant and a grant from the University Research Committee Email correspondence with trial authors: May 2014. We obtained supplemental information from trial authors (Magnusson 2014c [pers comm])

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From correspondence: "generated by pharmacist" (Magnusson 2014c [pers comm])
Allocation concealment (selection bias)	Low risk	From correspondence: "recruiter had no involvement in and was blinded to allocation sequence" (Magnusson 2014c [pers comm])
Blinding of participants and personnel (performance bias) All outcomes	Low risk	From correspondence: "pharmacist instructed parents (via instructions on pill bottle) regarding which pills should be administered and at what time" (Magnusson 2014c [pers comm])
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	From correspondence: "approximately 2% of skin conductance and heart rate data were affected by participant movement and were replaced with interpolated values Physiological data were lost for 2 participants with ADHD and for 2 participants without ADHD. For 3 of the remaining 28 participants, 1 of the 4 repeated measurements of interbeat intervals was replaced with the mean of the participant's diagnostic group because his ECG recordings were inadequate" (Magnusson 2014c [pers comm]) Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	No indication of reporting bias

Wodrich 1998

Study characteristics

Methods	3-week cross-over trial with 3 interventions: • MPH 5 mg, twice daily • MPH 15 mg, twice daily • placebo Phases • Each drug condition lasted 7 days (Thursday through Wednesday) • "No washout period was deemed necessary, given the brief half-life and absence of carry-over effects of MPH [methylphenidate]"
Participants	Number of participants screened: 123 ("treated in the clinic")

Wodrich 1998 *(Continued)*

	Number of participants included: 57 (47 boys, 10 girls) Number of participants followed up: 57 Number of withdrawals: 66. Away on summer vacation (n = 30), teacher failed to complete all rating forms (n = 29), teacher marked 2 values indicated on a single dimension (n = 3), adverse medication side effect (n = 2), dropped out before child's medication trial was completed (n = 2) Diagnosis of ADHD: DSM-III-R Age: mean 8.5 years (SD 2.1; range 6-14) IQ: not stated MPH-naive: not stated Ethnicity: white "Anglo" 54 (95%), Hispanic 3 (5%) Country: USA Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Other sociodemographics: none **Inclusion criteria** • DSM-III-R Diagnosis of ADHD, confirmed by a clinical psychologist **Exclusion criteria** • No primary disorder "better explained the child's presenting symptoms" (e.g. mood disorder, anxiety disorder, adjustment disorder, pervasive developmental disorder)
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders (5 mg MPH or 15 mg MPH) and placebo Mean MPH dosage: 10 mg/d, 30 mg/d and placebo Administration schedule: twice/d at 8:00 am and 12:00 pm Duration of each medication condition: 1 week Washout before trial initiation: approximately 20 h (lunchtime until "immediately before school" the next day) Titration period: not stated Treatment compliance: not stated Number of withdrawals: 2. Parents dropped out of the trial before their child's medication trial was completed
Outcomes	**ADHD symptoms** • Abbreviated Conners' Rating Form • School Situations Questionnaire: "As our research concern was to locate tools helpful to school psychologists, we chose to address only the utility of using SSQ. For statistical analysis, scores from zero (no problem) to 9 (severe problem) were entered for each situation" (p 84) **Serious AEs** • Side Effects Questionnaire

Wodrich 1998 *(Continued)*

General behaviour

- Personality Inventory for Children

Non-serious AEs

- Side Effects Questionnaire

Notes	Sample calculation: not stated Ethics approval: not stated **Key conclusions of trial authors** • School Situation Questionnaire ratings improved with MPH treatment in all situations related to task performance (i.e. arriving at school; during individual seatwork, small group activities and lectures) but less so in non-task or unstructured situations • Many change scores were large enough to be clinically meaningful • Use of School Situations Questionnaire by school psychologists was discussed as a means of efficiently providing contextual information not available from ADHD dimensional rating scales Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no Any withdrawals due to AEs: yes Funding source: not declared Email correspondence with trial authors: June 2014. We obtained supplemental information from trial authors. We contacted trial author to ask for missing data, but s/he was not able to supply the data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects then underwent a three-week, triple-blinded, cross-over medication trial consisting of placebo, 5 mg, and 15 mg of MPH dose twice a day (immediately before school and at lunchtime)" (p 83); "Order of administration was counterbalanced so that equivalent numbers of children received each sequence" (p 83)
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects then underwent a three-week, triple-blinded, cross-over medication trial consisting of placebo, 5 mg, and 15 mg of MPH dose twice a day (immediately before school and at lunchtime). Each drug condition lasted 7 days (Thursday through Wednesday)" (p 83); "Doses were prepared and packaged for the three week trial by a licensed pharmacist who split MPH tablets and placed them with lactose into re-sealable capsules. The placebo dose consisted of lactose-filled capsules only. Equivalent numbers of capsules (three) were dispensed at each dosing time to maintain uniformity and disguise presence/amount of medication, as three capsules were required to encompass the largest dose (15 mg)" (p 83)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"This procedure was followed for three weeks, with the medication code being broken the final week and determination about medication efficacy and decision to continue addressed at that time" (p 84)
Incomplete outcome data (attrition bias)	Unclear risk	Not stated Selection bias (e.g. titration after randomisation → exclusion): no

Wodrich 1998 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No protocol identified

Wolraich 2001

Study characteristics	
Methods	28-day, randomised, parallel, double-blind clinical trial with 3 arms: • OROS-MPH • IR-MPH • placebo
Participants	Number of participants screened: 405 Number of participants included: 312 (233 boys, 49 girls) Number of participants followed up: 206 (OROS-MPH 79, IR-MPH 81, placebo 46) Number of withdrawals: 71 (OROS-MPH 15, IR-MPH 13, placebo 43) Diagnosis of ADHD: DSM-IV (combined (73.4%), hyperactive-impulsive (7.1%), inattentive (19.5%)) Age: mean 9.0 years (range 6-12) IQ: > 70 MPH-naive: 20.2% Ethnicity: white (84.4%), African American (7.4%), Asian (0.4%), Hispanic (3.5%), other (4.3%) Country: USA Setting: outpatient clinic Comorbidity: ODD (41.8%), CD (11.3%), tic disorder (5.3%), anxiety disorder (1.4%), depression (0.7%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • 6-12 years of age • Clinical diagnosis of any subtype of ADHD - had to be confirmed by the DISC-4, administered by a trained interviewer • Patients who were taking MPH or had taken it in the past had to have been on a total daily dose of MPH (IR-or a combination of IR/ER) of ≥ 10 mg but ≤ 60 mg • Patients had to agree to take the supplied trial drug as the only medication for ADHD during the 4-week trial period • IQ > 70 **Exclusion criteria** • Acute or serious chronic disease • Hypersensitivity to MPH • Significant adverse experiences from MPH • Taking a medication that would interfere with safe administration of MPH

Wolraich 2001 *(Continued)*

- Glaucoma, Tourette's syndrome, ongoing seizure disorder or psychotic disorder
- Girls who had reached menarche

During the course of the trial, participants were allowed to receive behavioural interventions as long as the interventions had been initiated before the start of the trial and did not change during the trial. New behavioural therapy was not allowed during the course of the trial

Interventions	Average total daily dose: IR-MPH 29.5 mg/d (0.90.4 mg/kg/d), OROS-MPH 34.3 mg/d (1.1 to 0.5 mg/kg/d)
	No. of participants randomised to each group: OROS-MPH 94, IR-MPH 94, placebo 89
	Administration schedule: 3 times/d
	Duration of intervention: 4 weeks
	Titration period: 4-week titration period before randomisation (open-label) for trial participants who had not received MPH for ADHD from their own practitioner in the 4 weeks before trial entry. Participants who had taken MPH during the 4 weeks before trial entry were assigned to a dose level based on their pre-trial therapeutic dose and regimen
	Treatment compliance: not stated
Outcomes	**ADHD symptoms** • IOWA CRS: teacher- and parent-rated on day 27 • SNAP, 4th Edition: teacher- and parent-rated, week 4 **Quality of life** • CGAS
Notes	Sample size calculation: yes
	Ethics approval: yes
	Key conclusion of trial authors • Results of this study show that OROS methylphenidate administered once a day and immediate-release methylphenidate administered 3 times a day were significantly better than placebo and were not significantly different from each other for the primary efficacy measure, teacher IOWA Conners' Rating Scale, Inattention-Impulsivity-Overactivity subscale score, which evaluated attention and behaviour at school. Furthermore, significant improvement in attention and behaviour was seen in the first week for participants who were taking OROS methylphenidate qd or immediate-release methylphenidate three times a day compared with placebo, and this improvement was maintained throughout the 4 weeks of the study. These results were consistent across settings (home and school), raters (parents, teachers, clinical investigators) and measures (IOWA Conners' Rating Scale; Swanson, Nolan and Pelham, Fourth Edition; Peer Interaction; Global Assessments; Parent Satisfaction) and were statistically significant
	Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: yes; 111 who had not received MPH before the study initially were enrolled into a dose-titration study. One of these did not enrol in the randomised study because the 54-mg dose was found to be ineffective
	Any withdrawals due to AEs: yes; 3
	Funding source: ALZA Corporation
	Comments from review authors in July 2013: corresponded with first trial author, Wolraich, who answered all of our questions (Krogh 2013c [pers comm]).

Risk of bias

Wolraich 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Within each dose level, participants were randomly assigned equally to OROS-MPH once/d, IR-MPH (over-encapsulated Ritalin) 3 times/d or placebo in a 3-group parallel design. Stratified randomisation was conducted centrally at ALZA Corporation
Allocation concealment (selection bias)	Low risk	Double-dummy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF Selection bias (e.g. titration after randomisation → exclusion): no, but 59 discontinued due to lack of efficacy.
Selective reporting (reporting bias)	Unclear risk	Not able to get trial protocol

Zeiner 1999

Study characteristics	
Methods	Cross-over trial with 2 interventions: • MPH • Placebo Phases: 7 weeks (3 weeks of medication, 1 week washout, 3 weeks of placebo) Zeiner 1995 (in Zeiner 1999): "extended treatment (mean duration 634 ± 130 days)"
Participants	Number of participants screened: 46 Number of participants included: 38 Number of participants followed up: 36 (36 boys, 0 girls) Number of withdrawals: 2 Diagnosis of ADHD: DSM-III-R or DSM-IV (combined type (> 75%), hyperactive-impulsive and inattentive types not stated) Age: mean 8.7 years (range 7-11) IQ: mean 102 (range 79-139) MPH-naive: 100% Ethnicity: not stated

Zeiner 1999 *(Continued)*

	Country: Norway Setting: outpatient clinic Comorbidity: ODD (23; 64%) Comedication: not stated Other sociodemographics: none **Inclusion criteria** • Male • Between 7 and 12 years of age • Fulfilled diagnostic criteria for ADHD • IQ ≥ 70 **Exclusion criteria** • Pervasive developmental disorder • Psychosis or mood disorder • Any acute or chronic medical or neurological disease • Used stimulants or any other psychotropic drug
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of MPH (0.5 mg/kg) and placebo. 31 children received a morning dose of 10 mg or 15 mg (and 5 young boys received 7.5 mg) Mean MPH dosage: not stated; "0.55 mg/kg to 0.56 mg/kg daily across the entire duration of the extended treatment period" (Zeiner 1995 in Zeiner 1999) Administration schedule: capsules were given in 2 doses (at 8 am and 11.30 am) Duration of each medication condition: 3 weeks Washout before trial initiation: not relevant MPH-naive: all Medication-free period between interventions: 1 week Titration period: none Treatment compliance: no information
Outcomes	**ADHD symptoms** • Parent Account of Childhood Symptoms, at home • CTRS, in classroom Assessments of the child were made during the last week of each trial period **Non-serious AEs** • Height, weight, heart rate, SBP, DBP
Notes	Sample calculation: no Ethics approval: no information **Comment from trial authors** • This study has obvious limitations. Sample size was limited, and heterogeneity was noted with regard to behavioural characteristics and test performance. This heterogeneity may conceal associations found in subgroups of children with ADHD. Boys between 7 and 11 years of age were chosen.

Zeiner 1999 *(Continued)*

They represent the majority of children admitted with hyperactivity and inattention, but boys of other age groups may show a different clinical picture

Key conclusions of trial authors

- Response to MPH was examined in 36 boys, 7-11 years of age, with ADHD in a double-blind, placebo-controlled trial of cross-over design
- Hyperactivity and conduct problems were significantly reduced during MPH treatment
- Stimulant medication was associated with improvement on tests of sustained attention, working memory and motor steadiness
- When individual changes were studied, it was found that 83% showed significant improvement in their hyperactivity at home or at school, and for 60%, levels of hyperactive behaviour were within the normal range
- High levels of hyperactivity at school at a relatively low age was a significant predictor of normalisation of hyperactivity in ≥ 1 setting. However, these predictors could classify correctly only 71% of children
- In clinical practice, a trial with stimulants is indicated for children with ADHD who show symptoms that are sufficiently severe to cause impairment at home and at school

Comments from review authors

- Generation of allocation sequence is unclear
- No sample size calculation was performed
- Number of screened patients is unclear
- In Zeiner 1995 (in Zeiner 1999), this was written: "no sociodemographic information"

Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no

Any withdrawals due to AEs: no

Funding: the Norwegian Medical Research Council, the Norwegian Public Health Association and the Legacy of Haldis and Josef Andresen

Email correspondence with trial authors: May-June 2014. We emailed Dr. Zeiner on 05 May 2014 and 02 June 2014 but never received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were randomly allocated to receive MPH first or placebo first
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A randomized crossover, double-blind design with methylphenidate and placebo". Placebo and MPH capsules that were used were identical, to ensure blindness to the drug condition
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All raters were blind to the drug condition"
Incomplete outcome data (attrition bias) All outcomes	High risk	"The report from a teacher during one of the periods was missing for one child. Owing to technical problems or unwillingness to participate data were missing on some of the test measures [which measured side effects] for a few children" (Zeiner 1995 in Zeiner 1999)

Zeiner 1999 *(Continued)*

		Selection bias: yes; only responders from the 7-week trial were included in the extended-treatment MPH group
Selective reporting (reporting bias)	Low risk	No selective outcome reporting

Zeni 2009

Study characteristics	
Methods	Randomised, cross-over trial with 2 interventions: • MPH and aripiprazole • placebo and aripiprazole Phases: 2; randomisation, cross-over
Participants	Number of participants screened: 30 Number of participants included: 16 (9 boys, 7 girls) Number of participants followed up: 14 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (combined (78.6%), hyperactive (14.3%), inattentive (7.1%) out of n = 14) Age: mean 10.71 years (SD 1.86; range 8-17) IQ: > 70 MPH-naive: not stated Ethnicity: European-Brazilian (71.4%), other (28.6%) Country: Brazil Setting: outpatient clinic Co-morbidity: bipolar disorder (71.4%), borderline personality disorder (28.6%), anxiety disorder (57.1%), CD (57.1%), ODD (78.6%), psychosis (50%), out of n = 14 Co-medication: aripiprazole (100%) Other sociodemographics: divorced parents (57.1%); socioeconomic level A + B + C: 92.9%; D + E: 7.1% **Inclusion criteria** • 8-17 years of age • Diagnosis of borderline personality disorder, Axis I or II, co-morbid with ADHD (DSM-IV) • ADHD symptom onset preceding mood symptoms • ≥ 30% improvement in mood symptoms in previous trial of aripiprazole • Residual attention hyperactivity and opposition symptoms defined as score > 1.5 on the SNAP, 4th Edition **Exclusion criteria** • IQ < 70 • Use of any medication other than aripiprazole 10 weeks before the trial • Diagnoses of pervasive developmental disorder

Zeni 2009 *(Continued)*

	• Schizophrenia • Substance abuse or dependence • Severe suicide/homicide risk counterindicating outpatient treatment • History of hypersensitivity to aripiprazole or MPH • Any other acute or chronic disease that may interfere with the trial • Pregnancy
Interventions	Participants were randomly assigned to different possible drug condition orders of MPH (0.3 mg/kg for the 1st week, 0.7 mg/kg for the 2nd week) and placebo, both alongside aripiprazole Mean MPH dosage: 15 mg in the 1st week (10 mg in the morning and 5 mg in the afternoon), 35 mg in the 2nd week (20 mg in the morning and 15 mg in the afternoon) Administration schedule: twice/d (morning and afternoon) Duration of each medication condition: 2 weeks Washout before trial initiation: none (but recruited from 6-week aripiprazole trial) Medication-free period between interventions: not stated Titration period: none Treatment compliance: self-report, mother's report, pill counting in returned blister packs
Outcomes	**ADHD symptoms** • SNAP, 4th Edition (Brazilian Version): rated weekly by parents **General behaviour** • Oppositional index of the SNAP, 4th Edition (Brazilian Version): rated weekly by parents **Non-serious AEs** • Serious Adverse Event Rating Scale (SAERS) • Open question
Notes	Sample calculation: no Ethics approval: yes **Comments from trial authors** • "The small sample size may not have allowed us to detect significant differences between placebo and MPH." • "The short-term duration of this trial may be an important limitation for the observation of significant differences in AEs between therapeutic agents." **Key conclusions of trial authors** • "MPH was not more effective than placebo in reducing attention or hyperactivity symptoms in this short-term trial." • "Secondary finding suggests that depressive symptoms can be ameliorated by the addition of MPH to aripiprazole." • "Although MPH was found to not de-stabilise borderline personality disorder, its use should be considered with caution because 1 participant presented a severe mixed episode needing hospitalisation during MPH treatment." Exclusion of MPH non-responders/children who have previously experienced AEs while taking MPH before randomisation: no. But only participants who reported improved borderline personality disorder in the previous aripiprazole trial were included. However, participants who reported that ADHD im-

Zeni 2009 *(Continued)*

proved too much (as indicated by a score < 1.5 on the SNAP, 4th Edition) in the previous aripiprazole trial were excluded (see 'Exclusion criteria')

Any withdrawals due to AEs: yes. 1; exacerbation of borderline personality disorder and ADHD requiring hospitalisation

Funding source: research grants from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq, Brazil) (Grant 471761=03-6) and Hospital de Clinicas de Porto Alegre (GPPG 03-325). Aripiprazole was provided by Bristol-Myers Squibb without restriction.

Email correspondence with trial authors: May 2014. We obtained supplemental information regarding data. Trial authors provided us with data from the first period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent third party randomly assigned participants to groups A and B
Allocation concealment (selection bias)	Low risk	A pharmacist packaged MPH and matching placebo in capsules, so they could not be differentiated by shape, colour, smell, weight or taste
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A pharmacist packaged MPH and matching placebo in capsules, so they could not be differentiated by shape, colour, smell, weight or taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	After all 4 assessments were completed, trial blinding was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses of primary and secondary outcome measures were performed using a mixed-effects model (MEM) approach, which provides a flexible framework for analysis of repeated measures, while accounting for missing data (i.e. lost to follow-up) Selection bias (e.g. titration after randomisation → exclusion): no
Selective reporting (reporting bias)	Low risk	Outcomes reported according to protocol

ABRS/ACRS/CARS: Conners' Abbreviated Rating Scale/Abbreviated Conners' Rating Scale/Conners' Abbreviated Rating Scale; **ACTerRS:** **ADD/H:** attention deficit disorder with hyperactivity Comprehensive Teacher Rating Scale; **ADD:** attention deficit disorder; **ADD-H:** attention deficit disorder with hyperactivity; **ADHD:** attention deficit hyperactivity disorder; **ADHD-RS(-IV/V):** Attention Deficit Hyperactivity Disorder Rating Scale(4th Edition/5th edition); **ADI-R:** Autism Diagnostic Interview-Revised; **ADOS:** Autism Diagnostic Observation Schedule; **AEs:** adverse events; **ALT:** alanine aminotransferase; **AMP:** amplitude of the sleep-wake rhythm; **ANOVA:** analysis of variance; **APRS:** Abbreviated Parent Rating Scale; **ASQ-Teacher:** attention deficit hyperactivity disorder Conners' Abbreviated Symptom Questionnaire for Teachers; **ASQ-parent:** attention deficit hyperactivity disorder Conners' Abbreviated Symptom Questionnaire for parents; **AST:** aspartate aminotransferase
BMI: body mass index; **BP:** blood pressure; **BRIEF:** Behavior Rating Inventory of Executive Function;
CASS:S: Conners-Wells Adolescent Self-Report; **CBCL:** Child Behavior Checklist; **CBT:** cognitive behavioural therapy; **CD:** conduct disorder; **CDC:** Centers for Disease Control and Prevention; **CDRS-R:** Children's Depression Rating Scale - Revised; **CGAS:** Children's Global Assessment Scale; **CGI:** Conners' Global Index; **CGI(-S):** Clinical Global Impressions(-Severity); **CLAM:** Conners, Loney and Milich Scale; **CNS:** central nervous system; **CPRS(R-S):** Conners' Parent Rating Scale (Revised, Short form); **CRS:** Conners' Rating Scale; **C-SSRS:** Columbia Suicide Severity Rating Scale; **CSHQ:** Children's or Adolescent Sleep Habits Questionnaire; **CTRS(R-S):** Conners' Teacher Rating Scale (Revised, Short form)
DBP: diastolic blood pressure; **DCD:** developmental co-ordination disorder; **DISC(-4):** Diagnostic Interview Schedule for Chldren (4th Edition); **d-MPH:** dexmethylphenidate; **d,l-MPH**: dex,levo-threo-methylphenidate; DR: delayed-release; **DR-MPH:** delayed-release methylphenidate;**DSM-III:***Diagnostic and Statistical Manual of Mental Disorders, Third Edition;* **DSM-III-R:***Diagnostic and Statistical Manual*

of Mental Disorders, Third Edition, Revised; **DSM-IV:***Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; **DSM-IV-TR:***Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; **DSM-5:***Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*;
ECG: electrocardiogram; **EEG:** electroencephalogram; **ER:** extended-release; **ER-d-MPH:** extended-release dexmethylphenidate; **ER-MAS:** extended-release mixed amphetamine sales; **ER-MPH:** extended-release methylphenidate; **EqXL**:Equasym;
FDA: Food and Drug Administration
HCG: human chorionic gonadotropin; **HD:** high-dose; **HD-MPH:** high-dose methylphenidate;
ICD-10:*International Classification of Diseases, Tenth Revision*; **IR:** immediate-release; **IR-MPH:** immediate-release methylphenidate; **ITT:** intention-to-treat; **IS:** interdaily stability; **IV:** intradaily variability; **IQ:** Intelligence quotient
KBIT-2: Kaufman Brief Intelligence Test; **K-SADS-E/PL:** Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children Epidemiological/Present and Lifetime version; ;
LA: long-acting; **LA-MPH:** long-acting methylphenidate; **LD:** low-dose; **LD-MPH:** low-dose methylphenidate; **LDX:** lisdexamphetamine; **LLC:** limited liability company; **LOCF:** last observation carried forward; **L-DOPA:** levedopa; **LTFU:** loss to follow-up; **L5:** the amount of activity during the 5 h with the lowest activity;
MAS: mixed amphetamine salts; **MAOI:** monoamine oxidase inhibitor; MD: moderate-dose; **MD-MPH:** moderate dose methylphenidate; **MedDRA:** Medical Dictionary for Regulatory Activities; **MINI-KID:** Mini International Neuropsychiatric Interview for Children and Adolescents; **MPH:** methylphenidate; **MPT:** methylphenidate trial; **MPH-IR**: Methylphenidate immediate release; **MPH-MLR:** multilayer extended-release bead methylphenidate capsule; **MR:** modified release; **MR-MPH:** modified-release methylphenidate; **MTA:** Multimodal Treatment Study of Children With ADHD;
NIH: National Institutes of Health; **NIMH:** National Institute of Mental Health; **NNTB:** number needed to treat for an additional beneficial outcome;
OCD: obsessive compulsive disorder; **ODD:** oppositional defiant disorder; **ODT:** orally disintegrating tablet; **OROS-MPH:** osmotic-controlled release oral delivery system methylphenidate; **ORADUR-MPH:** long-acting methylphenidate formulation; **OTMP:** Organisational, Time Management and Planning treatment;
PDD: pervasive developmental disorder; **PICS:** Parental Interview for Child Symptoms; **PERMP**: Permanent Product Measure of Performance; **PREMB-R AM:** Parent Rating of Evening and Morning Behavior-Revised, Morning; **PREMB-R PM:** Parent Rating of Evening and Morning Behavior-Revised, Evening; **PSQI:** Pittsburg Sleep Quality Inventory; **PTS:** placebo transdermal system; **PTSD:** post-traumatic stress disorder
RCT: randomised clinical trial;
SA: short-acting; **SA-MPH:** short-acting methylphenidate; **SAERS:** Serious Adverse Event Rating Scale; **SCT:** sluggish cognitive temp; **SBP:** systolic blood pressure; **SD:** standard deviation; **SDX:** serdexmethylphenidate; **SDX/d-MPH**: serdexmethylphenidate/dexamphetamine-methylphenidate; **SE**: standard error; **SIB-R:** Scales of Independent Behavior Revised; **SKAMP:** Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale; **SNAP(-IV):** Swanson, Nolan and Pelham scale(4th Edition); **SODAS:** spheroidal oral drug absorption system; **SSRIs:** selective serotonin reuptake inhibitors; **STAI:** Spielberger State-Trait Anxiety Inventory; **SWAN:** Strength and Weakness of Attention-Deficit/Hyperactivity Disorder-symptoms and Normal Behavior Rating Scale;
TEAE: treatment emergent adverse event; **TIB:** total in-bed time; **TOTS:** Loney's Time on Task Scale; **TRS:** Teacher Rating Scale; **TSH:** thyroid stimulating hormone; **TSSR:** Tic Symptom Self-Report Scale; **TTI:** Teacher Telephone Interview;
VADPRS: Vanderbilt ADHD Diagnostic Parent Rating Scale; **VADTRS:** Vanderbilt ADHD Diagnostic Teacher Rating Scale;
WASO: wake after sleep onset; **WASI(-II):** Wechsler Abbreviated Scale of Intelligence(- Second Edition); **WBnumber:** number of wake bouts; **WBmean:** mean wake bout time; **WISC(-II, III, IV, R):** Wechsler Intelligence Scale for Children(-2nd, 3rd, 4th, Revised edition); **WRAT-R:** Wide Range Achievement Test;
XR: extended release;
YGTSS: Yale Global Tic Severity Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12608000059369	Likely no relevant outcomes for our review as outcomes were structural imaging results: volume and activation of different brain regions
An 2013	Likely no relevant outcome for our review as this was resting state brain function only
Anderson 2002	Likely no relevant outcome for our review as this was functional magnetic resonance relaxometry only
Barkley 1988a	Likely no relevant outcomes for our review as outcomes were Home Situations Questionnaire, Parenting Stress Index, and Beck Depression Inventory

Study	Reason for exclusion
Barkley 1997	Likely no relevant outcomes for our review as these were "2 questionnaires", and "Electronic apparatus"
Bart 2013	Likely no relevant outcomes for our review as these were Movement Assessment Battery for Children – Second edition, and Online Continuous Performance Test
Bedard 2002	Likely no relevant outcomes for our review as these were response interference, and Stroop Naming Speed
Bedard 2003	Likely no relevant outcomes for our review as these were Parent Interview for Child Symptoms, Teacher Telephone Interview–IV, and Selective Stop-Signal Task
Bedard 2004	Likely no relevant outcomes for our review as these were Parent Interview for Child Symptoms; Teacher Telephone Interview–IV, Reading subtest/Wide Range Achievement Test - 3, Word Attack and Word Identification subtests of the Woodcock Reading Mastery, and Test-Revised Cambridge Neuropsychological Testing Automated Battery
Bedard 2007	Likely no relevant outcomes for our review as these were focusing on working memory; Test of Word and Language Efficiency, Wide Range Achievement Test - 3, Woodcock-Johnson Tests of Achievement, and Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Span
Beery 1994	Likely no relevant outcomes for our review as these were focusing on behavioural management and behavioural disinhibition
Beery 2017	Likely no relevant outcomes for our review as these was focusing on social behavior
Ben-Pazi 2006	Likely no relevant outcome for our review as this was focusing on hastening phenomena only
Bental 2008	Likely no relevant outcomes for our review as these was focusing on reading measures
Beyer 2014	Likely no relevant outcomes for our review as these were The Frankfurt Test and training of social affect
Bouziane 2019	Likely no relevant outcome for our review as this was MRI measuring only
Brown 1984b	Likely no relevant outcome for our review as this was Children's Checking Task only
Buhrmester 1992	Likely no relevant outcome for our review as this was focusing on prosocial behavior only
Campbell 1996	Likely no relevant outcome for our review as this was reaction times on Tachistoscopic Task only
Carlson 1991	Likely no relevant outcomes for our review as these were focusing on reaction times and other cognitive tasks
Carlson 1992	Likely no relevant outcomes for our review as these were focusing on task and disruptive behaviour; academic work completion and accuracy
Cohen 2020	Likely no relevant outcome for our review as this was focusing on Go/No-Go Task only
Cox 2004b	Likely no relevant outcome for our review as this was focusing on driving performance - measured by computer only
Cubillo 2014	Likely no relevant outcome for our review as this were focusing on Stop Task combined with fMRI only

Study	Reason for exclusion
Cubillo 2020	Likely no relevant outcome for our review as this was focusing on fMRI during Sustained Attention Task only
Dawson 1998	Likely no relevant outcomes for our review as these were focusing on Mirsky's proposed factors of attention: sustained attention, focus/execute, encode, and stability of attention
De Sonneville 1991	Likely no relevant outcomes for our review as these were focusing on specific attention function: sustained attention, information processing, response organization
DeVito 2008	Likely no relevant outcomes for our review as these were focusing on Cambridge Gamble Task; measures of response inhibition and reflection-impulsivity on the information Sampling Task
Dougherty 2016	Likely no relevant outcomes for our review as these were focusing on Immediate Memory Task, GoStop Impulsivity Paradigm, Two Choice Impulsivity Paradigm
Evans 1986	Likely no relevant outcomes for our review as these were focusing on verbal memory and learning
Fosco 2017	Likely no relevant outcomes for our review as these were focusing on cognitive domains, including working memory, inhibitory control and attention
Fosco 2021	Likely no relevant outcomes for our review as these were focusing on inhibitory control, visuospatial working memory, reaction time variability, and delay discounting
Fox 2014	Likely no relevant outcomes for our review as these were focusing on memory tasks
Francis 2001	Likely no relevant outcomes for our review as these were focusing story telling and story grammar analysis
Gan 1982	Likely no relevant outcome for our review as this was focusing on performance on Paired Associate Learning task only
Golubchik 2018	Likely no relevant outcome for our review as this was focusing on changes in school report cards only
González-Carpio Hernández 2016	Likely no relevant outcome for our review as this was focusing on creativity measurements only
Granger 1996	Likely no relevant outcome for our review as this was focusing on social behaviour only
Grizenko 2010	Likely no relevant outcomes for our review as these were focusing on academic behaviour; sustained attention; impulse inhibition control
Günther 2010	Likely no relevant outcomes for our review as these were focusing on sustained attention measured by computer attention tests
Hadar 2020	Likely no relevant outcomes for our review as these were focusing on Visuo-Motor Attention Test and multiple cognitive tasks measuring auditory and visual executive functions
Halliday 1983	Likely no relevant outcomes for our review as these were focusing on event-related potentials
Hanisch 2004	Likely no relevant outcomes for our review as these were focusing on computerised attention tasks
Hazel-Fernandez 2006	Likely no relevant outcome for our review as this was focusing on Paired Associates Learning task; Tower of Hanoi only

Study	Reason for exclusion
Helseth 2015	Likely no relevant outcomes for our review as these were focusing on children's rates of reinforcement for deviant peer behavior
Hinshaw 1989	Likely no relevant outcome for our review as this was focusing on prosocial behaviour only
Hinshaw 1993	Likely no relevant outcome for our review as this was focusing on antisocial behaviour only
Horowitz 2020	Likely no relevant outcomes for our review as these were focusing on Sustained Attention to Response Task, N-Back Task, Stroop Color and Word Task
Humphries 1979	Likely no relevant outcome for our review as this was focusing on maze-tracking performance only
Ishii-Takahashi 2015	Likely no relevant outcomes for our review as these were focusing on prefrontal haemodynamics measured by fNIRS
ISRCTN52376787	Likely no relevant outcomes for our review as these were focusing on information about effects of MPH on cognitive function (including the possibility of cognitive toxicity) in children with ADHD, greater understanding of the underlying cognitive processes in ADHD, identification of potential cognitive deficits in ADHD.
JPRN-UMIN000008831	Likely no relevant outcomes for our review as these were focusing on fNIRS analysis and behavioral performance
JPRN-UMIN000027533	Likely no relevant outcome for our review as this was focusing on rsfMRI only
King 2009a	Likely no relevant outcomes for our review as these were focusing on social information processing
King 2009b	Likely no relevant outcomes for our review as these were focusing on laboratory provocation task, measuring hostile, instrumental, reactive, and proactive aggression
Kobayashi 2020	Likely no relevant outcomes for our review as these were focusing on haemodynamic changes measured by fNIRS during observation of happy and angry facial expressions
Kowalczyk 2019	Likely no relevant outcome for our review as these were focusing on sustained attention/vigilance task in a 3T MRI scanner only
Lange 2007	Likely no relevant outcome for our review as these were focusing on reaction time, alertness, vigilance, and divided attention
Leitner 2007b	Likely no relevant outcomes for our review as these were focusing on gait; stride to stride variability, memory, visual-spatial, verbal, and attention domains
Levi-Shachar 2020	Likely no relevant outcomes for our review as these were focusing on Dimensional Change Card Sort Test (DCCS) and the Flanker Inhibitory Control and Attention Test, Theory of Mind tests, oxytocin levels
Luman 2015	Likely no relevant outcomes for our review as these were focusing on time production task, accuracy and response latency in an instrumental learning task
Malone 1988	Likely no relevant outcomes for our review as these were focusing on word processing, reaction time, and cognitive decision task
Malone 1993	Likely no relevant outcome for our review as this was focusing on impulsive responding only
Malone 1994	Likely no relevant outcome for our review as this was focusing on right hemisphere dysfunction only

Study	Reason for exclusion
Martin 2007	Likely no relevant outcomes for our review as these were focusing on depression; addiction rate; Continuous Performance Task; heart rate and blood pressure
Mazzetti 2022	Likely no relevant outcome for our review as this was focusing on spatial attention task only
Mehta 2004	Likely no relevant outcome for our review as this was focusing on working memory only
Merrill 2022	Likely no relevant outcome for our review as these were focusing on novel mindwandering sustained attention to response task only
Milich 1989	Likely no relevant outcome for our review as this was focusing on Continuous Performance Task only
Milich 1991	Likely no relevant outcome for our review as this was focusing on task persistence only
Mizuno 2021	Likely no relevant outcomes for our review as these were focusing on Sustained attention examined using a continuous performance test. MRI scans
Morris 2022	Likely no relevant outcomes for our review as these were focusing on electrocardiographic and electrodermal outcomes
Nagashima 2015	Likely no relevant outcomes for our review as these were focusing on oxy-hb changes measured with fNIRS during Go/No-Go Task
NCT00485797	Likely no relevant outcome for our review as this was focusing on postural sway measures
NCT00778310	Likely no relevant outcomes for our review as these were focusing on brain oxygenation level-dependent signal in the fusiform gyrus and the amygdala on Concerta vs placebo
NCT02318017	Likely no relevant outcomes for our review as these were focusing on electroencephalography data during neurocognitive tasks
NCT03788902	Likely no relevant outcomes for our review as these were focusing on Theory of Mind, Faux-Pas Recognition Test, and salivary oxytocin levels
NCT04349917	Likely no relevant outcomes for our review as these were focusing on Go/No Go Task and fMRI
Novak 1995	Likely no relevant outcomes for our review as these were focusing on reaction time and visuospatial attention
O'Toole 1997	Likely no relevant outcome for our review as this was focusing on non-verbal learning only
Pakdaman 2018	Likely no relevant outcome for our review as this was focusing on neuropsychological tests only
Peeke 1984	Likely no relevant outcome for our review as this was focusing on verbal information processing only
Pelham 1985	Likely no relevant outcomes for our review as these were focusing on classroom academic and social behaviour
Pelham 1990b	Likely no relevant outcomes for our review as these were focusing on attention during baseball game; on task behaviour; and ability to answer question about the status of the game
Pelham 1992	Likely no relevant outcomes for our review as these were self-reported attribution and evaluation of behaviour

Study	Reason for exclusion
Pelham 1997	Likely no relevant outcomes for our review as these were focusing on performance, self-evaluation, persistence, and attributions on cognitive task
Pelham 2001b	Likely no relevant outcomes for our review as these were focusing on a large number of different measures of behaviour
Pelham 2017a	Likely no relevant outcomes for our review as these were focusing on daily contact reports, Good Day/Bad Day Questionnaire, and self-perceived medication status
Pelham 2017b	Likely no relevant outcomes for our review as these were focusing mother and child relationship
Rapport 1995	Likely no relevant outcome for our review as this was focusing on Paired Associates Learning task only
Ratzon 2017	Likely no relevant outcomes for our review as these were focusing on driving skills tested by the STISIM Drive simulator
Richardson 1988	Likely no relevant outcome for our review as this was focusing on reading achievement only
Rubia 2003	Likely no relevant outcome for our review as this was focusing on motor timing only
Rubinson 2019	Likely no relevant outcomes for our review as these were focusing on Go/No-Go Task and electroencephalography
Sangal 2006	Likely no relevant outcome for our review as this was focusing on auditory amplitude only
Silk 2012	Likely no relevant outcome for our review as this was focusing on neural substrates only
Silk 2014	Likely no relevant outcome for our review as this was focusing on a visual attention task only
Silk 2017	Likely no relevant outcome for our review as this was focusing on rsfMRI only
Slama 2015	Likely no relevant outcomes for our review as these were focusing on Continuous Performance Test and Counting Stroop Task
Smith 2013	Likely no relevant outcome for our review as this was focusing on fMRI only
Solanto 1986	Likely no relevant outcomes for our review as these were focusing on attention during play measured by locomotor activity; Children's Checking Test; and fine motor control
Solanto 1997	Likely no relevant outcome for our review as this was focusing on Continuous Performance Test only
Srinivas 1992	Likely no relevant outcomes for our review as these were focusing on sustained attention measured by computer attention tests
Strand 2012	Likely no relevant outcome for our review as this was focusing on working memory only
Stray 2009	Likely no relevant outcome for our review as this was focusing on motor functions only
Sunohara 1997	Likely no relevant outcome for our review as this was focusing on event-related potentials only
Sutoko 2019	Likely no relevant outcome for our review as this was focusing on fNIRS during Go/No-Go Task only
Swanson 1993	Likely no relevant outcome for our review as this was focusing on impulsive responding

Study	Reason for exclusion
Szobot 2003	Likely no relevant outcome for our review as this was focusing on cerebral blood flow only
Tannock 2000	Likely no relevant outcomes for our review as these were focusing on naming speed and academic measures
Teicher 2003	Likely no relevant outcomes for our review as these were focusing on computerised Contiuous Performance Test and fMRI
Teicher 2006	Likely no relevant outcome for our review as this was focusing on rate-dependent behavioural effects only
Teicher 2007	Likely no relevant outcome for our review as this was focusing on McLean Motion Attention Test only
Tillery 2000	Likely no relevant outcome for our review as this was focusing on auditory performance only
Trommer 1991	Likely no relevant outcome for our review as this was focusing on Go-No-Go performance only
Tsang 2012	Likely no relevant outcomes for our review as these were focusing on cognitive tasks, and emotional functions
Tucha 2006	Likely no relevant outcome for our review as this was focusing on reaction time tasks only
Van den Driessche 2017	Likely no relevant outcome for our review as this was focusing on mind blanking during Go/No-Go Task only
Van Lith 2018	Likely no relevant outcome for our review as this was focusing on region-of-interest analysis of fMRI data during fear learning only
Verbaten 1994	Likely no relevant outcome for our review as this was focusing on Continuous Performance Test only
Waschbusch 2007	Likely no relevant outcome for our review as this was focusing on academic-oriented tasks only
Whalen 1987	Likely no relevant outcome for our review as this was focusing on social behaviour only
Wong 2012	Likely no relevant outcome for our review as this was focusing on Sternberg Working Memory fMRI Task only
Wu 2017	Likely no relevant outcome for our review as this was focusing on brain activation during verbal working memory task only
Yarmolovsky 2017	Likely no relevant outcome for our review as this was focusing on executive control test - Stroop-like task only

ADHD: attention deficit hyperactivity disorder; **fMRI:** functional magnetic resonance imaging; **fNIRS:** functional near-infrared spectroscopy; **MPH:** methylphenidate; **MRI:** magnetic resonance imaging; **n:** number; **oxy-hb:** oxygen-haemoglobin; **rsfMRI:** resting state functional magnetic resonance imaging; **STISIM Drive:** Systems Technology, Inc. Simulation Drive; **3T:** 3 Tesla

Characteristics of studies awaiting classification *[ordered by study ID]*

Drtílková 1997

Methods	2-week RCT

Drtílková 1997 *(Continued)*

Participants	118 children
Interventions	• MPH • Amphetaminil • Mesocarb • Placebo
Outcomes	
Notes	Article is written in Czech. We have not yet been able to have the article translated.

Wang 2020

Methods	No information currently available
Participants	No information currently available
Interventions	No information currently available
Outcomes	No information currently available
Notes	No access with institutional ID. Authors contacted but have yet to reply

ID: identifier; **MPH:** methylphenidate;**RCT:** randomised clinical trial

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1800014945

Study name	Public title: Effect of the intervention combining medicine and education on school-age children with attention deficit hyperactivity disorder Scientific title: as above
Methods	Randomised controlled parallel-group trial Study duration: 6 months
Participants	Sample size (target): 120 **Inclusion criteria** • Children who have been diagnosed with ADHD strictly in accordance with the DSM-5 of the American Psychiatric Society • Grades 1 to 5 • Children accompanied by their parents • Caregivers who can read Chinese and communicate • Children in the intervention group agree to receive school intervention and parental intervention • Willing to be followed up for 6 months **Exclusion criteria** • Allergic to MPH or atomoxetine hydrochloride • Epilepsy, mental disability, severe psychosis and other organic brain disease • Participation in ADHD training

ChiCTR1800014945 *(Continued)*

	• Cannot accept long-term follow-up
Interventions	• ER-MPH plus education (unspecified) • Education (unspecified)
Outcomes	**ADHD symptoms** • ADHD Scale. Timing of outcome assessment not reported **Non-serious AEs** • Parenting Stress Index Timing of outcome assessment not reported
Starting date	22 January 2018-1 January 2019
Contact information	Name: Yu Guangjun Telephone: + 86 18917762998 Email: gjyu@shchildren.com.cn
Notes	Sponsor: School of Public Health, Shanghai Jiao Tong University Declaration of interests: not reported

EUCTR2007-004664-46-NL

Study name	Public title: not reported Scientific title: Influence of methylphenidate on sleep and circadian rhythm in children with attention-deficit/hyperactivity disorder (ADHD)
Methods	Double-blind, randomised controlled, parallel-group trial Study duration: 14 months
Participants	Sample size (target): 140 **Inclusion criteria** • Aged 6-12 years • Recently diagnosed ADHD • Indication for starting with MPH treatment **Exclusion criteria:** • IQ < 80 • Treatment with stimulants, melatonin, clonidine, risperidone, benzodiazepines • Prior treatment with melatonin (> 0.1 mg) • Contraindications for using MP • Tourette's syndrome, depression; anxiety disorder, pervasive developmental disorder or psychosis
Interventions	• MPH 10 mg-30 mg • Placebo
Outcomes	**Non-serious AEs**

EUCTR2007-004664-46-NL *(Continued)*

	• Sleep latency. Timing of outcome assessment not reported • Sleep onset time. Timing of outcome assessment not reported • Total time asleep (from actigraphy). Timing of outcome assessment not reported • Difficulty falling asleep (from sleep log) and dim light melatonin onset from salivary melatonin Timing of outcome assessment not reported
Starting date	29 July 2008 (date of registration). Starting date not reported
Contact information	Not reported
Notes	Sponsor: no sponsor Declaration of interests: not reported

EUCTR2008-001291-71-DE

Study name	Public title: not reported Scientific title: Electrophysiological correlates of putative endophenotypes of attention-deficit/hyperactivity disorder (ADHD)
Methods	Single-blind, randomised controlled, parallel-group trial Study duration: 3 years
Participants	Sample size (target): 120 Inclusion criteria • Aged 10-50 years • DSM-IV criteria of ADHD must be met (during childhood and actual) **Exclusion criteria** • Significant psychiatric axis-I comorbidities (bipolar disorder, psychosis, depression, drug addiction) • Suicidal tendencies • Epilepsy • Metal parts in the head, heart pacemakers • Pregnancy • Severe medical comorbidities (cardiovascular or cerebrovascular illnesses, liver and kidney diseases hyperthyreosis) • Pre-treatment with MPH or atomoxetine • Known incompatibility of MPH or atomoxetine • Intake of MAOIs within the last 14 days prior to pharmacological challenge • Actual treatment with other psychiatric medications
Interventions	• Atomoxetine hydrochloride 10 mg • MPH 10 mg • Placebo
Outcomes	**Non-serious AEs** • Neurophysiological measures (instrument not reported)

EUCTR2008-001291-71-DE *(Continued)*

	Timing of outcome assessment not reported
Starting date	23 July 2008 (date of registration). Starting date not reported
Contact information	Not available
Notes	Sponsor: University of Wuerzburg Declaration of interest: not reported

EUCTR2008-004425-42-NL

Study name	Public title: not reported Scientific title: Neurocognitive testing in children with ADHD
Methods	Randomised controlled, double blind cross-over trial Study duration: 3 months
Participants	Sample size (target): 20 **Inclusion criteria** • Written informed consent from parents having parental responsibility or from the legal guardian (in the case of a child aged 12 years, the written informed consent of the child is needed in addition to that of parents having responsibility/legal guardian) • Aged 8-12 years • Able to communicate with the investigator in Dutch • Confirmed DSM-IV diagnosis of ADHD (based on examination by a psychiatrist or paediatrician) • Classifying as clinical ADHD on the "ADHD Vragenlijst" • Currently receiving treatment with IR-MPH or ER-MPH **Exclusion criteria** • Use of drugs other than MPH with known psychotropic effects
Interventions	• MPH • Placebo
Outcomes	**ADHD symptoms** • "ADHD Vragenlijst" **Non-serious AEs** • Cardiovascular parameters (blood pressure and heart rate) Timing of outcome assessments not reported
Starting date	15 September 2008 (date of registration). Start date not reported
Contact information	Not reported
Notes	Sponsor: Centre for Human Drug Research Decleration of interests: not reported

EUCTR2020-003660-11-NL

Study name	Public title: Methylphenidate long-term study Scientific title: Do effects of methylphenidate decline after long-term use? A double-blind, placebo-controlled cross-over study of effects of methylphenidate on cognitive functioning and real world behavior in treatment naive children compared to effects after 9 months of treatment in clinical practice
Methods	Randomized, double-blind, placebo-controlled cross-over trial Study duration: 3 years
Participants	Sample size (target): 60 **Inclusion criteria** • Children between the ages of 6 and 12, any ethnicity or cultural background • Diagnosed with ADHD as confirmed with the PICS (obtained during routine clinical assessment) • Going to start MPH as per clinical decision • No use of MPH for the past 6 months • Bodyweight of at least 20 kg • Deemed reliable and compliant with the protocol • parents (or the legal guardian) and children (12 years) have provided informed consent to participate in the study **Exclusion criteria** • Intellectual disability (based on available IQ < 70 or the clinical opinion of the investigator, taking into account relevant psychosocial information, e.g. educational level/academic achievements; or as confirmed by the IDS-2 IQ screener obtained in each participant)
Interventions	• MPH 10 mg • Placebo
Outcomes	**General behaviour** • ADHD-related behaviour (measurement scale not reported) Assessed at baseline, week 2 and week 40
Starting date	21 December 2020 (entered into trial registry). Start date not reported
Contact information	Name: Andrea Dietrich Affiliation: Accare, Lübeckweg 2, Groningen, 9723 HE, Netherlands Telephone: + 310613807225
Notes	Sponsor: Accare Declaration of interest: not reported

IRCT138804132000N2

Study name	Public title: Neurofeedback in the treatment of attention deficit hyperactivity disorder Scientific title: Effectiveness of neurofeedback versus methylphenidate in the treatment of children with attention deficit hyperactivity disorder

IRCT138804132000N2 *(Continued)*

Methods	Parallel RCT Study duration: 3 months
Participants	Sample size (target): 90 **Inclusion criteria**: • Diagnosis of ADHD based on DSM-IV criteria by child and adolescent psychiatrists • Age of 7-18 years • IQ > 85 based on WISC-III-R **Exclusion criteria**: • Major learning problems • Request of parent to exit from the study • Use of antipsychotic drugs in the month before the initiation of the study • History of neurofeedback intervention at least for 10 sessions
Interventions	• Neurofeedback • MPH (starting at 5 mg) • MPH plus neurofeedback MPH dose will be adjusted based on optimal dose by a child and adolescent psychiatrist who visits all the participants. They will be assessed 1 week before the start and each month through the study. The last assessment will be on a week after the completion of the research. The rater will be blind to the groups of participants.
Outcomes	**ADHD symptoms** • Conners. Timing of outcome assessment not reported
Starting date	22 December 2014
Contact information	Name: Dr Javad Alaghband Rad, Associate Professor, Child & Adolescent Psychiatrist Affiliation: Tehran University of Medical Sciences, Roozbeh Hospital, South Kargar Street, Tehran Telephone: + 98 21 5541 9151 Email: alaghbandrad@gmail.com
Notes	Sponsor: Behavioral Sciences Research Center, Shahid Beheshti University of Medical Sciences Declaration of interests: not reported

IRCT201701131556N94

Study name	Public title: Saffron versus methylphenidate in the treatment of attention deficit/hyperactivity disorder Scientific title: Saffron versus methylphenidate in the treatment of attention deficit/hyperactivity disorder: a double-blind and randomized trial
Methods	Parallel RCT Study duration: 6-weeks
Participants	Sample size (target): 40 **Inclusion criteria**

IRCT201701131556N94 *(Continued)*

	• 6-17 years • Clearly meeting the DSM-5 diagnostic criteria for ADHD **Exclusion criteria** • Intellectual disability • Presence of any psychiatric disorders except for ODD • History of allergy to saffron or Ritalin • Presence of any medical problem including cardiovascular diseases • Presence of uncontrolled seizures • SBP >120 mm Hg • Resting pulse rate < 60/min or > 115/min • Receiving warfarin, ASA and other antiplatelet agents • Receiving any herbal medicine including fever few, garlic, ginseng, dong quai, and red clover • 14 days before any surgery • Nursing and pregnancy
Interventions	• Saffron capsules (20 mg/d) • MPH (0.4 mg-1 mg/d) • Placebo
Outcomes	**ADHD symptoms** • Teacher and Parent ADHD-RS assessed at baseline, week 3 and six
Starting date	20 January 2017
Contact information	Name: Shahin Akhondzadeh Telephone: + 98 21 5541 2222 Email: s.akhond@sina.tums.ac.ir
Notes	Sponsor: Tehran University of Medical Sciences Declaration of interests: not reported

IRCT20190317043079N

Study name	Public title: The effect of neurofeedback/biofeedback on brain's waves amplitude and attention deficit in children with ADHD Scientific title: The effectiveness of neurofeedback and heart rate variability training on QEEG baseline and sustained attention in children with ADHD
Methods	A randomised controlled parallel single-blinded study without placebo Study duration: 12 weeks + 6 months follow-up
Participants	Sample size (target): 160 **Inclusion criteria** • 7-12 years; 2) • Definite diagnosis of attention deficit/hyperactivity disorder by a psychiatrist, based on DSM-5 diagnostic criteria, semi-structured interview and developmental history • Referred to the Psychiatric Clinic of Yahya Nejad Hospital and Private Center for Psychiatric Disorder

IRCT20190317043079N *(Continued)*

	Exclusion criteria • Identification of ADHD in children with other psychiatric and neurological disorders • Mental disability
Interventions	There are 5 interventions in this study, the 2 that can be used for this review are: • neurofeedback (2 distinct theta/beta ratio and theta/sensorimotor rhythm training neurofeedback protocols 15 min each over a 45-min period in 30 sessions/12 weeks) • neurofeedback (as described above) plus MPH twice/d
Outcomes	**ADHD symptoms** • Attention deficit and impulsivity: CPRS • Sustained attention and impulsivity: continuous performance testing Timing of outcome assessments not reported
Starting date	9 April 2021
Contact information	Name: Soheila Hosseinzadeh Afilliation: Babol University of Medical Sciences 4717647745 Babol Iran (Islamic Republic of) Telephone: +98 11 3219 9592 Email: hoseinzadeh_soheila@yahoo.com
Notes	Sponsor: Babol University of Medical Sciences Declaration of interests: not reported

Müller 2021

Study name	Public title: Methylphenidate for attention-deficit/hyperactivity disorder in patients with Smith-Magenis syndrome: protocol for a series of N-of-1 trials Scientific title: as above
Methods	Each trial will be randomised placebo-controlled and double-blind with multiple cross-overs within a single patient. The trial will consist of a baseline period, a dose titration phase and 3 cycles each consisting of 1 period of placebo treatment and 1 period of MPH treatment both followed by a 1-week washout period. Study duration: each trial will last for 14 weeks with a 3-month follow-up.
Participants	Sample size (target): 6 **Inclusion criteria** • Minimum 6 years old • A genetically confirmed diagnosis of SMS • Availability of a caregiver for proxy-reports **Exclusion criteria** • Presence of a contra-indication for MPH • Planned general anaesthesia • Pregnancy and breastfeeding • Current treatment with biologically interfering drugs • Substance or alcohol abuse

Müller 2021 *(Continued)*

	• Incapacity to swallow tablets
Interventions	• MPH • Placebo Administered twice/d in a cross-over design with a 1-week washout period.
Outcomes	**ADHD symptoms** • Hyperactivity/Inattention subscale of the Strengths and Difficulties Questionnaire. Timing of outcome assessment not reported **Numbers of serious AEs** • Serious adverse events. Timing of outcome assessment unclear **Non-serious AEs** • Side effects determined by the Side Effect Checklist. Timing of outcome assessment not reported
Starting date	Starting date not reported
Contact information	Email: a.m.vaneeghen@amsterdamumc.nl
Notes	Sponsor: the trial is financially sponsored by the Amsterdam UMC and healthcare institution's Heeren Loo. Declaration of interests: no competing interest declared This is a published protocol for a series of N-of-1 trials.

NCT00141050

Study name	Public title: Safety and efficacy study of dexmethylphenidate in children with ADHD Scientific title: as above
Methods	Randomised controlled double-blind, cross-over trial Study duration: not reported
Participants	Sample size (actual): 90 **Inclusion criteria** • DSM-IV diagnosis of ADHD • Male and female participants aged 6-12 years **Exclusion criteria** • Inability to understand or follow instructions • Is pregnant • Diagnosis of tic disorder
Interventions	• d-MPH (2 unspecified doses) • MPH (2 unspecified doses) • Placebo
Outcomes	**ADHD symptoms**

NCT00141050 *(Continued)*

	• Reduction of symptoms in attention and deportment assessed at 0.5, 1, 2, 3, 4, 6, 8, 10, 11, and 12 h post-dose **Total number of serious AEs** • Safety and tolerability. Scale/measurement methods and timing of outcome assessment not reported **General behaviour** • Parent's assessment of patient behaviour across all treatment periods as measured by change from baseline **Non-serious AEs** • Safety and tolerability. Scale/measurement methods and timing of outcome assessment not reported
Starting date	May 2005 (registration date). Starting date not reported
Contact information	Name: Matthew Brams, MD (Principal Investigator) Affiliation: Bayou City Research
Notes	Sponsor: Novartis Pharmaceuticals Declaration of interest: not reported

NCT00254878

Study name	Public title: Placebo-controlled comparison of two different brands of modified-release oral dosage forms regarding safety and efficacy in children with attention deficit hyperactivity disorder (ADHD) aged 6-14 Scientific title: A 7-week multicenter, double-blind, randomized, placebo-controlled cross-over evaluation of the efficacy and safety of two different brands of modified-release oral dosage forms of methylphenidate-hcl (20 mg, qd) in children with attention deficit hyperactivity disorder (ADHD) aged 6-14
Methods	Randomised controlled double-blind, cross-over trial Study duration: 7 weeks
Participants	Sample size: 130 (actual) **Inclusion criteria**: • Male and female patients aged 6-14 • Patients having a diagnosis of ADHD of any type according to DSM-IV criteria, as established by history, psychiatric examination and a structured diagnostic interview (K-SADS-PL) • Patients, whose symptoms are adequately controlled by a stable and well-tolerated dose of a IR-MPH equivalent of 20 mg for 1 month before screening **Exclusion criteria**: • Patients with comorbid psychiatric conditions with symptoms requiring current pharmacological treatment (e.g. major depression, psychosis) • Patients who are taking any concomitant medications likely to interfere with the study drug or confound efficacy or safety assessments (e.g. tricyclic antidepressants, bupropion, clonidine, buspirone 2 weeks before randomisation; atomoxetine 2 weeks before randomisation; fluoxetine or

NCT00254878 *(Continued)*

	antipsychotics 1 month before randomisation; pemoline and amphetamines 1 week before randomisation) • Patients with a known non-response to MPH • Other protocol-defined exclusion criteria may apply
Interventions	• MPH (Novartis) • MPH (Medice, Germany) • Placebo
Outcomes	**ADHD symptoms** • Attention (measurement scale not reported). Assessed at 1.5, 3.0 and 4.5 h after drug intake **Total numbers of serious AEs** • Safety. Measurement scale/method and timing of outcome assessment not reported **General behaviour** • Deportment (measurement scale not reported). Assessed at 1.5, 3.0 and 4.5 h after drug intake **Non-serious AEs** • Safety. Measurement scale/method and timing of outcome assessment not reported
Starting date	October 2005
Contact information	Not reported
Notes	Sponsor: Novartis Pharmaceuticals Declaration of interests: not reported

NCT00414921

Study name	Public title: Preschool supplement to clonidine in ADHD (Kiddie-CAT) Scientific title: as above
Methods	Randomised controlled parallel-group trial Study duration: 16 weeks
Participants	Sample size (actual): 30 **Inclusion criteria**: • Child with ADHD • Child aged 4-6 years • Child attending a structured preschool or daycare **Exclusion criteria** • Presence of a tic disorder of any kind or a known active heart disease for which it would be unsafe to use the study drugs • Presence of pervasive developmental disorder, autism, mental disability, or serious psychiatric illness; • Child not attending a structured preschool or daycare

NCT00414921 *(Continued)*

Interventions	• Clonidine • MPH • Clonidine plus PH • Placebo
Outcomes	**ADHD symptoms** • ASQ-T. Assessed at baseline and at 16 weeks • ASQ-P. Assessed at baseline and at 16 weeks **Quality of life** • CGAS. Assessed at baseline and at 16 weeks **Non-serious AEs** • AEs logs. Assessed at baseline and at 16 weeks • Pittsburgh Side Effects Rating Scale. Assessed at baseline and at 16 weeks • Vital signs. Assessed at baseline and at 16 weeks • ECGs. Assessed at baseline and at 16 weeks
Starting date	September 2003
Contact information	Only names of primary investigators available: Floyd Randy Sallee, MD/PhD; Oscar Bukstein, MD; Donna Palumbo, PhD; William Pelham, PhD
Notes	Sponsor: University of Cincinnati and National Institute of Neurological Disorders and Stroke (NINDS) Declaration of interests: not reported

NCT00446537

Study name	Public title: Procedural learning in participants with ADHD Scientific title: not reported
Methods	Randomised controlled cross-over trial Study duration: not reported
Participants	Sample size: not reported **Inclusion criteria** • aged 12-50 years • IQ > 85 **Exclusion criteria** • Not reported
Interventions	• MPH • Placebo
Outcomes	No outcomes reported

NCT00446537 *(Continued)*

Starting date	Not reported
Contact information	Name: Esther Adi-Japha, PhD Telephone: 972-3-5318704 Email: japhae@mail.biu.ac.il
Notes	Sponsor: Shaare Zedek Medical Center Declaration of interests: not reported

NCT00485550

Study name	Public title: Comparison of atomoxetine plus either comparator or placebo in children with ADHD who haven't responded to stimulant therapy Scientific title: A randomized, double-blind comparison of atomoxetine hydrochloride augmented with either extended-release methylphenidate Hydrochloride (Concerta-TM) or placebo in children with attention-deficit/hyperactivity disorder (ADHD) who have not responded to stimulant mono therapy
Methods	Double-blind, parallel-group trial Study duration: not reported
Participants	Sample size (actual): 14 **Inclusion criteria** • Patients at least 6 years of age and not more than 12 years of age at visit 1 • Patients meet DSM-IV diagnostic criteria for ADHD • Patients retrospectively identified as stimulant non-responders • Patients of normal intelligence as assessed by the investigator (that is, without a general impairment of intelligence and likely, in the investigator's judgment, to achieve a score of ≥ 70 on an IQ test) • Patients must be able to swallow capsules **Exclusion criteria** • Patients who weigh < 22 kg or > 60 kg at study entry • Patients who have a history of bipolar I or bipolar II disorder, psychosis, or pervasive developmental disorder • Patients who meet DSM-IV criteria for anxiety disorder or autism • Patients with a history of any seizure disorder and/or rolandic seizures (other than febrile seizures) or prior ECG abnormalities in the absence of seizures, or patients who have taken (or are currently taking) anticonvulsants for seizure control • Patients with a history of severe allergies to > 1 class of medication or multiple adverse drug reactions, including hypersensitivity to MPH
Interventions	• Atomoxetin plus placebo • Atomoxetin plus MPH
Outcomes	**ADHD symptoms** • Efficacy. Measurement scale and timing of outcome assessment not reported **Numbers of serious AEs**

NCT00485550 *(Continued)*

- Safety assessment (unspecified). Measurement scale/method and timing of outcome assessment not reported

Non-serious AEs

- ECGs. Timing of outcome assessment not reported
- Clinical laboratory tests (unspecified). Timing of outcome assessment not reported
- Spontaneous reporting. Timing of outcome assessment not reported

Starting date	January 2004
Contact information	Telephone: 1-877-CTLILLY (1-877-285-4559) or 1-317-615-4559 Monday to Friday 9 AM to 5 PM Eastern time (UTC/GMT - 5 h, EST)
Notes	Sponsor: Eli Lilly and Company Declaration of interests: not reported

NCT02807870

Study name	Public title: Early interventions in children with attention deficit/hyperactivity disorder Scientific title: Early interventions in children with attention deficit/hyperactivity disorder: randomized controlled trial comparing methylphenidate parental training in treating preschool children with attention deficit /hyperactivity disorder
Methods	Randomised, double-blind, parallel controlled trial Study duration: 8 weeks
Participants	Sample size (actual): 153 **Inclusion criteria** • Diagnosis of ADHD according to DSM-5 • Score > 32 on the SNAP-IV Scale; • Child registered in a school or day care centre • Children without the use of stimulants or any psychotropic in the last 30 days **Exclusion criteria** • Intelligence quotient < 70 • Presence of a clinical condition or history of neurological disorder or head trauma with conscience loss • Presence of affective and psychotic disorders, as well as autism spectrum disorders • Absence of a legal representative with the capacity to understand the study objectives and the instructions related to its participation
Interventions	• MPHJ plus educational information for parents • Placebo medication plus educational information for parents • Placebo medication plus parental training
Outcomes	**ADHD symptom severity** • SNAP scale. Assessed at baseline, 8 weeks (post intervention) and at follow-up 1, 2 and 3 years after the end of the intervention

NCT02807870 *(Continued)*

- CPT. Assessed at baseline, 8 weeks (post intervention) and at follow-up 1, 2 and 3 years after the end of the intervention

General behaviour

- CGI scale. Assessed at baseline, 8 weeks (post intervention) and at follow-up 1, 2 and 3 years after the end of the intervention
- Changes in disruptive behaviour symptoms (time frame: baseline, after 8 weeks (post-intervention) and follow-up 1, 2 and 3 years after the end of the intervention). The child will be assessed with the MAP-DB
- Changes in irritability symptoms (time frame: baseline and after 8 weeks (post-intervention) and follow-up 1, 2 and 3 years after the end of the intervention). The child will be assessed with the ARI scale

Quality of life

- CGAS. Assessed at baseline, 8 weeks (post-intervention) and at follow-up 1, 2 and 3 years after the end of the intervention

Starting date	June 2016
Contact information	Name: Guilherme V Polanczyk (PI) Affiliation: University of Sao Paulo Medical School
Notes	Sponsor: University of Sao Paulo, Conselho Nacional de Desenvolvimento Científico e Tecnológico Declaration of interest: not reported

Verlaet 2017

Study name	Public title: Effect of Pycnogenoll® on ADHD Scientific title: Effect of Pycnogenoll® on attention-deficit hyperactivity disorder (ADHD): study protocol for a randomised controlled trial
Methods	Randomised, double-blind, placebo- and active treatment-controlled multicentre trial, with 3 parallel treatment arms Study duration: 10 weeks
Participants	Sample size (actual): 144 **Inclusion criteria** • Patient is between 6-12 years old (both inclusive) • Patient satisfies the DSM-IV criteria for ADHD or ADD • Patient has a responsible caregiver who is able to provide information about the patient's functional status • Written informed consent is obtained from the patient and the legally accepted representative **Exclusion criteria** • Autism spectrum disorder according to DSM-IV • Situational hyperactivity, pervasive developmental disorders, schizophrenia, other psychotic disorders such as mood or anxiety disorder, personality disorder, unsocial behaviour, personality change due to a general medical condition, mental disability (IQ < 70), understimulating environments, CD, chorea and other dyskinesias, tics or Tourette's syndrome • Personal or family history of psychotic disorder, bipolar illness, depression, or suicide attempt

Verlaet 2017 *(Continued)*

	• Any chronic medical disorder (diabetes, epilepsy or other seizure disorder, autoimmune disorder, gastrointestinal disorder, renal or cardiovascular disorders, etc.) or acute inflammatory disease • Glaucoma, heart disease, heart rhythm disorder, high blood pressure, or peripheral vascular disease such as Raynaud's syndrome • Use of clonidine, guanethidine, blood thinners (e.g. warfarin or Coumadin), antidepressants (e.g. amitriptyline, citalopram, doxepin, fluoxetine, nortriptyline, paroxetine, sertraline), cold or allergy medicine at any point in the 3 months prior to entering the study • Use of MAOI (isocarboxazid, linezolid, phenelzine, rasagiline, selegiline or tranylcypromine) in the past 14 days • Any contraindication for the use of MPH • Use of vitamin/mineral/herbal/omega-3 supplements or other any medication (psychoactive medication, antibiotics, anti-inflammatory drugs, melatonin, etc.) > 1 week during the 3 months before inclusion
Interventions	• MPH • Pycnogenol • Placebo
Outcomes	**ADHD symptoms** • ADHD-RS. Assessed at baseline, week 5 and 10 • SEQ. Assessed at baseline, and week 10 **General behaviour** • Social behavior problems subscale of the SEQ. Assessed at baseline, and week 10 **Non-serious AEs** • Immunity (plasma cytokine and antibody levels, white blood cell counts and faecal microbial composition). Assessed at baseline, and week 10 • Oxidative stress (erythrocyte glutathione, plasma lipid-soluble vitamins and malondialdehyde and urinary 8-OHdG levels, as well as antioxidant enzyme activity and gene expression). Assessed at baseline, and week 10 • Serum zinc and neuropeptide Y level. Assessed at baseline, and week 10 • Urinary catecholamines. Assessed at baseline, and week 10 • Physical and sleep complaints (Physical Complaints Questionnaire). Assessed at baseline, week 5, and 10
Starting date	1 September 2017
Contact information	Name: Nina Hermans, PhD Affiliation: Department of Pharmaceutical Sciences, Laboratory of Nutrition and Functional Food Science, University of Antwerp, Belgium Email: Annelies.verlaet@uantwerpen.be
Notes	Sponsor: Fund for Scientific Research Flanders (Fonds Wetenschappelijk Onderzoek (FWO); FWO MAND 2013 - 11U8316N 5 W) Declaration of interests: no competing interests declared

ADD: attention deficit disorder; **ADHD:** attention deficit hyperactivity disorder; **AE:** adverse event; **ARI:** Affective Reactivity Index scale; **ASA:** acetylsalicylic acid; **ASQ(-T)/(-P):** Conners' Abbreviated Symptom Questionnaire (for teachers/parents); **CD:** conduct disorder; **CGAS:** Child Global Assessment Scales; **CGI:** Clinical Global Impressions; **CPRS:** Conners' Parent Rating Scale; **CPT:** Continuous Performance Test; **d-MPH:** dexmethylphenidate; **DSM(-IV/-5):** *Diagnostic and Statistical Manual of Mental Disorders (-Fourth Edition/Fifth Edition);* **ECG:** electroencephalogram; **ER-MPH:** extended-release methylphenidate; **EST:** Eastern Standard Time; **GMT:** Greenwich Mean Time; **IDS-2:** Intelligence and Development 2nd Version; **IR-MPH:** immediate-release methylphenidate; **IQ:** intelligence quotient; **K-SADS-PL:** Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime version; **MAOI:** monoamine oxidase

inhibitor; **MAP-DB:** Multidimensional Assessment Profile of Disruptive Behavior; **MPH:** methylphenidate; **ODD:** oppositional defiant disorder; **PI:** principal investigator
PICS: Parent Interview for Child Symptoms; **QEEG:** quantitative electroencephalography; **RCT:** randomised controlled trial; **SBP:** systolic blood pressure; **SEQ:** Social-Emotional Questionnaire; **SMS:** Smith - Magenis Syndrome; **SNAP(-IV):** Swanson, Nolan and Pelham scale (Fourth Edition); **UMC:** University Medical Centre; **UTC:** Universal Time Coordinated; **WISC-III-R:** Wechsler Intelligence Scale for Children; **8-OHdG:** 8-hydroxy-2'-deoxyguanosine

DATA AND ANALYSES

Comparison 1. Teacher-rated ADHD symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All parallel-group trials and first-period cross-over trials	21	1728	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-0.88, -0.61]
1.1.1 Low risk of bias	3	206	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.11, -0.22]
1.1.2 High risk of bias	18	1522	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.90, -0.61]
1.2 Subgroup analysis: types of scales	20		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 Conners' Teacher Rating Scale (CTRS)	9	470	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.82, -0.45]
1.2.2 Abbreviated Conners' Rating Scale (ACRS) - Teacher	2	105	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.79, 0.29]
1.2.3 Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher)	1	59	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.79, 0.23]
1.2.4 IOWA Conners' Teacher Rating Scale (IOWA CTRS) - hyperactivity	2	193	Std. Mean Difference (IV, Random, 95% CI)	-1.08 [-1.39, -0.77]
1.2.5 The Swanson, Nolan, and Pelham (SNAP) Scale - Teacher	2	328	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-0.96, -0.25]
1.2.6 Teacher ratings of attention	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.45, 0.35]
1.2.7 Teacher ratings of impulsivity	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.83, 0.92]
1.2.8 IOWA Conners' Teacher Rating Scale - Inattention/Overactivity (IOWA-I/O)	2	197	Std. Mean Difference (IV, Random, 95% CI)	-1.03 [-1.36, -0.69]
1.2.9 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)	1	85	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-1.52, -0.61]

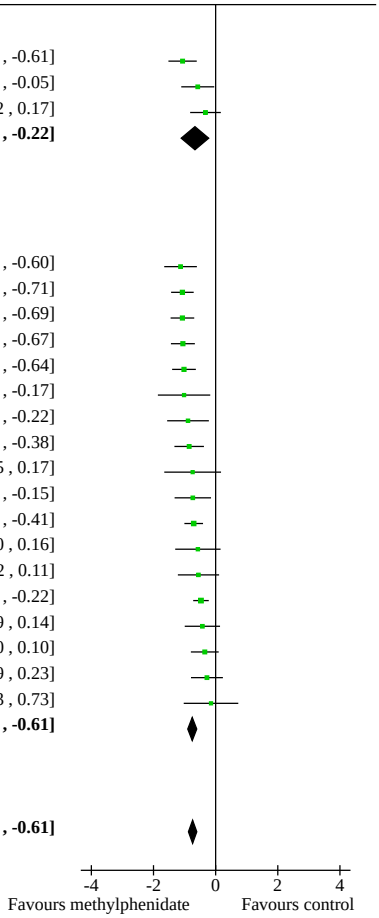
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.10 Conners' ADHD/DSM-IV Scales - Teacher (CADS-T)	2	254	Std. Mean Difference (IV, Random, 95% CI)	-1.05 [-1.31, -0.78]
1.2.11 Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale	1	64	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.82, 0.17]
1.3 Subgroup analysis: duration of treatment	21	1728	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-0.88, -0.61]
1.3.1 Short term (up to 6 months)	20	1475	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-0.91, -0.64]
1.3.2 Long term (over 6 months)	1	253	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.72, -0.22]
1.4 Subgroup analysis: dose	21		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Low dose	7	361	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.82, -0.39]
1.4.2 High dose	8	766	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.00, -0.50]
1.4.3 Unknown dose	8	753	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-1.02, -0.68]
1.5 Subgroup analysis: medication status - medication naive versus not medication naive	11	882	Std. Mean Difference (IV, Random, 95% CI)	-0.76 [-0.94, -0.59]
1.5.1 Medication naive	7	480	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-0.88, -0.51]
1.5.2 Not medication naive	4	402	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-1.20, -0.50]
1.6 Subgroup analysis: trials with enrichment design compared with trials without enrichment design	20	1679	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.89, -0.62]
1.6.1 Trials with enrichment design of all participants	8	1072	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-0.96, -0.53]
1.6.2 Trials without enrichment design of all participants	12	607	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-0.96, -0.60]
1.7 Subgroup analysis: parallel-group trials compared with first-period cross-over trials	21	1728	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-0.88, -0.61]
1.7.1 Parallel-group trials	19	1633	Std. Mean Difference (IV, Random, 95% CI)	-0.76 [-0.90, -0.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 First-period cross-over trials	2	95	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.98, -0.15]
1.8 Subgroup analysis: vested interest	18	1460	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-0.90, -0.58]
1.8.1 Low risk of vested interest	4	186	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-0.79, -0.20]
1.8.2 High risk of vested interest	14	1274	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-0.96, -0.60]
1.9 Subgroup analysis: type of control group	21	1728	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-0.88, -0.61]
1.9.1 Placebo control group	17	1358	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-0.92, -0.63]
1.9.2 No-intervention control group	4	370	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.99, -0.24]
1.10 Cross-over trial (endpoint data)	64	6341	Std. Mean Difference (IV, Random, 95% CI)	-0.88 [-1.01, -0.75]
1.10.1 Low risk of bias	7	733	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.84, -0.40]
1.10.2 High risk of bias	57	5608	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.06, -0.77]
1.11 Subgroup analysis: cross-over trials (endpoint data): dose	58	7403	Std. Mean Difference (IV, Random, 95% CI)	-0.82 [-0.93, -0.71]
1.11.1 Low dose	43	4530	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-0.86, -0.59]
1.11.2 High dose	31	2873	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.15, -0.77]
1.12 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)	81	7564	Std. Mean Difference (IV, Fixed, 95% CI)	-0.82 [-0.87, -0.77]
1.12.1 All parallel-group trials and first-period cross-over trials	21	1728	Std. Mean Difference (IV, Fixed, 95% CI)	-0.74 [-0.84, -0.64]
1.12.2 Cross-over trials (endpoint data)	60	5836	Std. Mean Difference (IV, Fixed, 95% CI)	-0.85 [-0.90, -0.79]
1.13 All parallel-group trials and cross-over trials: risk of bias	81	7564	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-0.96, -0.74]
1.13.1 Low risk of bias	8	518	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-0.91, -0.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.13.2 High risk of bias	73	7046	Std. Mean Difference (IV, Random, 95% CI)	-0.87 [-0.99, -0.75]
1.14 All parallel-group trials and cross-over trials: vested interest	77	7212	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-0.96, -0.73]
1.14.1 Low risk of vested interest	23	1446	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.08, -0.58]
1.14.2 High risk of vested interest	54	5766	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-0.98, -0.72]

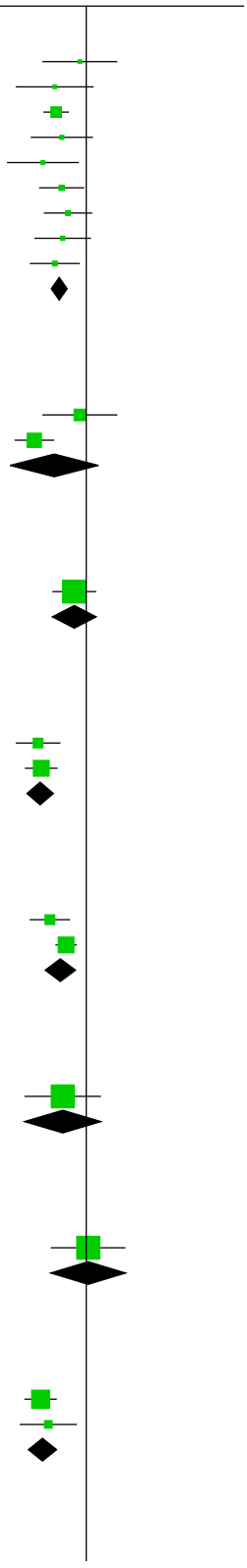
Analysis 1.1. Comparison 1: Teacher-rated ADHD symptoms, Outcome 1: All parallel-group trials and first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Low risk of bias								
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	5.3%	-1.06 [-1.52 , -0.61]
Moshe 2012	58	10.3	28	64.7	12.5	29	4.3%	-0.58 [-1.11 , -0.05]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	4.8%	-0.33 [-0.82 , 0.17]
Subtotal (95% CI)			**103**			**103**	**14.4%**	**-0.67 [-1.11 , -0.22]**
Heterogeneity: Tau² = 0.09; Chi² = 4.84, df = 2 (P = 0.09); I² = 59%								
Test for overall effect: Z = 2.95 (P = 0.003)								
1.1.2 High risk of bias								
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	4.4%	-1.13 [-1.65 , -0.60]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	6.8%	-1.07 [-1.43 , -0.71]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	6.5%	-1.07 [-1.45 , -0.69]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	6.4%	-1.05 [-1.44 , -0.67]
Childress 2009	16.4	13.44	57	30	13.1	63	6.5%	-1.02 [-1.40 , -0.64]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	2.1%	-1.02 [-1.86 , -0.17]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	3.1%	-0.89 [-1.56 , -0.22]
Arnold 2004	0.7	0.7	35	1.4	0.9	40	5.0%	-0.85 [-1.33 , -0.38]
Butter 1983	30.47	17.3	10	42.7	14.2	10	1.9%	-0.74 [-1.65 , 0.17]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	3.8%	-0.73 [-1.32 , -0.15]
Findling 2008	18.3	17.44	94	31.6	20.07	88	8.1%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	2.7%	-0.57 [-1.30 , 0.16]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	3.1%	-0.55 [-1.22 , 0.11]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	9.2%	-0.47 [-0.72 , -0.22]
Tannock 2018	62	13.6	23	67.9	13.6	26	4.0%	-0.43 [-0.99 , 0.14]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	5.4%	-0.35 [-0.80 , 0.10]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	4.6%	-0.28 [-0.79 , 0.23]
Brown 1985	15.1	4.6	10	15.7	2.9	10	2.0%	-0.15 [-1.03 , 0.73]
Subtotal (95% CI)			**823**			**699**	**85.6%**	**-0.75 [-0.90 , -0.61]**
Heterogeneity: Tau² = 0.03; Chi² = 27.45, df = 17 (P = 0.05); I² = 38%								
Test for overall effect: Z = 10.22 (P < 0.00001)								
Total (95% CI)			**926**			**802**	**100.0%**	**-0.74 [-0.88 , -0.61]**
Heterogeneity: Tau² = 0.03; Chi² = 32.46, df = 20 (P = 0.04); I² = 38%								
Test for overall effect: Z = 10.82 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.71), I² = 0%								



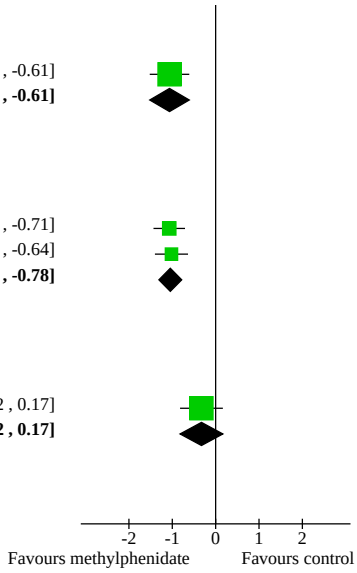
Analysis 1.2. Comparison 1: Teacher-rated ADHD symptoms, Outcome 2: Subgroup analysis: types of scales

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Conners' Teacher Rating Scale (CTRS)								
Brown 1985	15.1	4.6	10	15.7	2.9	10	4.5%	-0.15 [-1.03 , 0.73]
Butter 1983	30.47	17.3	10	42.7	14.2	10	4.2%	-0.74 [-1.65 , 0.17]
Findling 2008	18.3	17.44	94	31.6	20.07	88	38.7%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	6.5%	-0.57 [-1.30 , 0.16]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	4.9%	-1.02 [-1.86 , -0.17]
Moshe 2012	58	10.3	28	64.7	12.5	29	12.4%	-0.58 [-1.11 , -0.05]
Tannock 2018	62	13.6	23	67.9	13.6	26	10.8%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	7.9%	-0.55 [-1.22 , 0.11]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	10.1%	-0.73 [-1.32 , -0.15]
Subtotal (95% CI)			**235**			**235**	**100.0%**	**-0.63 [-0.82 , -0.45]**
Heterogeneity: Tau² = 0.00; Chi² = 2.99, df = 8 (P = 0.93); I² = 0%								
Test for overall effect: Z = 6.66 (P < 0.00001)								
1.2.2 Abbreviated Conners' Rating Scale (ACRS) - Teacher								
Brown 1985	15.1	4.6	10	15.7	2.9	10	43.6%	-0.15 [-1.03 , 0.73]
Lehmkuhl 2002	7	6.5574	43	15	6.4807	42	56.4%	-1.22 [-1.68 , -0.75]
Subtotal (95% CI)			**53**			**52**	**100.0%**	**-0.75 [-1.79 , 0.29]**
Heterogeneity: Tau² = 0.44; Chi² = 4.43, df = 1 (P = 0.04); I² = 77%								
Test for overall effect: Z = 1.42 (P = 0.16)								
1.2.3 Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher)								
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	100.0%	-0.28 [-0.79 , 0.23]
Subtotal (95% CI)			**29**			**30**	**100.0%**	**-0.28 [-0.79 , 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.28)								
1.2.4 IOWA Conners' Teacher Rating Scale (IOWA CTRS) - hyperactivity								
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	35.0%	-1.13 [-1.65 , -0.60]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	65.0%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**118**			**75**	**100.0%**	**-1.08 [-1.39 , -0.77]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 6.82 (P < 0.00001)								
1.2.5 The Swanson, Nolan, and Pelham (SNAP) Scale - Teacher								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	35.3%	-0.85 [-1.33 , -0.38]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	64.7%	-0.47 [-0.72 , -0.22]
Subtotal (95% CI)			**169**			**159**	**100.0%**	**-0.61 [-0.96 , -0.25]**
Heterogeneity: Tau² = 0.03; Chi² = 1.92, df = 1 (P = 0.17); I² = 48%								
Test for overall effect: Z = 3.34 (P = 0.0008)								
1.2.6 Teacher ratings of attention								
Brown 1985	46.6	7.5	10	51.4	9.1	10	100.0%	-0.55 [-1.45 , 0.35]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**-0.55 [-1.45 , 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.20 (P = 0.23)								
1.2.7 Teacher ratings of impulsivity								
Brown 1985	61.6	8.1	10	61.2	9	10	100.0%	0.04 [-0.83 , 0.92]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**0.04 [-0.83 , 0.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.2.8 IOWA Conners' Teacher Rating Scale - Inattention/Overactivity (IOWA-I/O)								
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	75.7%	-1.07 [-1.45 , -0.69]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	24.3%	-0.89 [-1.56 , -0.22]
Subtotal (95% CI)			**140**			**57**	**100.0%**	**-1.03 [-1.36 , -0.69]**
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%								
Test for overall effect: Z = 6.08 (P < 0.00001)								
1.2.9 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)								



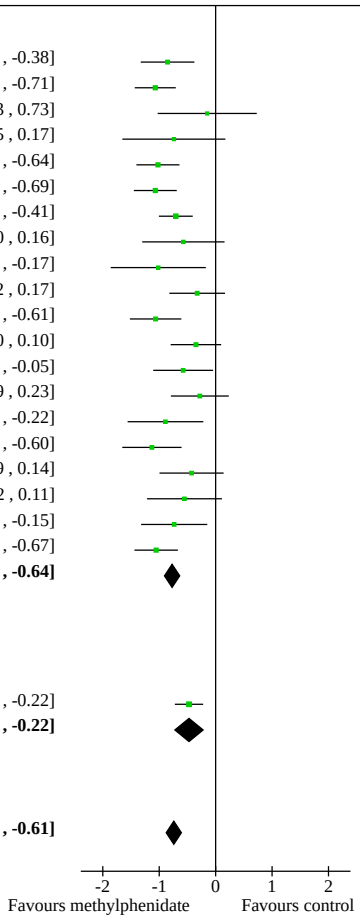
Analysis 1.2. (Continued)

1.2.9 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)								
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	100.0%	-1.06 [-1.52 , -0.61]
Subtotal (95% CI)			**43**			**42**	**100.0%**	**-1.06 [-1.52 , -0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.58 (P < 0.00001)								
1.2.10 Conners' ADHD/DSM-IV Scales - Teacher (CADS-T)								
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	52.4%	-1.07 [-1.43 , -0.71]
Childress 2009	16.4	13.44	57	30	13.1	63	47.6%	-1.02 [-1.40 , -0.64]
Subtotal (95% CI)			**120**			**134**	**100.0%**	**-1.05 [-1.31 , -0.78]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%								
Test for overall effect: Z = 7.79 (P < 0.00001)								
1.2.11 Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale								
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	100.0%	-0.33 [-0.82 , 0.17]
Subtotal (95% CI)			**32**			**32**	**100.0%**	**-0.33 [-0.82 , 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
Test for subgroup differences: Chi² = 0.00, df = 10 (P < 0.00001), I² = 0%								



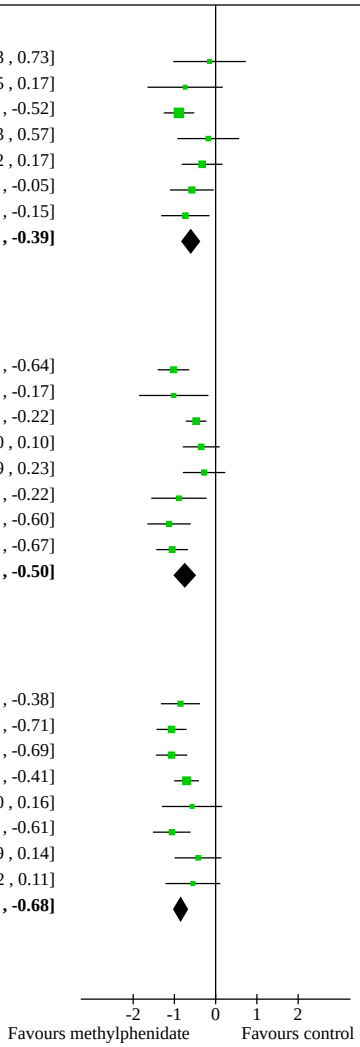
Analysis 1.3. Comparison 1: Teacher-rated ADHD symptoms, Outcome 3: Subgroup analysis: duration of treatment

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 Short term (up to 6 months)								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	5.0%	-0.85 [-1.33 , -0.38]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	6.8%	-1.07 [-1.43 , -0.71]
Brown 1985	15.1	4.6	10	15.7	2.9	10	2.0%	-0.15 [-1.03 , 0.73]
Butter 1983	30.47	17.3	10	42.7	14.2	10	1.9%	-0.74 [-1.65 , 0.17]
Childress 2009	16.4	13.44	57	30	13.01	63	6.5%	-1.02 [-1.40 , -0.64]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	6.5%	-1.07 [-1.45 , -0.69]
Findling 2008	18.3	17.44	94	31.6	20.07	88	8.1%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	2.7%	-0.57 [-1.30 , 0.16]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	2.1%	-1.02 [-1.86 , -0.17]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	4.8%	-0.33 [-0.82 , 0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	5.3%	-1.06 [-1.52 , -0.61]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	5.4%	-0.35 [-0.80 , 0.10]
Moshe 2012	58	10.3	28	64.7	12.5	29	4.4%	-0.58 [-1.11 , -0.05]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	4.6%	-0.28 [-0.79 , 0.23]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	3.1%	-0.89 [-1.56 , -0.22]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	4.4%	-1.13 [-1.65 , -0.60]
Tannock 2018	62	13.6	23	67.9	13.6	26	4.0%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	3.1%	-0.55 [-1.22 , 0.11]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	3.8%	-0.73 [-1.32 , -0.15]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	6.4%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**792**			**683**	**90.8%**	**-0.77 [-0.91 , -0.64]**
Heterogeneity: Tau² = 0.03; Chi² = 27.33, df = 19 (P = 0.10); I² = 30%								
Test for overall effect: Z = 11.20 (P < 0.00001)								
1.3.2 Long term (over 6 months)								
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	9.2%	-0.47 [-0.72 , -0.22]
Subtotal (95% CI)			**134**			**119**	**9.2%**	**-0.47 [-0.72 , -0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.70 (P = 0.0002)								
Total (95% CI)			**926**			**802**	**100.0%**	**-0.74 [-0.88 , -0.61]**
Heterogeneity: Tau² = 0.03; Chi² = 32.51, df = 20 (P = 0.04); I² = 38%								
Test for overall effect: Z = 10.81 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.26, df = 1 (P = 0.04), I² = 76.5%								



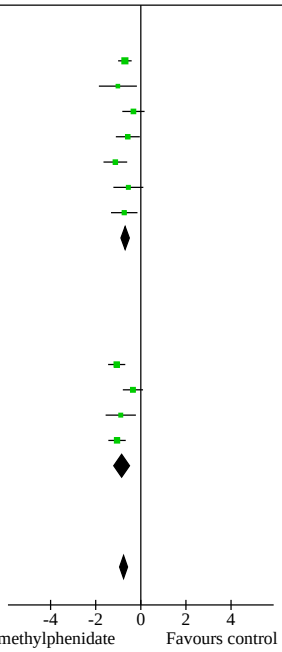
Analysis 1.4. Comparison 1: Teacher-rated ADHD symptoms, Outcome 4: Subgroup analysis: dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Low dose								
Brown 1985	15.1	4.6	10	15.7	2.9	10	5.9%	-0.15 [-1.03 , 0.73]
Butter 1983	30.47	17.3	10	42.7	14.2	10	5.5%	-0.74 [-1.65 , 0.17]
Childress 2009	18.3	13.12	61	30	13.01	63	32.7%	-0.89 [-1.26 , -0.52]
Ialongo 1994	13.87	7.71	16	15.25	7.27	12	8.1%	-0.18 [-0.93 , 0.57]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	18.6%	-0.33 [-0.82 , 0.17]
Moshe 2012	58	10.3	28	64.7	12.5	29	16.1%	-0.58 [-1.11 , -0.05]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	13.2%	-0.73 [-1.32 , -0.15]
Subtotal (95% CI)			**181**			**180**	**100.0%**	**-0.60 [-0.82 , -0.39]**
Heterogeneity: Tau² = 0.00; Chi² = 6.07, df = 6 (P = 0.42); I² = 1%								
Test for overall effect: Z = 5.54 (P < 0.00001)								
1.4.2 High dose								
Childress 2009	16.4	13.44	57	30	13.01	63	14.9%	-1.02 [-1.40 , -0.64]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	6.5%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	18.5%	-0.47 [-0.72 , -0.22]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	13.3%	-0.35 [-0.80 , 0.10]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	11.7%	-0.28 [-0.79 , 0.23]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	8.8%	-0.89 [-1.56 , -0.22]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	11.5%	-1.13 [-1.65 , -0.60]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	14.8%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**411**			**355**	**100.0%**	**-0.75 [-1.00 , -0.50]**
Heterogeneity: Tau² = 0.07; Chi² = 17.51, df = 7 (P = 0.01); I² = 60%								
Test for overall effect: Z = 5.78 (P < 0.00001)								
1.4.3 Unknown dose								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	11.1%	-0.85 [-1.33 , -0.38]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	17.7%	-1.07 [-1.43 , -0.71]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	16.3%	-1.07 [-1.45 , -0.69]
Findling 2008	18.3	17.44	94	31.6	20.07	88	24.1%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	5.0%	-0.57 [-1.30 , 0.16]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	11.9%	-1.06 [-1.52 , -0.61]
Tannock 2018	62	13.6	23	67.9	13.6	26	8.0%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	6.0%	-0.55 [-1.22 , 0.11]
Subtotal (95% CI)			**411**			**342**	**100.0%**	**-0.85 [-1.02 , -0.68]**
Heterogeneity: Tau² = 0.01; Chi² = 7.88, df = 7 (P = 0.34); I² = 11%								
Test for overall effect: Z = 10.01 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%								



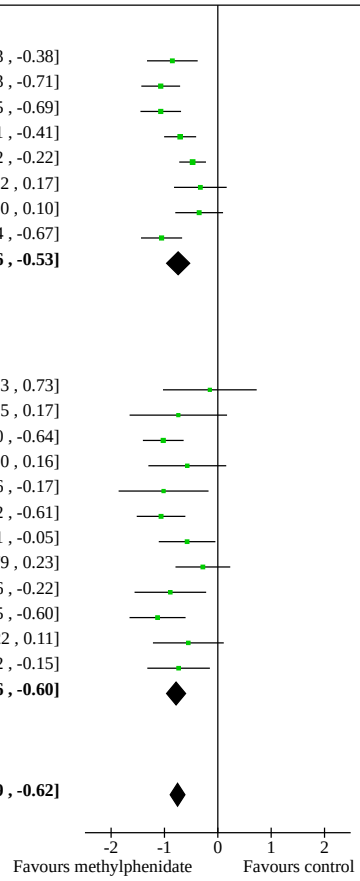
Analysis 1.5. Comparison 1: Teacher-rated ADHD symptoms, Outcome 5: Subgroup analysis: medication status - medication naive versus not medication naive

Study or Subgroup	Favours methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Medication naive								
Findling 2008	18.3	17.44	94	31.6	20.07	88	16.5%	-0.71 [-1.01 , -0.41]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	3.8%	-1.02 [-1.86 , -0.17]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	9.1%	-0.33 [-0.82 , 0.17]
Moshe 2012	58	10.3	28	64.7	12.5	29	8.2%	-0.58 [-1.11 , -0.05]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	8.3%	-1.13 [-1.65 , -0.60]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	5.8%	-0.55 [-1.22 , 0.11]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	7.0%	-0.73 [-1.32 , -0.15]
Subtotal (95% CI)			**243**			**237**	**58.6%**	**-0.70 [-0.88 , -0.51]**
Heterogeneity: Tau² = 0.00; Chi² = 5.72, df = 6 (P = 0.46); I² = 0%								
Test for overall effect: Z = 7.34 (P < 0.00001)								
1.5.2 Not medication naive								
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	12.8%	-1.07 [-1.45 , -0.69]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	10.4%	-0.35 [-0.80 , 0.10]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	5.7%	-0.89 [-1.56 , -0.22]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	12.6%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**261**			**141**	**41.4%**	**-0.85 [-1.20 , -0.50]**
Heterogeneity: Tau² = 0.07; Chi² = 7.13, df = 3 (P = 0.07); I² = 58%								
Test for overall effect: Z = 4.78 (P < 0.00001)								
Total (95% CI)			**504**			**378**	**100.0%**	**-0.76 [-0.94 , -0.59]**
Heterogeneity: Tau² = 0.03; Chi² = 14.32, df = 10 (P = 0.16); I² = 30%								
Test for overall effect: Z = 8.50 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%								



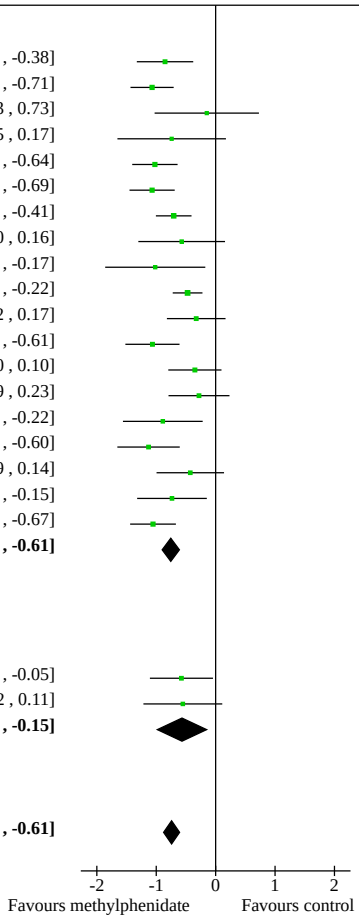
Analysis 1.6. Comparison 1: Teacher-rated ADHD symptoms, Outcome 6: Subgroup analysis: trials with enrichment design compared with trials without enrichment design

Study or Subgroup	Favours methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 Trials with enrichment design of all participants								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	5.2%	-0.85 [-1.33 , -0.38]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	7.1%	-1.07 [-1.43 , -0.71]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	6.7%	-1.07 [-1.45 , -0.69]
Findling 2008	18.3	17.44	94	31.6	20.07	88	8.4%	-0.71 [-1.01 , -0.41]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	9.5%	-0.47 [-0.72 , -0.22]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	5.0%	-0.33 [-0.82 , 0.17]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	5.6%	-0.35 [-0.80 , 0.10]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	6.7%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**599**			**473**	**54.3%**	**-0.74 [-0.96 , -0.53]**
Heterogeneity: Tau² = 0.06; Chi² = 18.83, df = 7 (P = 0.009); I² = 63%								
Test for overall effect: Z = 6.75 (P < 0.00001)								
1.6.2 Trials without enrichment design of all participants								
Brown 1985	15.1	4.6	10	15.7	2.9	10	2.1%	-0.15 [-1.03 , 0.73]
Butter 1983	30.47	17.3	10	42.7	14.2	10	2.0%	-0.74 [-1.65 , 0.17]
Childress 2009	16.4	13.44	57	30	13.01	63	6.7%	-1.02 [-1.40 , -0.64]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	2.8%	-0.57 [-1.30 , 0.16]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	2.2%	-1.02 [-1.86 , -0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	5.5%	-1.06 [-1.52 , -0.61]
Moshe 2012	58	10.3	28	64.7	12.5	29	4.5%	-0.58 [-1.11 , -0.05]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	4.7%	-0.28 [-0.79 , 0.23]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	3.2%	-0.89 [-1.56 , -0.22]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	4.6%	-1.13 [-1.65 , -0.60]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	3.3%	-0.55 [-1.22 , 0.11]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	4.0%	-0.73 [-1.32 , -0.15]
Subtotal (95% CI)			**304**			**303**	**45.7%**	**-0.78 [-0.96 , -0.60]**
Heterogeneity: Tau² = 0.01; Chi² = 12.12, df = 11 (P = 0.35); I² = 9%								
Test for overall effect: Z = 8.63 (P < 0.00001)								
Total (95% CI)			**903**			**776**	**100.0%**	**-0.75 [-0.89 , -0.62]**
Heterogeneity: Tau² = 0.04; Chi² = 31.31, df = 19 (P = 0.04); I² = 39%								
Test for overall effect: Z = 10.73 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%								



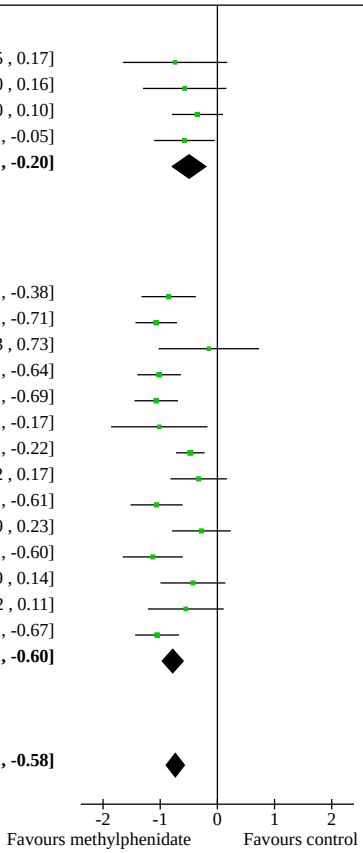
Analysis 1.7. Comparison 1: Teacher-rated ADHD symptoms, Outcome 7: Subgroup analysis: parallel-group trials compared with first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.7.1 Parallel-group trials								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	5.0%	-0.85 [-1.33 , -0.38]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	6.8%	-1.07 [-1.43 , -0.71]
Brown 1985	15.1	4.6	10	15.7	2.9	10	2.0%	-0.15 [-1.03 , 0.73]
Butter 1983	30.47	17.3	10	42.7	14.2	10	1.9%	-0.74 [-1.65 , 0.17]
Childress 2009	16.4	13.44	57	30	13.01	63	6.5%	-1.02 [-1.40 , -0.64]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	6.5%	-1.07 [-1.45 , -0.69]
Findling 2008	18.3	17.44	94	31.6	20.07	88	8.1%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	2.7%	-0.57 [-1.30 , 0.16]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	2.1%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	9.2%	-0.47 [-0.72 , -0.22]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	4.8%	-0.33 [-0.82 , 0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	5.3%	-1.06 [-1.52 , -0.61]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	5.4%	-0.35 [-0.80 , 0.10]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	4.6%	-0.28 [-0.79 , 0.23]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	3.1%	-0.89 [-1.56 , -0.22]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	4.4%	-1.13 [-1.65 , -0.60]
Tannock 2018	62	13.6	23	67.9	13.6	26	4.0%	-0.43 [-0.99 , 0.14]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	3.8%	-0.73 [-1.32 , -0.15]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	6.4%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**883**			**750**	**92.5%**	**-0.76 [-0.90 , -0.61]**
Heterogeneity: Tau² = 0.04; Chi² = 31.80, df = 18 (P = 0.02); I² = 43%								
Test for overall effect: Z = 10.21 (P < 0.00001)								
1.7.2 First-period cross-over trials								
Moshe 2012	58	10.3	28	64.7	12.5	29	4.4%	-0.58 [-1.11 , -0.05]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	3.1%	-0.55 [-1.22 , 0.11]
Subtotal (95% CI)			**43**			**52**	**7.5%**	**-0.57 [-0.98 , -0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Total (95% CI)			**926**			**802**	**100.0%**	**-0.74 [-0.88 , -0.61]**
Heterogeneity: Tau² = 0.03; Chi² = 32.51, df = 20 (P = 0.04); I² = 38%								
Test for overall effect: Z = 10.81 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.71, df = 1 (P = 0.40), I² = 0%								

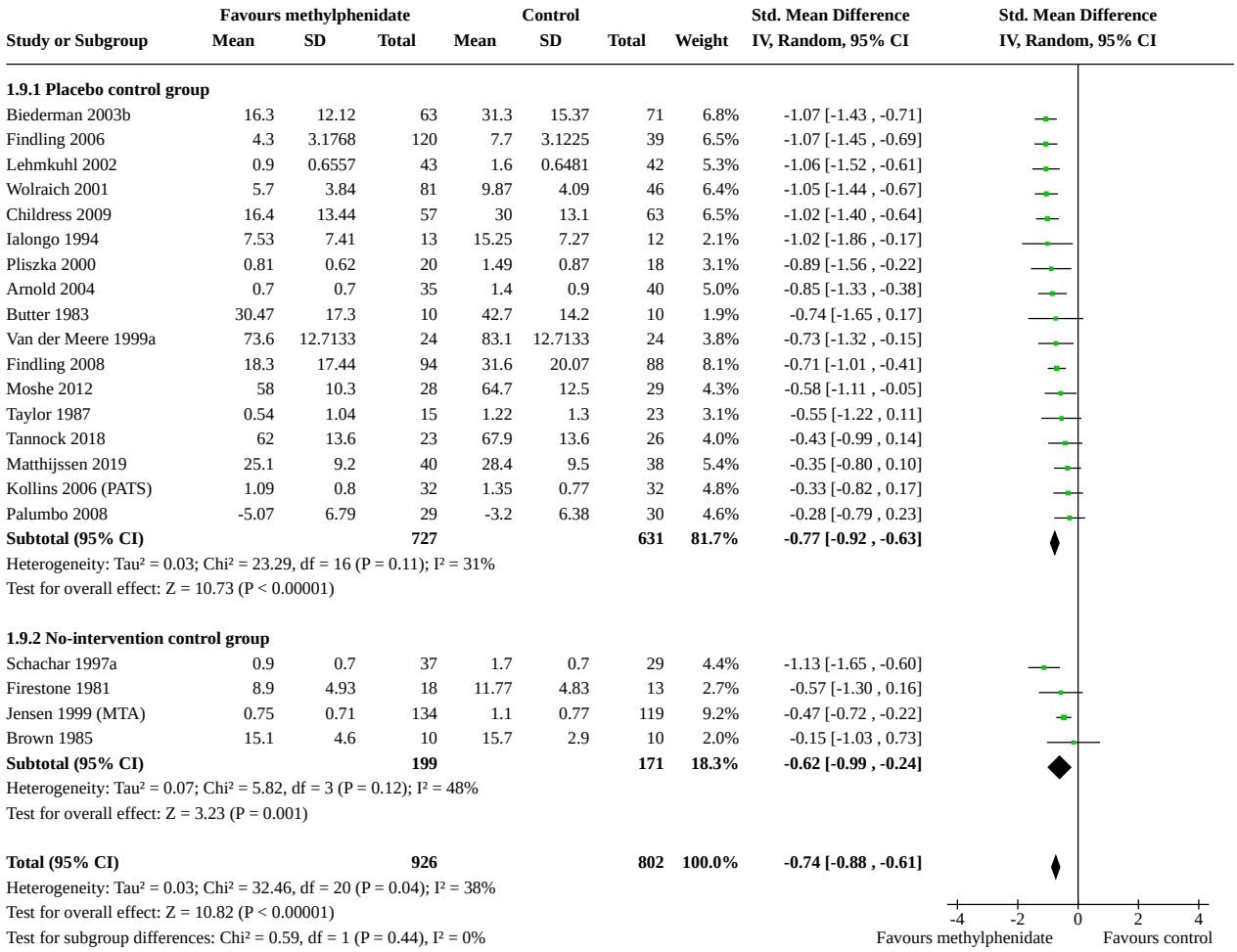


Analysis 1.8. Comparison 1: Teacher-rated ADHD symptoms, Outcome 8: Subgroup analysis: vested interest

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.8.1 Low risk of vested interest								
Butter 1983	30.47	17.3	10	42.7	14.2	10	2.4%	-0.74 [-1.65 , 0.17]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	3.5%	-0.57 [-1.30 , 0.16]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	6.4%	-0.35 [-0.80 , 0.10]
Moshe 2012	58	10.3	28	64.7	12.5	29	5.3%	-0.58 [-1.11 , -0.05]
Subtotal (95% CI)			**96**			**90**	**17.5%**	**-0.49 [-0.79 , -0.20]**
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 3 (P = 0.85); I² = 0%								
Test for overall effect: Z = 3.31 (P = 0.0009)								
1.8.2 High risk of vested interest								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	6.0%	-0.85 [-1.33 , -0.38]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	7.7%	-1.07 [-1.43 , -0.71]
Brown 1985	15.1	4.6	10	15.7	2.9	10	2.6%	-0.15 [-1.03 , 0.73]
Childress 2009	16.4	13.44	57	30	13.1	63	7.4%	-1.02 [-1.40 , -0.64]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	7.4%	-1.07 [-1.45 , -0.69]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	2.8%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	9.7%	-0.47 [-0.72 , -0.22]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	5.7%	-0.33 [-0.82 , 0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	6.2%	-1.06 [-1.52 , -0.61]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	5.5%	-0.28 [-0.79 , 0.23]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	5.3%	-1.13 [-1.65 , -0.60]
Tannock 2018	62	13.6	23	67.9	13.6	26	4.9%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	4.0%	-0.55 [-1.22 , 0.11]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	7.3%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**692**			**582**	**82.5%**	**-0.78 [-0.96 , -0.60]**
Heterogeneity: Tau² = 0.06; Chi² = 28.31, df = 13 (P = 0.008); I² = 54%								
Test for overall effect: Z = 8.36 (P < 0.00001)								
Total (95% CI)			**788**			**672**	**100.0%**	**-0.74 [-0.90 , -0.58]**
Heterogeneity: Tau² = 0.05; Chi² = 32.22, df = 17 (P = 0.01); I² = 47%								
Test for overall effect: Z = 9.09 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.64, df = 1 (P = 0.10), I² = 62.1%								



Analysis 1.9. Comparison 1: Teacher-rated ADHD symptoms, Outcome 9: Subgroup analysis: type of control group



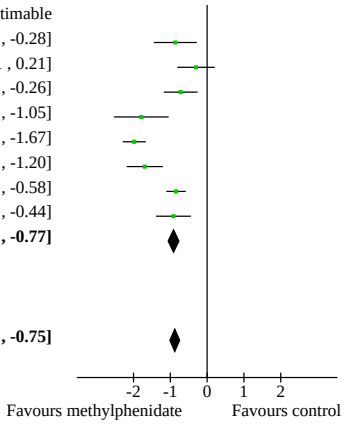
Study or Subgroup	Favours methylphenidate Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.9.1 Placebo control group								
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	6.8%	-1.07 [-1.43 , -0.71]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	6.5%	-1.07 [-1.45 , -0.69]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	5.3%	-1.06 [-1.52 , -0.61]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	6.4%	-1.05 [-1.44 , -0.67]
Childress 2009	16.4	13.44	57	30	13.1	63	6.5%	-1.02 [-1.40 , -0.64]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	2.1%	-1.02 [-1.86 , -0.17]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	3.1%	-0.89 [-1.56 , -0.22]
Arnold 2004	0.7	0.7	35	1.4	0.9	40	5.0%	-0.85 [-1.33 , -0.38]
Butter 1983	30.47	17.3	10	42.7	14.2	10	1.9%	-0.74 [-1.65 , 0.17]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	3.8%	-0.73 [-1.32 , -0.15]
Findling 2008	18.3	17.44	94	31.6	20.07	88	8.1%	-0.71 [-1.01 , -0.41]
Moshe 2012	58	10.3	28	64.7	12.5	29	4.3%	-0.58 [-1.11 , -0.05]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	3.1%	-0.55 [-1.22 , 0.11]
Tannock 2018	62	13.6	23	67.9	13.6	26	4.0%	-0.43 [-0.99 , 0.14]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	5.4%	-0.35 [-0.80 , 0.10]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	4.8%	-0.33 [-0.82 , 0.17]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	4.6%	-0.28 [-0.79 , 0.23]
Subtotal (95% CI)			**727**			**631**	**81.7%**	**-0.77 [-0.92 , -0.63]**
Heterogeneity: Tau² = 0.03; Chi² = 23.29, df = 16 (P = 0.11); I² = 31%								
Test for overall effect: Z = 10.73 (P < 0.00001)								
1.9.2 No-intervention control group								
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	4.4%	-1.13 [-1.65 , -0.60]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	2.7%	-0.57 [-1.30 , 0.16]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	9.2%	-0.47 [-0.72 , -0.22]
Brown 1985	15.1	4.6	10	15.7	2.9	10	2.0%	-0.15 [-1.03 , 0.73]
Subtotal (95% CI)			**199**			**171**	**18.3%**	**-0.62 [-0.99 , -0.24]**
Heterogeneity: Tau² = 0.07; Chi² = 5.82, df = 3 (P = 0.12); I² = 48%								
Test for overall effect: Z = 3.23 (P = 0.001)								
Total (95% CI)			**926**			**802**	**100.0%**	**-0.74 [-0.88 , -0.61]**
Heterogeneity: Tau² = 0.03; Chi² = 32.46, df = 20 (P = 0.04); I² = 38%								
Test for overall effect: Z = 10.82 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%								

Analysis 1.10. Comparison 1: Teacher-rated ADHD symptoms, Outcome 10: Cross-over trial (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.10.1 Low risk of bias								
Cook 1993	0.6	0.137	15	0.69	0.143	15	1.3%	-0.63 [-1.36 , 0.11]
DuPaul 1996	15.17	9.19	24	23	9.35	24	1.5%	-0.83 [-1.42 , -0.24]
Flapper 2008	12.5	9.445	12	19.174	10.143	12	1.2%	-0.66 [-1.48 , 0.17]
Kollins 2006 (PATS)	1	0.74	142	1.31	0.79	165	2.1%	-0.40 [-0.63 , -0.18]
McGough 2006	3.2	5.1877	80	8	5.1877	80	1.9%	-0.92 [-1.25 , -0.59]
Moshe 2012	55.5	9.5	57	62.1	7.9	57	1.9%	-0.75 [-1.13 , -0.37]
Stein 1996	15.5	4.8	25	16.3	4.6	25	1.6%	-0.17 [-0.72 , 0.39]
Subtotal (95% CI)			**355**			**378**	**11.5%**	**-0.62 [-0.84 , -0.40]**
Heterogeneity: Tau² = 0.03; Chi² = 10.14, df = 6 (P = 0.12); I² = 41%								
Test for overall effect: Z = 5.56 (P < 0.00001)								
1.10.2 High risk of bias								
Abikoff 2009	1.13	0.46	19	1.5	0.55	19	1.4%	-0.71 [-1.37 , -0.06]
Barkley 2000	14	12.3	15	17.7	13.8	15	1.3%	-0.28 [-0.99 , 0.44]
Bhat 2020	55.9	11.4	526	64.8	13.1	526	2.2%	-0.72 [-0.85 , -0.60]
Blum 2011	58.1	22.1	24	75.2	19.8	24	1.5%	-0.80 [-1.39 , -0.21]
Brown 1984a	7.45	3.72	11	16.73	7.58	11	1.0%	-1.50 [-2.46 , -0.53]
Brown 1988	10	6.69	11	8	0.63	11	1.2%	0.40 [-0.44 , 1.25]
Bukstein 1998	3.59	2.64	18	5.49	3.32	18	1.4%	-0.62 [-1.29 , 0.05]
Chronis 2003	0.9	0.8	21	3.9	2.8	21	1.4%	-1.43 [-2.11 , -0.74]
Coghill 2007	58.5	12.8	75	73	11.3	75	1.9%	-1.19 [-1.54 , -0.85]
Corkum 2008	59.65	11.46	21	67.4	10.49	21	1.5%	-0.69 [-1.32 , -0.07]
Corkum 2020	58.4	11.2	26	64	13.5	26	1.6%	-0.44 [-1.00 , 0.11]
Douglas 1986	0.56	0.6	16	1.07	0.6	16	1.3%	-0.83 [-1.55 , -0.10]
Epstein 2011	17.5	10.87	93	26.67	12.04	93	2.0%	-0.80 [-1.10 , -0.50]
Fabiano 2007	1.4	2.46	48	5.86	4.68	48	1.8%	-1.18 [-1.62 , -0.75]
Fitzpatrick 1992a	0.73	0.65	19	1.36	0.8	19	1.4%	-0.85 [-1.51 , -0.18]
Gadow 1990	6	6.68	11	14	7.87	11	1.1%	-1.05 [-1.96 , -0.15]
Gadow 1995	7.1	5.4	34	14.2	4.6	34	1.6%	-1.40 [-1.93 , -0.87]
Gadow 2007	5.7	5.1	71	11.6	6.9	71	1.9%	-0.97 [-1.32 , -0.62]
Gadow 2011	5.9	5.3	54	10.9	8.1	54	1.8%	-0.73 [-1.12 , -0.34]
Garfinkel 1983	4.887	4.8416	12	6.371	6.3118	12	1.2%	-0.25 [-1.06 , 0.55]
Gorman 2006	0.66	0.8964	41	1.52	1.0885	41	1.7%	-0.85 [-1.31 , -0.40]
Hawk 2018	1.35	2.73	80	3.41	2.33	80	1.9%	-0.81 [-1.13 , -0.49]
Hoeppner 1997	8.2	6.85	50	14.23	8.31	50	1.8%	-0.79 [-1.19 , -0.38]
Huang 2021	7.3	6.9	99	8.5	7.3	99	2.0%	-0.17 [-0.45 , 0.11]
Kaplan 1990	0.9	0.8	6	1.7	0.9	6	0.8%	-0.87 [-2.08 , 0.34]
Kolko 1999	3.3	2.9	22	9.9	3.8	22	1.3%	-1.92 [-2.64 , -1.19]
Konrad 2004	26.3	5.2	60	42.5	6.1	60	1.7%	-2.84 [-3.35 , -2.33]
Konrad 2005	14.3	10.1	44	22.2	13.8	44	1.8%	-0.65 [-1.08 , -0.22]
Kortekaas-Rijlaarsdam 2017	-9.2	16.8	65	-19.57	16.84	65	1.9%	0.61 [0.26 , 0.96]
Lufi 1997	30.85	15.19	20	32.6	12.75	20	1.5%	-0.12 [-0.74 , 0.50]
Lufi 2007	6.97	3.8	19	12.56	6.69	19	1.4%	-1.01 [-1.69 , -0.33]
Manos 1999	56.12	11.81	117	64.38	15.41	117	2.0%	-0.60 [-0.86 , -0.34]
McBride 1988a	7.5	4.5	46	17	6.5	46	1.7%	-1.69 [-2.16 , -1.21]
Pearson 2013	59.3	12.7	24	75.6	11.5	24	1.5%	-1.32 [-1.95 , -0.69]
Pelham 1989	2.45	3.8669	24	4.2	6.624	24	1.6%	-0.32 [-0.89 , 0.25]
Pelham 1990a	2.3	2	22	3.8	4.6	22	1.5%	-0.42 [-1.01 , 0.18]
Pelham 1993a	2	2.1	31	6	4.3	31	1.6%	-1.17 [-1.71 , -0.63]
Pelham 1999	1.1	1.2	25	3.7	2.6	25	1.5%	-1.26 [-1.88 , -0.65]
Pelham 2001a	7.94	5.83	68	16.4	7.74	68	1.9%	-1.23 [-1.60 , -0.86]
Pelham 2002	1.8	1.7	133	3.5	2.9	133	2.0%	-0.71 [-0.96 , -0.47]
Pelham 2005	2.3	2.7	29	5.7	5.9	29	1.6%	-0.73 [-1.26 , -0.20]
Pelham 2011	6	4.3	10	9.7	51	10	1.1%	-0.10 [-0.98 , 0.78]
Pliszka 1990	13.8	8.8	30	25.2	15.3	30	1.6%	-0.90 [-1.43 , -0.37]
Quinn 2004	1.58	3.85	32	6.39	6.81	32	1.7%	-0.86 [-1.37 , -0.35]
Rapport 1987	7.16	5	31	15.84	5.06	31	1.5%	-1.70 [-2.29 , -1.12]
Reitman 2001	12	2	3	23	2	3	0.1%	-4.40 [-8.94 , 0.14]
Silva 2008	1.4	2.46	68	5.86	4.68	68	1.9%	-1.19 [-1.55 , -0.82]
Smith 1998	1.2	1.5	45	4.4	3.5	45	1.8%	-1.18 [-1.63 , -0.73]
Smith 2004	10.3	0.2108	1	15.3	0.1031	1		Not estimable
Smithee 1998	0.647	0.51	25	1.1249	0.5766	25	1.5%	-0.86 [-1.45 , -0.28]

Analysis 1.10. (Continued)

Smith 2004	10.3	0.2108	1	15.3	0.1031	1		Not estimable
Smithee 1998	0.647	0.51	25	1.1249	0.5766	25	1.5%	-0.86 [-1.45 , -0.28]
Solanto 2009	60.04	10.57	30	63.28	10.55	30	1.7%	-0.30 [-0.81 , 0.21]
Taylor 1987	0.85	1	39	1.59	1.04	39	1.7%	-0.72 [-1.18 , -0.26]
Tirosh 1993a	17.6	6.3	20	32	9.2	20	1.3%	-1.79 [-2.53 , -1.05]
Ullmann 1986	-45.6	19.2	118	-11.3	15.1	118	2.0%	-1.98 [-2.29 , -1.67]
Wigal 2013	7.1	5.64	44	19.3	8.38	44	1.7%	-1.69 [-2.18 , -1.20]
Wilens 2008	15.4	10.7354	120	24.5	10.7354	120	2.0%	-0.84 [-1.11 , -0.58]
Zeiner 1999	8.83	6.49	38	14.69	6.17	38	1.7%	-0.92 [-1.39 , -0.44]
Subtotal (95% CI)			**2804**			**2804**	**88.5%**	**-0.91 [-1.06 , -0.77]**
Heterogeneity: Tau² = 0.23; Chi² = 320.35, df = 55 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 12.29 (P < 0.00001)								
Total (95% CI)			**3159**			**3182**	**100.0%**	**-0.88 [-1.01 , -0.75]**
Heterogeneity: Tau² = 0.21; Chi² = 340.77, df = 62 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 13.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.76, df = 1 (P = 0.03), I² = 79.0%								

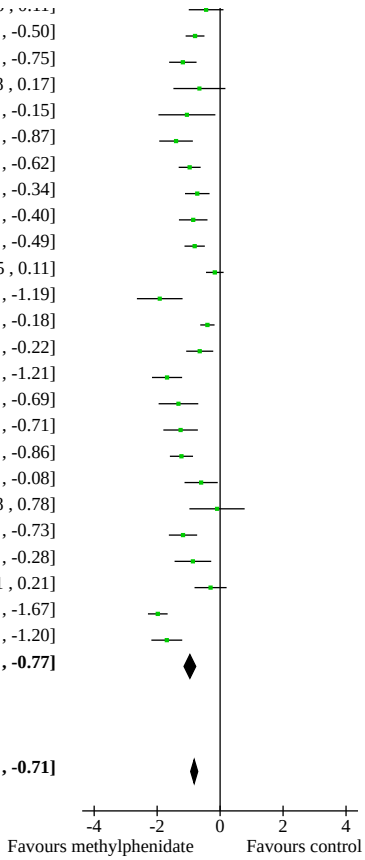


Analysis 1.11. Comparison 1: Teacher-rated ADHD symptoms, Outcome 11: Subgroup analysis: cross-over trials (endpoint data): dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Low dose								
Barkley 2000	14	12.3	15	17.7	13.8	15	1.1%	-0.28 [-0.99 , 0.44]
Bhat 2020	55.9	11.4	526	64.8	13.1	526	1.9%	-0.72 [-0.85 , -0.60]
Brown 1984a	7.45	3.72	11	16.73	7.58	11	0.8%	-1.50 [-2.46 , -0.53]
Brown 1988	9.5	5.04	11	8	0.63	11	0.9%	0.40 [-0.44 , 1.25]
Chronis 2003	2	2	21	3.9	2.8	21	1.2%	-0.77 [-1.40 , -0.14]
Coghill 2007	65	14.1	75	73	11.3	75	1.6%	-0.62 [-0.95 , -0.30]
Cook 1993	0.6	0.137	15	0.69	0.143	15	1.0%	-0.63 [-1.36 , 0.11]
Douglas 1986	0.56	0.6	16	1.07	0.6	16	1.1%	-0.83 [-1.55 , -0.10]
DuPaul 1996	19.46	9.28	24	23	9.35	24	1.3%	-0.37 [-0.94 , 0.20]
DuPaul 1996	15.17	9.19	24	23	9.35	24	1.2%	-0.83 [-1.42 , -0.24]
Fabiano 2007	3.17	3.54	48	5.86	4.68	48	1.5%	-0.64 [-1.05 , -0.23]
Fitzpatrick 1992a	0.73	0.65	19	1.36	0.8	19	1.1%	-0.85 [-1.51 , -0.18]
Flapper 2008	17.435	10.48	12	19.174	10.143	12	1.0%	-0.16 [-0.96 , 0.64]
Gadow 1990	9	6.15	11	14	7.87	11	0.9%	-0.68 [-1.55 , 0.18]
Gadow 1995	9.3	6.4	34	14.2	4.6	34	1.4%	-0.87 [-1.37 , -0.37]
Gadow 2007	7.3	5.8	71	11.6	6.9	71	1.6%	-0.67 [-1.01 , -0.33]
Gadow 2011	9.2	5.9	54	10.9	8.1	54	1.6%	-0.24 [-0.62 , 0.14]
Garfinkel 1983	4.887	4.8416	12	6.371	6.3118	12	1.0%	-0.25 [-1.06 , 0.55]
Hoeppner 1997	8.2	6.85	50	13.54	8.66	50	1.5%	-0.68 [-1.08 , -0.28]
Kaplan 1990	0.9	0.8	6	1.7	0.9	6	0.6%	-0.87 [-2.08 , 0.34]
Kolko 1999	4.1	4.4	22	9.9	3.8	22	1.1%	-1.39 [-2.05 , -0.72]
Kollins 2006 (PATS)	1.25	0.84	165	1.31	0.79	165	1.8%	-0.07 [-0.29 , 0.14]
Konrad 2004	26.3	5.2	60	42.5	6.1	60	1.4%	-2.84 [-3.35 , -2.33]
Konrad 2005	17.9	13.3	44	22.2	13.8	44	1.5%	-0.31 [-0.74 , 0.11]
Lufi 1997	30.85	15.19	20	32.6	12.75	20	1.2%	-0.12 [-0.74 , 0.50]
Lufi 2007	6.97	3.8	19	12.56	6.69	19	1.1%	-1.01 [-1.69 , -0.33]
Manos 1999	56.12	11.81	117	64.38	15.41	117	1.7%	-0.60 [-0.86 , -0.34]
McGough 2006	3.2	5.1877	80	8	5.1877	80	1.6%	-0.92 [-1.25 , -0.59]
Moshe 2012	55.5	9.5	57	62.1	7.9	57	1.6%	-0.75 [-1.13 , -0.37]
Pearson 2013	63.4	12.8	24	75.6	11.5	24	1.2%	-0.99 [-1.59 , -0.38]
Pelham 1989	2.45	3.8669	24	4.2	6.624	24	1.3%	-0.32 [-0.89 , 0.25]
Pelham 1990a	2.3	2	22	3.8	4.6	22	1.2%	-0.42 [-1.01 , 0.18]
Pelham 1993a	2	2.1	31	6	4.3	31	1.3%	-1.17 [-1.71 , -0.63]
Pelham 1999	1.1	1.2	25	3.7	2.6	25	1.2%	-1.26 [-1.88 , -0.65]
Pelham 2002	1.8	1.7	133	3.5	2.9	133	1.7%	-0.71 [-0.96 , -0.47]
Pelham 2005	2.3	2.7	29	5.7	5.9	29	1.3%	-0.73 [-1.26 , -0.20]
Quinn 2004	1.47	2.37	32	6.39	6.81	32	1.3%	-0.95 [-1.47 , -0.43]
Rapport 1987	7.16	5	31	15.84	5.06	31	1.2%	-1.70 [-2.29 , -1.12]
Silva 2008	3.17	3.54	68	5.86	4.68	68	1.6%	-0.64 [-0.99 , -0.30]
Silva 2008	1.4	2.46	68	5.86	4.68	68	1.6%	-1.19 [-1.55 , -0.82]
Smith 1998	2.7	2.7	45	4.4	3.5	45	1.5%	-0.54 [-0.96 , -0.12]
Smith 2004	10.3	0.2108	1	15.3	0.1031	1		Not estimable
Solanto 2009	61.52	7.98	30	63.28	10.55	30	1.4%	-0.19 [-0.69 , 0.32]
Stein 1996	15.5	4.8	25	16.3	4.6	25	1.3%	-0.17 [-0.72 , 0.39]
Zeiner 1999	8.83	6.49	38	14.69	6.17	38	1.4%	-0.92 [-1.39 , -0.44]
Subtotal (95% CI)			**2265**			**2265**	**57.9%**	**-0.72 [-0.86 , -0.59]**
Heterogeneity: Tau² = 0.13; Chi² = 172.45, df = 43 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 10.49 (P < 0.00001)								
1.11.2 High dose								
Abikoff 2009	1.13	0.46	19	1.5	0.55	19	1.1%	-0.71 [-1.37 , -0.06]
Blum 2011	58.1	22.1	24	75.2	19.8	24	1.2%	-0.80 [-1.39 , -0.21]
Bukstein 1998	3.59	2.64	18	5.49	3.32	18	1.1%	-0.62 [-1.29 , 0.05]
Chronis 2003	0.9	0.8	21	3.9	2.8	21	1.1%	-1.43 [-2.11 , -0.74]
Coghill 2007	58.5	12.8	75	73	11.3	75	1.6%	-1.19 [-1.54 , -0.85]
Corkum 2008	59.65	11.46	21	67.4	10.49	21	1.2%	-0.69 [-1.32 , -0.07]
Corkum 2020	58.4	11.2	26	64	13.5	26	1.3%	-0.44 [-1.00 , 0.11]
Epstein 2011	17.5	10.87	93	26.67	12.04	93	1.7%	-0.80 [-1.10 , -0.50]
Fabiano 2007	1.4	2.46	48	5.86	4.68	48	1.5%	-1.18 [-1.62 , -0.75]

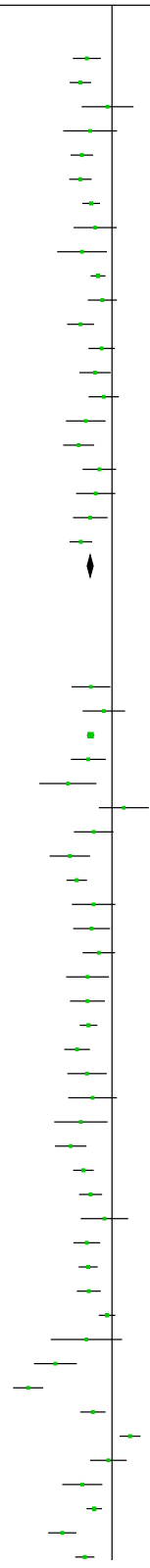
Analysis 1.11. (Continued)

Epstein 2011	17.5	10.87	93	26.67	12.04	93	1.7%	-0.80 [-1.10 , -0.50]
Fabiano 2007	1.4	2.46	48	5.86	4.68	48	1.5%	-1.18 [-1.62 , -0.75]
Flapper 2008	12.5	9.445	12	19.174	10.143	12	0.9%	-0.66 [-1.48 , 0.17]
Gadow 1990	6	6.68	11	14	7.87	11	0.8%	-1.05 [-1.96 , -0.15]
Gadow 1995	7.1	5.4	34	14.2	4.6	34	1.3%	-1.40 [-1.93 , -0.87]
Gadow 2007	5.7	5.1	71	11.6	6.9	71	1.6%	-0.97 [-1.32 , -0.62]
Gadow 2011	5.9	5.3	54	10.9	8.1	54	1.5%	-0.73 [-1.12 , -0.34]
Gorman 2006	0.66	0.8964	41	1.52	1.0885	41	1.5%	-0.85 [-1.31 , -0.40]
Hawk 2018	1.35	2.73	80	3.41	2.33	80	1.6%	-0.81 [-1.13 , -0.49]
Huang 2021	7.3	6.9	99	8.5	7.3	99	1.7%	-0.17 [-0.45 , 0.11]
Kolko 1999	3.3	2.9	22	9.9	3.8	22	1.1%	-1.92 [-2.64 , -1.19]
Kollins 2006 (PATS)	1	0.74	142	1.31	0.79	165	1.8%	-0.40 [-0.63 , -0.18]
Konrad 2005	14.3	10.1	44	22.2	13.8	44	1.5%	-0.65 [-1.08 , -0.22]
McBride 1988a	7.5	4.5	46	17	6.5	46	1.4%	-1.69 [-2.16 , -1.21]
Pearson 2013	59.3	12.7	24	75.6	11.5	24	1.2%	-1.32 [-1.95 , -0.69]
Pelham 1993a	1.7	2.1	31	6	4.3	31	1.3%	-1.25 [-1.80 , -0.71]
Pelham 2001a	7.94	5.83	68	16.4	7.74	68	1.6%	-1.23 [-1.60 , -0.86]
Pelham 2005	2.8	3.2	29	5.7	5.9	29	1.3%	-0.60 [-1.13 , -0.08]
Pelham 2011	6	4.3	10	9.7	51	10	0.9%	-0.10 [-0.98 , 0.78]
Smith 1998	1.2	1.5	45	4.4	3.5	45	1.5%	-1.18 [-1.63 , -0.73]
Smithee 1998	0.647	0.51	25	1.1249	0.5766	25	1.3%	-0.86 [-1.45 , -0.28]
Solanto 2009	60.04	10.57	30	63.28	10.55	30	1.4%	-0.30 [-0.81 , 0.21]
Ullmann 1986	-45.6	19.2	118	-11.3	15.1	118	1.7%	-1.98 [-2.29 , -1.67]
Wigal 2013	7.1	5.64	44	19.3	8.38	44	1.4%	-1.69 [-2.18 , -1.20]
Subtotal (95% CI)			**1425**			**1448**	**42.1%**	**-0.96 [-1.15 , -0.77]**
Heterogeneity: Tau² = 0.21; Chi² = 154.01, df = 30 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 10.15 (P < 0.00001)								
Total (95% CI)			**3690**			**3713**	**100.0%**	**-0.82 [-0.93 , -0.71]**
Heterogeneity: Tau² = 0.17; Chi² = 346.89, df = 74 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 14.48 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.12, df = 1 (P = 0.04), I² = 75.7%								



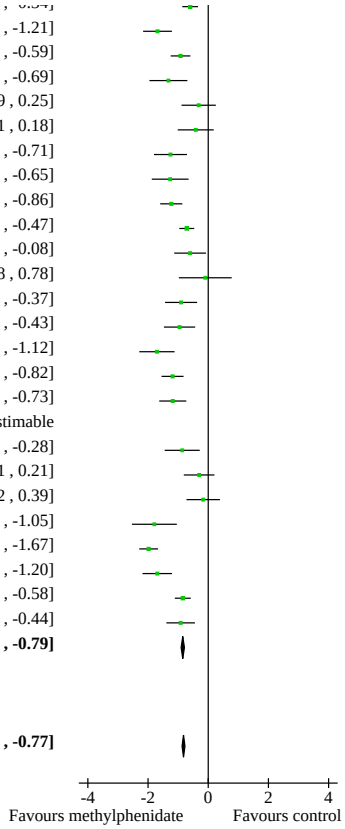
Analysis 1.12. Comparison 1: Teacher-rated ADHD symptoms, Outcome 12: Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.12.1 All parallel-group trials and first-period cross-over trials								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	1.0%	-0.85 [-1.33 , -0.38]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	1.7%	-1.07 [-1.43 , -0.71]
Brown 1985	15.1	4.6	10	15.7	2.9	10	0.3%	-0.15 [-1.03 , 0.73]
Butter 1983	30.47	17.3	10	42.7	14.2	10	0.3%	-0.74 [-1.65 , 0.17]
Childress 2009	16.4	13.44	57	30	13.01	63	1.6%	-1.02 [-1.40 , -0.64]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	1.6%	-1.07 [-1.45 , -0.69]
Findling 2008	18.3	17.44	94	31.6	20.07	88	2.5%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	0.4%	-0.57 [-1.30 , 0.16]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	0.3%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	3.6%	-0.47 [-0.72 , -0.22]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	0.9%	-0.33 [-0.82 , 0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	1.1%	-1.06 [-1.52 , -0.61]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	1.1%	-0.35 [-0.80 , 0.10]
Moshe 2012	58	10.3	28	64.7	12.5	29	0.8%	-0.58 [-1.11 , -0.05]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	0.9%	-0.28 [-0.79 , 0.23]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	0.5%	-0.89 [-1.56 , -0.22]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	0.8%	-1.13 [-1.65 , -0.60]
Tannock 2018	62	13.6	23	67.9	13.6	26	0.7%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	0.5%	-0.55 [-1.22 , 0.11]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	0.7%	-0.73 [-1.32 , -0.15]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	1.5%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**926**			**802**	**23.0%**	**-0.74 [-0.84 , -0.64]**
Heterogeneity: Chi² = 32.51, df = 20 (P = 0.04); I² = 38%								
Test for overall effect: Z = 14.54 (P < 0.00001)								
1.12.2 Cross-over trials (endpoint data)								
Abikoff 2009	1.13	0.46	19	1.5	0.55	19	0.5%	-0.71 [-1.37 , -0.06]
Barkley 2000	14	12.3	15	17.7	13.8	15	0.4%	-0.28 [-0.99 , 0.44]
Bhat 2020	55.9	11.4	526	64.8	13.1	526	14.7%	-0.72 [-0.85 , -0.60]
Blum 2011	58.1	22.1	24	75.2	19.8	24	0.7%	-0.80 [-1.39 , -0.21]
Brown 1984a	7.45	3.72	11	16.73	7.58	11	0.2%	-1.50 [-2.46 , -0.53]
Brown 1988	9.5	5.04	11	8	0.63	11	0.3%	0.40 [-0.44 , 1.25]
Bukstein 1998	3.59	2.64	18	5.49	3.32	18	0.5%	-0.62 [-1.29 , 0.05]
Chronis 2003	0.9	0.8	21	3.9	2.8	21	0.5%	-1.43 [-2.11 , -0.74]
Coghill 2007	58.5	12.8	75	73	11.3	75	1.9%	-1.19 [-1.54 , -0.85]
Cook 1993	0.6	0.137	15	0.69	0.143	15	0.4%	-0.63 [-1.36 , 0.11]
Corkum 2008	59.65	11.46	21	67.4	10.49	21	0.6%	-0.69 [-1.32 , -0.07]
Corkum 2020	58.4	11.2	26	64	13.5	26	0.8%	-0.44 [-1.00 , 0.11]
Douglas 1986	0.56	0.6	16	1.07	0.6	16	0.4%	-0.83 [-1.55 , -0.10]
DuPaul 1996	15.17	9.19	24	23	9.35	24	0.7%	-0.83 [-1.42 , -0.24]
Epstein 2011	17.5	10.87	93	26.67	12.04	93	2.6%	-0.80 [-1.10 , -0.50]
Fabiano 2007	1.4	2.46	48	5.86	4.68	48	1.2%	-1.18 [-1.62 , -0.75]
Fitzpatrick 1992a	0.73	0.65	19	1.36	0.8	19	0.5%	-0.85 [-1.51 , -0.18]
Flapper 2008	12.5	9.445	12	19.174	10.143	12	0.3%	-0.66 [-1.48 , 0.17]
Gadow 1990	6	6.68	11	14	7.87	11	0.3%	-1.05 [-1.96 , -0.15]
Gadow 1995	7.1	5.4	34	14.2	4.6	34	0.8%	-1.40 [-1.93 , -0.87]
Gadow 2007	5.7	5.1	71	11.6	6.9	71	1.9%	-0.97 [-1.32 , -0.62]
Gadow 2011	5.9	5.3	54	10.9	8.1	54	1.5%	-0.73 [-1.12 , -0.34]
Garfinkel 1983	4.887	4.8416	12	6.371	6.3118	12	0.4%	-0.25 [-1.06 , 0.55]
Gorman 2006	0.66	0.8964	41	1.52	1.0885	41	1.1%	-0.85 [-1.31 , -0.40]
Hawk 2018	1.35	2.73	80	3.41	2.33	80	2.2%	-0.81 [-1.13 , -0.49]
Hoeppner 1997	8.2	6.85	50	14.23	8.31	50	1.4%	-0.79 [-1.19 , -0.38]
Huang 2021	7.3	6.9	99	8.5	7.3	99	2.9%	-0.17 [-0.45 , 0.11]
Kaplan 1990	0.9	0.8	6	1.7	0.9	6	0.2%	-0.87 [-2.08 , 0.34]
Kolko 1999	3.3	2.9	22	9.9	3.8	22	0.4%	-1.92 [-2.64 , -1.19]
Konrad 2004	26.3	5.2	60	42.5	6.1	60	0.9%	-2.84 [-3.35 , -2.33]
Konrad 2005	14.3	10.1	44	22.2	13.8	44	1.2%	-0.65 [-1.08 , -0.22]
Kortekaas-Rijlaarsdam 2017	-9.2	16.8	65	-19.57	16.84	65	1.8%	0.61 [0.26 , 0.96]
Lufi 1997	30.85	15.19	20	32.6	12.75	20	0.6%	-0.12 [-0.74 , 0.50]
Lufi 2007	6.97	3.8	19	12.56	6.69	19	0.5%	-1.01 [-1.69 , -0.33]
Manos 1999	56.12	11.81	117	64.38	15.41	117	3.3%	-0.60 [-0.86 , -0.34]
McBride 1988a	7.5	4.5	46	17	6.5	46	1.0%	-1.69 [-2.16 , -1.21]
McGough 2006	3.2	5.1877	80	8	5.1877	80	2.1%	-0.92 [-1.25 , -0.59]



Analysis 1.12. (Continued)

McBride 1988a	7.5	4.5	46	17	6.5	46	1.0%	-1.69 [-2.16 , -1.21]
McGough 2006	3.2	5.1877	80	8	5.1877	80	2.1%	-0.92 [-1.25 , -0.59]
Pearson 2013	59.3	12.7	24	75.6	11.5	24	0.6%	-1.32 [-1.95 , -0.69]
Pelham 1989	2.45	3.8669	24	4.2	6.624	24	0.7%	-0.32 [-0.89 , 0.25]
Pelham 1990a	2.3	2	22	3.8	4.6	22	0.6%	-0.42 [-1.01 , 0.18]
Pelham 1993a	1.7	2.1	31	6	4.3	31	0.8%	-1.25 [-1.80 , -0.71]
Pelham 1999	1.1	1.2	25	3.7	2.6	25	0.6%	-1.26 [-1.88 , -0.65]
Pelham 2001a	7.94	5.83	68	16.4	7.74	68	1.7%	-1.23 [-1.60 , -0.86]
Pelham 2002	1.8	1.7	133	3.5	2.9	133	3.7%	-0.71 [-0.96 , -0.47]
Pelham 2005	2.8	3.2	29	5.7	5.9	29	0.8%	-0.60 [-1.13 , -0.08]
Pelham 2011	6	4.3	10	9.7	51	10	0.3%	-0.10 [-0.98 , 0.78]
Pliszka 1990	13.8	8.8	30	25.2	15.3	30	0.8%	-0.90 [-1.43 , -0.37]
Quinn 2004	1.47	2.37	32	6.39	6.81	32	0.8%	-0.95 [-1.47 , -0.43]
Rapport 1987	7.16	5	31	15.84	5.06	31	0.7%	-1.70 [-2.29 , -1.12]
Silva 2008	1.4	2.46	68	5.86	4.68	68	1.7%	-1.19 [-1.55 , -0.82]
Smith 1998	1.2	1.5	45	4.4	3.5	45	1.1%	-1.18 [-1.63 , -0.73]
Smith 2004	10.3	0.2108	1	15.3	0.1031	1		Not estimable
Smithee 1998	0.647	0.51	25	1.1249	0.5766	25	0.7%	-0.86 [-1.45 , -0.28]
Solanto 2009	60.04	10.57	30	63.28	10.55	30	0.9%	-0.30 [-0.81 , 0.21]
Stein 1996	15.5	4.8	25	16.3	4.6	25	0.7%	-0.17 [-0.72 , 0.39]
Tirosh 1993a	17.6	6.3	20	32	9.2	20	0.4%	-1.79 [-2.53 , -1.05]
Ullmann 1986	-45.6	19.2	118	-11.3	15.1	118	2.3%	-1.98 [-2.29 , -1.67]
Wigal 2013	7.1	5.64	44	19.3	8.38	44	1.0%	-1.69 [-2.18 , -1.20]
Wilens 2008	15.4	10.7354	120	24.5	10.7354	120	3.3%	-0.84 [-1.11 , -0.58]
Zeiner 1999	8.83	6.49	38	14.69	6.17	38	1.0%	-0.92 [-1.39 , -0.44]
Subtotal (95% CI)			**2918**			**2918**	**77.0%**	**-0.85 [-0.90 , -0.79]**
Heterogeneity: Chi² = 325.76, df = 58 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 30.45 (P < 0.00001)								
Total (95% CI)			**3844**			**3720**	**100.0%**	**-0.82 [-0.87 , -0.77]**
Heterogeneity: Chi² = 361.68, df = 79 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 33.69 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.41, df = 1 (P = 0.06), I² = 70.6%								

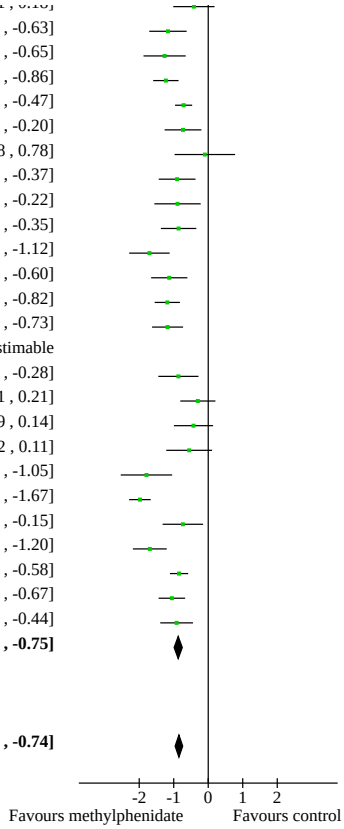


Analysis 1.13. Comparison 1: Teacher-rated ADHD symptoms, Outcome 13: All parallel-group trials and cross-over trials: risk of bias

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.13.1 Low risk of bias								
Cook 1993	0.6	0.137	15	0.69	0.143	15	1.0%	-0.63 [-1.36 , 0.11]
DuPaul 1996	15.17	9.19	24	23	9.35	24	1.2%	-0.83 [-1.42 , -0.24]
Flapper 2008	12.5	9.445	12	19.174	10.143	12	0.9%	-0.66 [-1.48 , 0.17]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	1.3%	-0.33 [-0.82 , 0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	1.4%	-1.06 [-1.52 , -0.61]
McGough 2006	3.2	5.1877	80	8	5.1877	80	1.6%	-0.92 [-1.25 , -0.59]
Moshe 2012	58	10.3	28	64.7	12.5	29	1.3%	-0.58 [-1.11 , -0.05]
Stein 1996	15.5	4.8	25	16.3	4.6	25	1.2%	-0.17 [-0.72 , 0.39]
Subtotal (95% CI)			**259**			**259**	**9.8%**	**-0.68 [-0.91 , -0.45]**
Heterogeneity: Tau² = 0.03; Chi² = 10.37, df = 7 (P = 0.17); I² = 33%								
Test for overall effect: Z = 5.87 (P < 0.00001)								
1.13.2 High risk of bias								
Abikoff 2009	1.13	0.46	19	1.5	0.55	19	1.1%	-0.71 [-1.37 , -0.06]
Arnold 2004	0.7	0.7	35	1.4	0.9	40	1.3%	-0.85 [-1.33 , -0.38]
Barkley 2000	14	12.3	15	17.7	13.8	15	1.0%	-0.28 [-0.99 , 0.44]
Bhat 2020	55.9	11.4	526	64.8	13.1	526	1.8%	-0.72 [-0.85 , -0.60]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	1.5%	-1.07 [-1.43 , -0.71]
Blum 2011	58.1	22.1	24	75.2	19.8	24	1.2%	-0.80 [-1.39 , -0.21]
Brown 1984a	7.45	3.72	11	16.73	7.58	11	0.7%	-1.50 [-2.46 , -0.53]
Brown 1985	15.1	4.6	10	15.7	2.9	10	0.8%	-0.15 [-1.03 , 0.73]
Brown 1988	10	6.69	11	8	0.63	11	0.9%	0.40 [-0.44 , 1.25]
Bukstein 1998	3.59	2.64	18	5.49	3.32	18	1.1%	-0.62 [-1.29 , 0.05]
Butter 1983	30.47	17.3	10	42.7	14.2	10	0.8%	-0.74 [-1.65 , 0.17]
Childress 2009	16.4	13.44	57	30	13.01	63	1.5%	-1.02 [-1.40 , -0.64]
Chronis 2003	0.9	0.8	21	3.9	2.8	21	1.1%	-1.43 [-2.11 , -0.74]
Coghill 2007	58.5	12.8	75	73	11.3	75	1.5%	-1.19 [-1.54 , -0.85]
Corkum 2008	59.65	11.46	21	67.4	10.49	21	1.1%	-0.69 [-1.32 , -0.07]
Corkum 2020	58.4	11.2	26	64	13.5	26	1.2%	-0.44 [-1.00 , 0.11]
Douglas 1986	0.56	0.6	16	1.07	0.6	16	1.0%	-0.83 [-1.55 , -0.10]
Epstein 2011	17.5	10.87	93	26.67	12.04	93	1.6%	-0.80 [-1.10 , -0.50]
Fabiano 2007	1.4	2.46	48	5.86	4.68	48	1.4%	-1.18 [-1.62 , -0.75]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	1.5%	-1.07 [-1.45 , -0.69]
Findling 2008	18.3	17.44	94	31.6	20.07	88	1.6%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	1.0%	-0.57 [-1.30 , 0.16]
Fitzpatrick 1992a	0.73	0.65	19	1.36	0.8	19	1.1%	-0.85 [-1.51 , -0.18]
Gadow 1990	6	6.68	11	14	7.87	11	0.8%	-1.05 [-1.96 , -0.15]
Gadow 1995	7.1	5.4	34	14.2	4.6	34	1.3%	-1.40 [-1.93 , -0.87]
Gadow 2007	5.7	5.1	71	11.6	6.9	71	1.5%	-0.97 [-1.32 , -0.62]
Gadow 2011	5.9	5.3	54	10.9	8.1	54	1.5%	-0.73 [-1.12 , -0.34]
Garfinkel 1983	4.887	4.8416	12	6.371	6.3118	12	0.9%	-0.25 [-1.06 , 0.55]
Gorman 2006	0.66	0.8964	41	1.52	1.0885	41	1.4%	-0.85 [-1.31 , -0.40]
Hawk 2018	1.35	2.73	80	3.41	2.33	80	1.6%	-0.81 [-1.13 , -0.49]
Hoeppner 1997	8.2	6.85	50	14.23	8.31	50	1.4%	-0.79 [-1.19 , -0.38]
Huang 2021	7.3	6.9	99	8.5	7.3	99	1.6%	-0.17 [-0.45 , 0.11]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	0.9%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	1.6%	-0.47 [-0.72 , -0.22]
Kaplan 1990	0.9	0.8	6	1.7	0.9	6	0.6%	-0.87 [-2.08 , 0.34]
Kolko 1999	3.3	2.9	22	9.9	3.8	22	1.0%	-1.92 [-2.64 , -1.19]
Konrad 2004	26.3	5.2	60	42.5	6.1	60	1.3%	-2.84 [-3.35 , -2.33]
Konrad 2005	14.3	10.1	44	22.2	13.8	44	1.4%	-0.65 [-1.08 , -0.22]
Kortekaas-Rijlaarsdam 2017	-9.2	16.8	65	-19.57	16.84	65	1.5%	0.61 [0.26 , 0.96]
Lufi 1997	30.85	15.19	20	32.6	12.75	20	1.1%	-0.12 [-0.74 , 0.50]
Lufi 2007	6.97	3.8	19	12.56	6.69	19	1.1%	-1.01 [-1.69 , -0.33]
Manos 1999	56.12	11.81	117	64.38	15.41	117	1.6%	-0.60 [-0.86 , -0.34]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	1.4%	-0.35 [-0.80 , 0.10]
McBride 1988a	7.5	4.5	46	17	6.5	46	1.3%	-1.69 [-2.16 , -1.21]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	1.3%	-0.28 [-0.79 , 0.23]
Pearson 2013	59.3	12.7	24	75.6	11.5	24	1.1%	-1.32 [-1.95 , -0.69]
Pelham 1989	2.45	3.8669	24	4.2	6.624	24	1.2%	-0.32 [-0.89 , 0.25]
Pelham 1990a	2.3	2	22	3.8	4.6	22	1.2%	-0.42 [-1.01 , 0.18]
Pelham 1993a	2	2.1	31	6	4.3	31	1.2%	-1.17 [-1.71 , -0.63]
Pelham 1999	1.1	1.2	25	3.7	2.6	25	1.2%	-1.26 [-1.88 , -0.65]

Analysis 1.13. (Continued)

Pelham 1993a	2	2.1	31	6	4.3	31	1.2%	-1.17 [-1.71 , -0.63]
Pelham 1999	1.1	1.2	25	3.7	2.6	25	1.2%	-1.26 [-1.88 , -0.65]
Pelham 2001a	7.94	5.83	68	16.4	7.74	68	1.5%	-1.23 [-1.60 , -0.86]
Pelham 2002	1.8	1.7	133	3.5	2.9	133	1.6%	-0.71 [-0.96 , -0.47]
Pelham 2005	2.3	2.7	29	5.7	5.9	29	1.3%	-0.73 [-1.26 , -0.20]
Pelham 2011	6	4.3	10	9.7	51	10	0.8%	-0.10 [-0.98 , 0.78]
Pliszka 1990	13.8	8.8	30	25.2	15.3	30	1.3%	-0.90 [-1.43 , -0.37]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	1.1%	-0.89 [-1.56 , -0.22]
Quinn 2004	1.58	3.85	32	6.39	6.81	32	1.3%	-0.86 [-1.37 , -0.35]
Rapport 1987	7.16	5	31	15.84	5.06	31	1.2%	-1.70 [-2.29 , -1.12]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	1.3%	-1.13 [-1.65 , -0.60]
Silva 2008	1.4	2.46	68	5.86	4.68	68	1.5%	-1.19 [-1.55 , -0.82]
Smith 1998	1.2	1.5	45	4.4	3.5	45	1.4%	-1.18 [-1.63 , -0.73]
Smith 2004	10.3	0.2108	1	15.3	0.1031	1		Not estimable
Smithee 1998	0.647	0.51	25	1.1249	0.5766	25	1.2%	-0.86 [-1.45 , -0.28]
Solanto 2009	60.06	10.57	30	63.28	10.55	30	1.3%	-0.30 [-0.81 , 0.21]
Tannock 2018	62	13.6	23	67.9	13.6	26	1.2%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	1.1%	-0.55 [-1.22 , 0.11]
Tirosh 1993a	17.6	6.3	20	32	9.2	20	1.0%	-1.79 [-2.53 , -1.05]
Ullmann 1986	-45.6	19.2	118	-11.3	15.1	118	1.6%	-1.98 [-2.29 , -1.67]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	1.2%	-0.73 [-1.32 , -0.15]
Wigal 2013	7.1	5.64	44	19.3	8.38	44	1.3%	-1.69 [-2.18 , -1.20]
Wilens 2008	15.4	10.7354	120	24.5	10.7354	120	1.6%	-0.84 [-1.11 , -0.58]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	1.5%	-1.05 [-1.44 , -0.67]
Zeiner 1999	8.83	6.49	38	14.69	6.17	38	1.3%	-0.92 [-1.39 , -0.44]
Subtotal (95% CI)			**3585**			**3461**	**90.2%**	**-0.87 [-0.99 , -0.75]**
Heterogeneity: Tau² = 0.18; Chi² = 348.15, df = 71 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 14.46 (P < 0.00001)								
Total (95% CI)			**3844**			**3720**	**100.0%**	**-0.85 [-0.96 , -0.74]**
Heterogeneity: Tau² = 0.17; Chi² = 360.13, df = 79 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 15.21 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.0%								

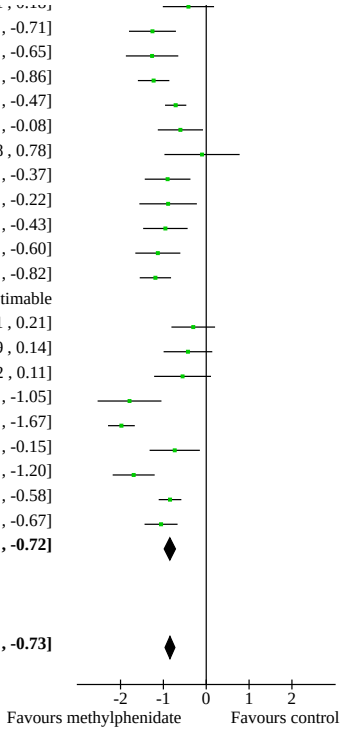


Analysis 1.14. Comparison 1: Teacher-rated ADHD symptoms, Outcome 14: All parallel-group trials and cross-over trials: vested interest

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.14.1 Low risk of vested interest								
Barkley 2000	14	12.3	15	17.7	13.8	15	1.1%	-0.28 [-0.99 , 0.44]
Brown 1988	9.5	5.04	11	8	0.63	11	0.9%	0.40 [-0.44 , 1.25]
Butter 1983	30.47	17.3	10	42.7	14.2	10	0.9%	-0.74 [-1.65 , 0.17]
Cook 1993	0.6	0.137	15	0.69	0.143	15	1.1%	-0.63 [-1.36 , 0.11]
Corkum 2008	59.65	11.46	21	67.4	10.49	21	1.2%	-0.69 [-1.32 , -0.07]
Corkum 2020	58.4	11.2	26	64	13.5	26	1.3%	-0.44 [-1.00 , 0.11]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	1.1%	-0.57 [-1.30 , 0.16]
Flapper 2008	12.5	9.445	12	19.174	10.143	12	0.9%	-0.66 [-1.48 , 0.17]
Gadow 1995	7.1	5.4	34	14.2	4.6	34	1.3%	-1.40 [-1.93 , -0.87]
Gadow 2007	5.7	5.1	71	11.6	6.9	71	1.6%	-0.97 [-1.32 , -0.62]
Garfinkel 1983	4.887	4.8416	12	6.371	6.3118	12	1.0%	-0.25 [-1.06 , 0.55]
Gorman 2006	0.66	0.8964	41	1.52	1.0885	41	1.4%	-0.85 [-1.31 , -0.40]
Hawk 2018	1.35	2.73	80	3.41	2.33	80	1.6%	-0.81 [-1.13 , -0.49]
Konrad 2004	26.3	5.2	60	42.5	6.1	60	1.4%	-2.84 [-3.35 , -2.33]
Konrad 2005	14.3	10.1	44	22.2	13.8	44	1.5%	-0.65 [-1.08 , -0.22]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	1.5%	-0.35 [-0.80 , 0.10]
Moshe 2012	58	10.3	28	64.7	12.5	29	1.3%	-0.58 [-1.11 , -0.05]
Pearson 2013	59.3	12.7	24	75.6	11.5	24	1.2%	-1.32 [-1.95 , -0.69]
Rapport 1987	7.16	5	31	15.84	5.06	31	1.3%	-1.70 [-2.29 , -1.12]
Smith 1998	1.2	1.5	45	4.4	3.5	45	1.4%	-1.18 [-1.63 , -0.73]
Smithee 1998	0.647	0.51	25	1.1249	0.5766	25	1.3%	-0.86 [-1.45 , -0.28]
Stein 1996	15.5	4.8	25	16.3	4.6	25	1.3%	-0.17 [-0.72 , 0.39]
Zeiner 1999	8.83	6.49	38	14.69	6.17	38	1.4%	-0.92 [-1.39 , -0.44]
Subtotal (95% CI)			**726**			**720**	**28.9%**	**-0.83 [-1.08 , -0.58]**
Heterogeneity: Tau² = 0.28; Chi² = 103.94, df = 22 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 6.57 (P < 0.00001)								
1.14.2 High risk of vested interest								
Abikoff 2009	1.13	0.46	19	1.5	0.55	19	1.2%	-0.71 [-1.37 , -0.06]
Arnold 2004	0.7	0.7	35	1.4	0.9	40	1.4%	-0.85 [-1.33 , -0.38]
Bhat 2020	55.9	11.4	526	64.8	13.1	526	1.8%	-0.72 [-0.85 , -0.60]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	1.6%	-1.07 [-1.43 , -0.71]
Blum 2011	58.1	22.1	24	75.2	19.8	24	1.2%	-0.80 [-1.39 , -0.21]
Brown 1984a	7.45	3.72	11	16.73	7.58	11	0.8%	-1.50 [-2.46 , -0.53]
Brown 1985	15.1	4.6	10	15.7	2.9	10	0.9%	-0.15 [-1.03 , 0.73]
Bukstein 1998	3.59	2.64	18	5.49	3.32	18	1.1%	-0.62 [-1.29 , 0.05]
Childress 2009	16.4	13.44	57	30	13.01	63	1.5%	-1.02 [-1.40 , -0.64]
Chronis 2003	0.9	0.8	21	3.9	2.8	21	1.1%	-1.43 [-2.11 , -0.74]
Coghill 2007	58.5	12.8	75	73	11.3	75	1.6%	-1.19 [-1.54 , -0.85]
DuPaul 1996	15.17	9.19	24	23	9.35	24	1.2%	-0.83 [-1.42 , -0.24]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	1.5%	-1.07 [-1.45 , -0.69]
Findling 2008	18.3	17.44	94	31.6	20.07	88	1.7%	-0.71 [-1.01 , -0.41]
Gadow 1990	6	6.68	11	14	7.87	11	0.9%	-1.05 [-1.96 , -0.15]
Gadow 2011	5.9	5.3	54	10.9	8.1	54	1.5%	-0.73 [-1.12 , -0.34]
Hoeppner 1997	8.2	6.85	50	14.23	8.31	50	1.5%	-0.79 [-1.19 , -0.38]
Huang 2021	7.3	6.9	99	8.5	7.3	99	1.7%	-0.17 [-0.45 , 0.11]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	0.9%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	1.7%	-0.47 [-0.72 , -0.22]
Kaplan 1990	0.9	0.8	6	1.7	0.9	6	0.6%	-0.87 [-2.08 , 0.34]
Kolko 1999	3.3	2.9	22	9.9	3.8	22	1.1%	-1.92 [-2.64 , -1.19]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	1.4%	-0.33 [-0.82 , 0.17]
Kortekaas-Rijlaarsdam 2017	-9.2	16.8	65	-19.57	16.84	65	1.6%	0.61 [0.26 , 0.96]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	1.4%	-1.06 [-1.52 , -0.61]
Lufi 1997	30.85	15.19	20	32.6	12.75	20	1.2%	-0.12 [-0.74 , 0.50]
Lufi 2007	6.97	3.8	19	12.56	6.69	19	1.1%	-1.01 [-1.69 , -0.33]
Manos 1999	56.12	11.81	117	64.38	15.41	117	1.7%	-0.60 [-0.86 , -0.34]
McBride 1988a	7.5	4.5	46	17	6.5	46	1.4%	-1.69 [-2.16 , -1.21]
McGough 2006	3.2	5.1877	80	8	5.1877	80	1.6%	-0.92 [-1.25 , -0.59]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	1.4%	-0.28 [-0.79 , 0.23]
Pelham 1989	2.45	3.8669	24	4.2	6.624	24	1.3%	-0.32 [-0.89 , 0.25]
Pelham 1990a	2.3	2	22	3.8	4.6	22	1.2%	-0.42 [-1.01 , 0.18]
Pelham 1993a	1.7	2.1	31	6	4.3	31	1.3%	-1.25 [-1.80 , -0.71]
Pelham 1999	1.1	1.2	25	3.7	2.6	25	1.2%	-1.26 [-1.88 , -0.65]

Analysis 1.14. (Continued)

Pelham 1993a	1.7	2.1	31	6	4.3	31	1.3%	-1.25 [-1.80 , -0.71]
Pelham 1999	1.1	1.2	25	3.7	2.6	25	1.2%	-1.26 [-1.88 , -0.65]
Pelham 2001a	7.94	5.83	68	16.4	7.74	68	1.6%	-1.23 [-1.60 , -0.86]
Pelham 2002	1.8	1.7	133	3.5	2.9	133	1.7%	-0.71 [-0.96 , -0.47]
Pelham 2005	2.8	3.2	29	5.7	5.9	29	1.3%	-0.60 [-1.13 , -0.08]
Pelham 2011	6	4.3	10	9.7	51	10	0.9%	-0.10 [-0.98 , 0.78]
Pliszka 1990	13.8	8.8	30	25.2	15.3	30	1.3%	-0.90 [-1.43 , -0.37]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	1.1%	-0.89 [-1.56 , -0.22]
Quinn 2004	1.47	2.37	32	6.39	6.81	32	1.3%	-0.95 [-1.47 , -0.43]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	1.3%	-1.13 [-1.65 , -0.60]
Silva 2008	1.4	2.46	68	5.86	4.68	68	1.6%	-1.19 [-1.55 , -0.82]
Smith 2004	10.3	0.2108	1	15.3	0.1031	1		Not estimable
Solanto 2009	60.04	10.57	30	63.28	10.55	30	1.4%	-0.30 [-0.81 , 0.21]
Tannock 2018	62	13.6	23	67.9	13.6	26	1.3%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	1.1%	-0.55 [-1.22 , 0.11]
Tirosh 1993a	17.6	6.3	20	32	9.2	20	1.0%	-1.79 [-2.53 , -1.05]
Ullmann 1986	-45.6	19.2	118	-11.3	15.1	118	1.6%	-1.98 [-2.29 , -1.67]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	1.3%	-0.73 [-1.32 , -0.15]
Wigal 2013	7.1	5.64	44	19.3	8.38	44	1.4%	-1.69 [-2.18 , -1.20]
Wilens 2008	15.4	10.7354	120	24.5	10.7354	120	1.7%	-0.84 [-1.11 , -0.58]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	1.5%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**2942**			**2824**	**71.1%**	**-0.85 [-0.98 , -0.72]**
Heterogeneity: Tau² = 0.17; Chi² = 253.69, df = 52 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 12.70 (P < 0.00001)								
Total (95% CI)			**3668**			**3544**	**100.0%**	**-0.85 [-0.96 , -0.73]**
Heterogeneity: Tau² = 0.18; Chi² = 358.96, df = 75 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 14.44 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%								



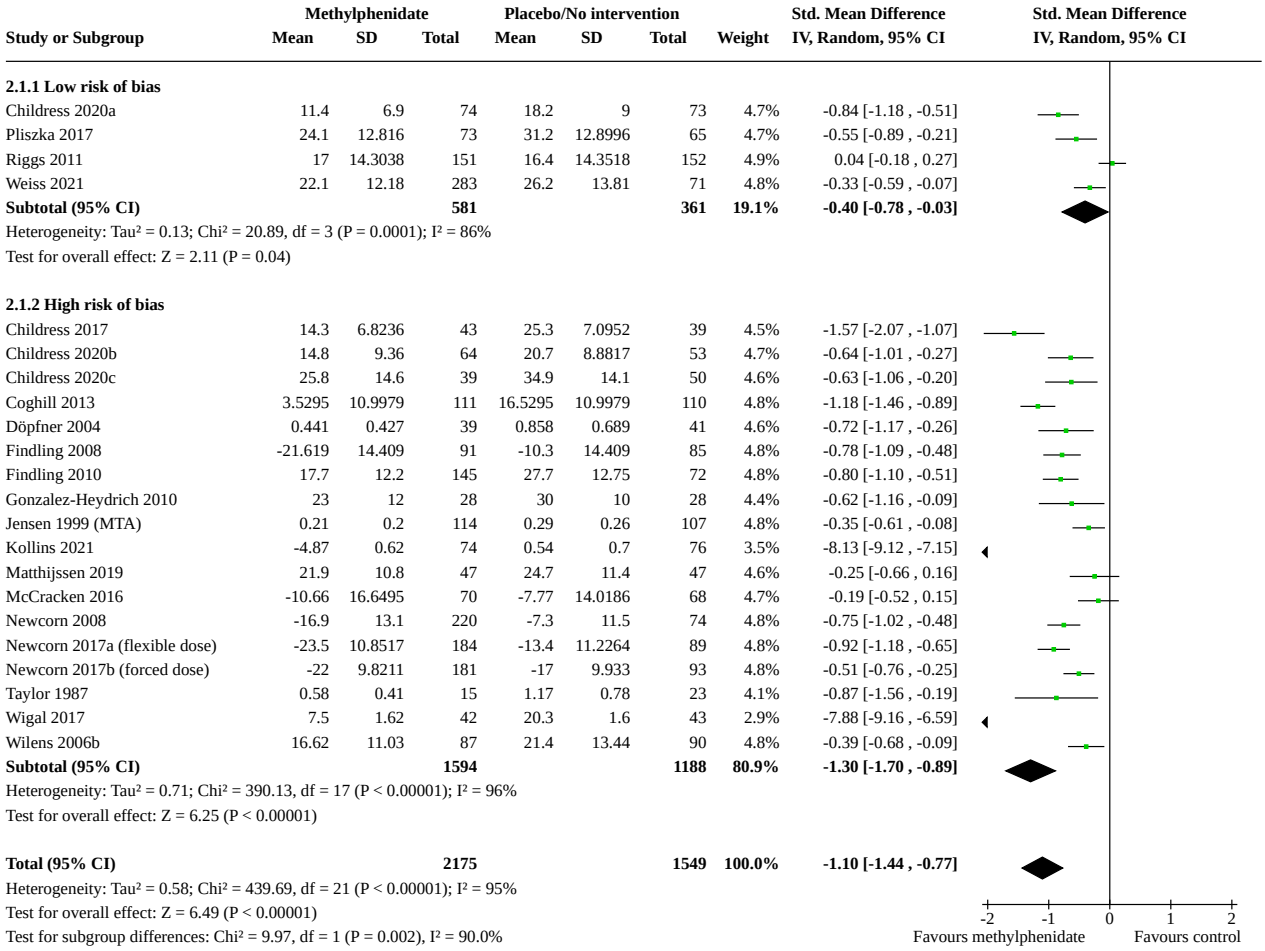
Comparison 2. Independent assessor-rated ADHD symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All parallel-group trials and first-period cross-over trials	22	3724	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.44, -0.77]
2.1.1 Low risk of bias	4	942	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.78, -0.03]
2.1.2 High risk of bias	18	2782	Std. Mean Difference (IV, Random, 95% CI)	-1.30 [-1.70, -0.89]
2.2 Subgroup analysis: types of scales	22		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 Swanson, Kotkin, Agler, M-Glynn and Pelham (SKAMP) Scale	6	778	Std. Mean Difference (IV, Random, 95% CI)	-2.79 [-4.10, -1.47]
2.2.2 ADHD Rating Scale (ADHD-RS)	14	2802	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.81, -0.38]
2.2.3 Swanson, Nolan and Pelham (SNAP) Scale	1	221	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.61, -0.08]
2.2.4 Unknown	1	78	Std. Mean Difference (IV, Random, 95% CI)	-0.94 [-1.41, -0.47]

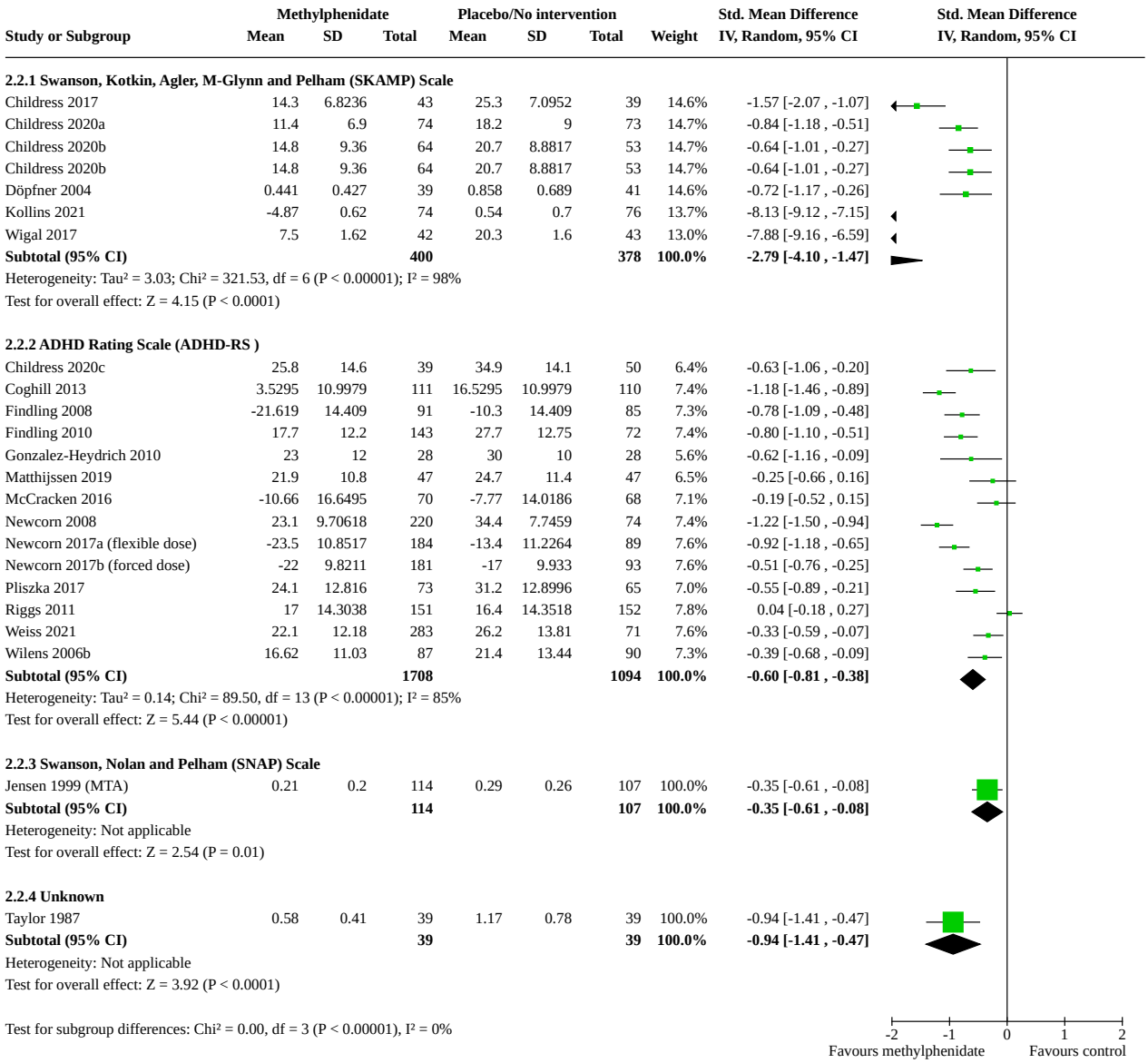
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Subgroup analysis: duration of treatment	22	3724	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.44, -0.77]
2.3.1 Short term (up to 6 months)	21	3503	Std. Mean Difference (IV, Random, 95% CI)	-1.15 [-1.50, -0.80]
2.3.2 Long term (over 6 months)	1	221	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.61, -0.08]
2.4 Subgroup analysis: dose	22	3724	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.44, -0.77]
2.4.1 Low dose	1	138	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.52, 0.15]
2.4.2 High dose	17	3005	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.13, -0.55]
2.4.3 Unknown dose	4	581	Std. Mean Difference (IV, Random, 95% CI)	-2.57 [-4.40, -0.74]
2.5 Subgroup analysis: trials with enrichment design compared with trials without enrichment design	22	3724	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.44, -0.77]
2.5.1 Trials with enrichment design of all participants	19	3245	Std. Mean Difference (IV, Random, 95% CI)	-1.24 [-1.61, -0.87]
2.5.2 Trials without enrichment design of all participants	3	479	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.62, 0.17]
2.6 Subgroup analysis: type of control group	22	3724	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.44, -0.77]
2.6.1 Placebo control group	20	3200	Std. Mean Difference (IV, Random, 95% CI)	-1.22 [-1.58, -0.85]
2.6.2 No-intervention control group	2	524	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.52, 0.23]
2.7 Subgroup analysis: parallel-group trials compared with first-period cross-over trials	22	3724	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.44, -0.77]
2.7.1 Parallel-group trials	19	3550	Std. Mean Difference (IV, Random, 95% CI)	-1.17 [-1.54, -0.80]
2.7.2 First-period cross-over trials	3	174	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-1.03, -0.41]
2.8 Cross-over trials (endpoint data)	22	3854	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-1.11, -0.83]
2.8.1 High risk of bias	22	3854	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-1.11, -0.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9 Subgroup analysis: cross-over trials (endpoint data): dose	22	5257	Std. Mean Difference (IV, Random, 95% CI)	-0.88 [-1.00, -0.76]
2.9.1 Low dose	17	3067	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-0.86, -0.58]
2.9.2 High dose	13	2051	Std. Mean Difference (IV, Random, 95% CI)	-1.07 [-1.27, -0.86]
2.9.3 Unknown dose	1	139	Std. Mean Difference (IV, Random, 95% CI)	-1.03 [-1.39, -0.68]
2.10 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)	42	7277	Std. Mean Difference (IV, Random, 95% CI)	-0.99 [-1.18, -0.80]
2.10.1 All parallel-group trials and first-period cross-over trials	21	3586	Std. Mean Difference (IV, Random, 95% CI)	-1.15 [-1.50, -0.81]
2.10.2 Cross-over trials (endpoint data)	21	3691	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.07, -0.78]
2.11 All parallel-group trials and cross-over trials: risk of bias	42	7277	Std. Mean Difference (IV, Random, 95% CI)	-0.99 [-1.18, -0.80]
2.11.1 Low risk of bias	4	942	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.78, -0.03]
2.11.2 High risk of bias	38	6335	Std. Mean Difference (IV, Random, 95% CI)	-1.06 [-1.25, -0.86]
2.12 All parallel-group trials and cross-over trials: vested interest	43	7414	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.17, -0.80]
2.12.1 Low risk of vested interest	6	600	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.43, -0.48]
2.12.2 High risk or unclear risk of vested interest	37	6814	Std. Mean Difference (IV, Random, 95% CI)	-0.99 [-1.19, -0.79]

Analysis 2.1. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 1: All parallel-group trials and first-period cross-over trials

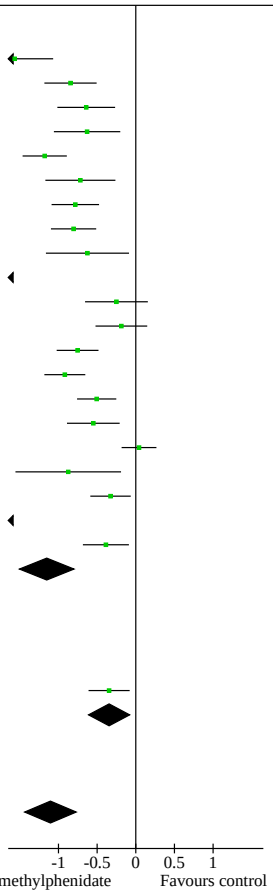


Analysis 2.2. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 2: Subgroup analysis: types of scales



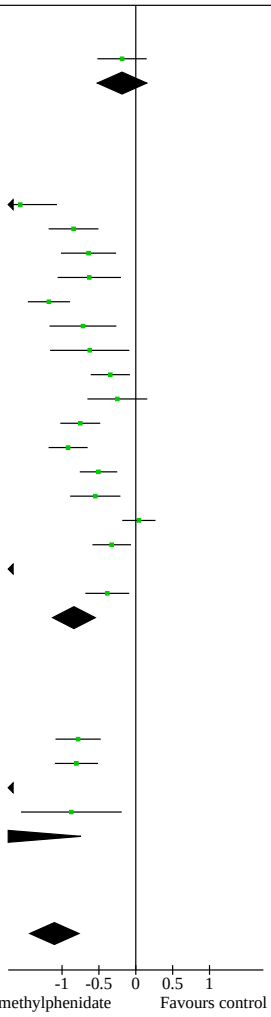
Analysis 2.3. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 3: Subgroup analysis: duration of treatment

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.3.1 Short term (up to 6 months)								
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	4.5%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	4.7%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	4.7%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	4.6%	-0.63 [-1.06 , -0.20]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	4.8%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	4.6%	-0.72 [-1.17 , -0.26]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	4.8%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	4.8%	-0.80 [-1.10 , -0.51]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	4.4%	-0.62 [-1.16 , -0.09]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	3.5%	-8.13 [-9.12 , -7.15]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	4.6%	-0.25 [-0.66 , 0.16]
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	4.7%	-0.19 [-0.52 , 0.15]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	4.8%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	4.8%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	4.8%	-0.51 [-0.76 , -0.25]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	4.7%	-0.55 [-0.89 , -0.21]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	4.9%	0.04 [-0.18 , 0.27]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	4.1%	-0.87 [-1.56 , -0.19]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	4.8%	-0.33 [-0.59 , -0.07]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	2.9%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	4.8%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**2061**			**1442**	**95.2%**	**-1.15 [-1.50 , -0.80]**
Heterogeneity: Tau² = 0.62; Chi² = 434.68, df = 20 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.40 (P < 0.00001)								
2.3.2 Long term (over 6 months)								
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	4.8%	-0.35 [-0.61 , -0.08]
Subtotal (95% CI)			**114**			**107**	**4.8%**	**-0.35 [-0.61 , -0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.54 (P = 0.01)								
Total (95% CI)			**2175**			**1549**	**100.0%**	**-1.10 [-1.44 , -0.77]**
Heterogeneity: Tau² = 0.58; Chi² = 439.69, df = 21 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.49 (P < 0.00001)								
Test for subgroup differences: Chi² = 12.82, df = 1 (P = 0.0003), I² = 92.2%								



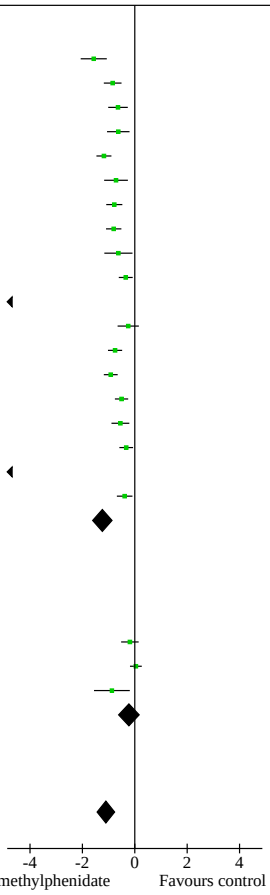
Analysis 2.4. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 4: Subgroup analysis: dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.4.1 Low dose								
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	4.7%	-0.19 [-0.52 , 0.15]
Subtotal (95% CI)			**70**			**68**	**4.7%**	**-0.19 [-0.52 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.09 (P = 0.27)								
2.4.2 High dose								
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	4.5%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	4.7%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	4.7%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	4.6%	-0.63 [-1.06 , -0.20]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	4.8%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	4.6%	-0.72 [-1.17 , -0.26]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	4.4%	-0.62 [-1.16 , -0.09]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	4.8%	-0.35 [-0.61 , -0.08]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	4.6%	-0.25 [-0.66 , 0.16]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	4.8%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	4.8%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	4.8%	-0.51 [-0.76 , -0.25]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	4.7%	-0.55 [-0.89 , -0.21]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	4.9%	0.04 [-0.18 , 0.27]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	4.8%	-0.33 [-0.59 , -0.07]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	2.9%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	4.8%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**1780**			**1225**	**78.1%**	**-0.84 [-1.13 , -0.55]**
Heterogeneity: Tau² = 0.33; Chi² = 206.80, df = 16 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 5.69 (P < 0.00001)								
2.4.3 Unknown dose								
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	4.8%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	4.8%	-0.80 [-1.10 , -0.51]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	3.5%	-8.13 [-9.12 , -7.15]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	4.1%	-0.87 [-1.56 , -0.19]
Subtotal (95% CI)			**325**			**256**	**17.1%**	**-2.57 [-4.40 , -0.74]**
Heterogeneity: Tau² = 3.38; Chi² = 203.89, df = 3 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 2.76 (P = 0.006)								
Total (95% CI)			**2175**			**1549**	**100.0%**	**-1.10 [-1.44 , -0.77]**
Heterogeneity: Tau² = 0.58; Chi² = 439.69, df = 21 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.49 (P < 0.00001)								
Test for subgroup differences: Chi² = 12.95, df = 2 (P = 0.002), I² = 84.6%								



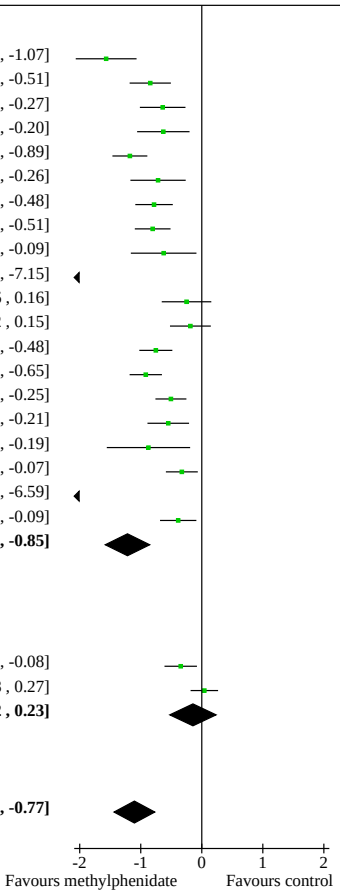
Analysis 2.5. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 5: Subgroup analysis: trials with enrichment design compared with trials without enrichment design

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.1 Trials with enrichment design of all participants								
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	4.5%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	4.7%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	4.7%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	4.6%	-0.63 [-1.06 , -0.20]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	4.8%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	4.6%	-0.72 [-1.17 , -0.26]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	4.8%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	4.8%	-0.80 [-1.10 , -0.51]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	4.4%	-0.62 [-1.16 , -0.09]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	4.8%	-0.35 [-0.61 , -0.08]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	3.5%	-8.13 [-9.12 , -7.15]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	4.6%	-0.25 [-0.66 , 0.16]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	4.8%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	4.8%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	4.8%	-0.51 [-0.76 , -0.25]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	4.7%	-0.55 [-0.89 , -0.21]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	4.8%	-0.33 [-0.59 , -0.07]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	2.9%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	4.8%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**1939**			**1306**	**86.3%**	**-1.24 [-1.61 , -0.87]**
Heterogeneity: Tau² = 0.62; Chi² = 390.73, df = 18 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.58 (P < 0.00001)								
2.5.2 Trials without enrichment design of all participants								
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	4.7%	-0.19 [-0.52 , 0.15]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	4.9%	0.04 [-0.18 , 0.27]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	4.1%	-0.87 [-1.56 , -0.19]
Subtotal (95% CI)			**236**			**243**	**13.7%**	**-0.22 [-0.62 , 0.17]**
Heterogeneity: Tau² = 0.08; Chi² = 6.69, df = 2 (P = 0.04); I² = 70%								
Test for overall effect: Z = 1.12 (P = 0.26)								
Total (95% CI)			**2175**			**1549**	**100.0%**	**-1.10 [-1.44 , -0.77]**
Heterogeneity: Tau² = 0.58; Chi² = 439.69, df = 21 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.49 (P < 0.00001)								
Test for subgroup differences: Chi² = 13.65, df = 1 (P = 0.0002), I² = 92.7%								



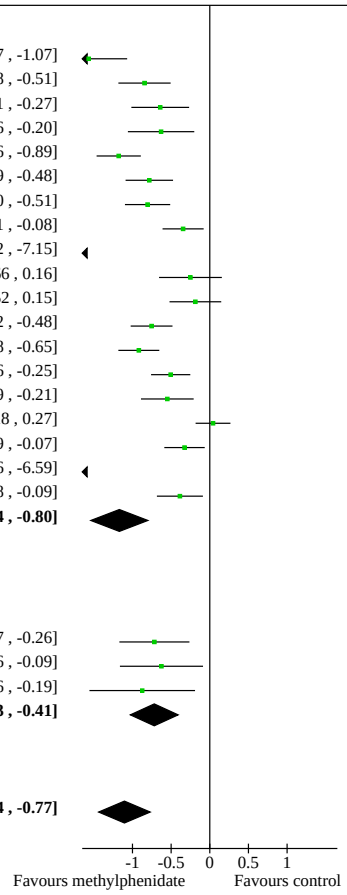
Analysis 2.6. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 6: Subgroup analysis: type of control group

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.6.1 Placebo control group								
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	4.5%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	4.7%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	4.7%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	4.6%	-0.63 [-1.06 , -0.20]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	4.8%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	4.6%	-0.72 [-1.17 , -0.26]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	4.8%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	4.8%	-0.80 [-1.10 , -0.51]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	4.4%	-0.62 [-1.16 , -0.09]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	3.5%	-8.13 [-9.12 , -7.15]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	4.6%	-0.25 [-0.66 , 0.16]
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	4.7%	-0.19 [-0.52 , 0.15]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	4.8%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	4.8%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	4.8%	-0.51 [-0.76 , -0.25]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	4.7%	-0.55 [-0.89 , -0.21]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	4.1%	-0.87 [-1.56 , -0.19]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	4.8%	-0.33 [-0.59 , -0.07]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	2.9%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	4.8%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**1910**			**1290**	**90.3%**	**-1.22 [-1.58 , -0.85]**
Heterogeneity: Tau² = 0.63; Chi² = 392.91, df = 19 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.56 (P < 0.00001)								
2.6.2 No-intervention control group								
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	4.8%	-0.35 [-0.61 , -0.08]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	4.9%	0.04 [-0.18 , 0.27]
Subtotal (95% CI)			**265**			**259**	**9.7%**	**-0.14 [-0.52 , 0.23]**
Heterogeneity: Tau² = 0.06; Chi² = 4.74, df = 1 (P = 0.03); I² = 79%								
Test for overall effect: Z = 0.75 (P = 0.45)								
Total (95% CI)			**2175**			**1549**	**100.0%**	**-1.10 [-1.44 , -0.77]**
Heterogeneity: Tau² = 0.58; Chi² = 439.69, df = 21 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.49 (P < 0.00001)								
Test for subgroup differences: Chi² = 16.00, df = 1 (P < 0.0001), I² = 93.8%								



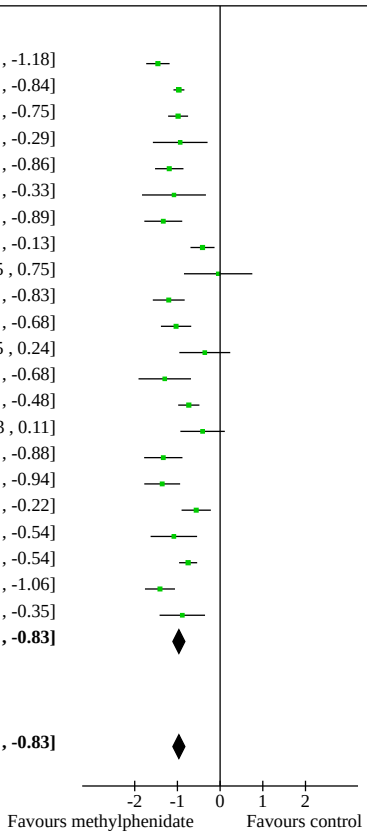
Analysis 2.7. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 7: Subgroup analysis: parallel-group trials compared with first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.7.1 Parallel-group trials								
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	4.5%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	4.7%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	4.7%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	4.6%	-0.63 [-1.06 , -0.20]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	4.8%	-1.18 [-1.46 , -0.89]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	4.8%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	4.8%	-0.80 [-1.10 , -0.51]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	4.8%	-0.35 [-0.61 , -0.08]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	3.5%	-8.13 [-9.12 , -7.15]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	4.6%	-0.25 [-0.66 , 0.16]
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	4.7%	-0.19 [-0.52 , 0.15]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	4.8%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	4.8%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	4.8%	-0.51 [-0.76 , -0.25]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	4.7%	-0.55 [-0.89 , -0.21]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	4.9%	0.04 [-0.18 , 0.27]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	4.8%	-0.33 [-0.59 , -0.07]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	2.9%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	4.8%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**2093**			**1457**	**86.9%**	**-1.17 [-1.54 , -0.80]**
Heterogeneity: Tau² = 0.62; Chi² = 439.10, df = 18 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 6.22 (P < 0.00001)								
2.7.2 First-period cross-over trials								
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	4.6%	-0.72 [-1.17 , -0.26]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	4.4%	-0.62 [-1.16 , -0.09]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	4.1%	-0.87 [-1.56 , -0.19]
Subtotal (95% CI)			**82**			**92**	**13.1%**	**-0.72 [-1.03 , -0.41]**
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.85); I² = 0%								
Test for overall effect: Z = 4.56 (P < 0.00001)								
Total (95% CI)			**2175**			**1549**	**100.0%**	**-1.10 [-1.44 , -0.77]**
Heterogeneity: Tau² = 0.58; Chi² = 439.69, df = 21 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.49 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.38, df = 1 (P = 0.07), I² = 70.4%								



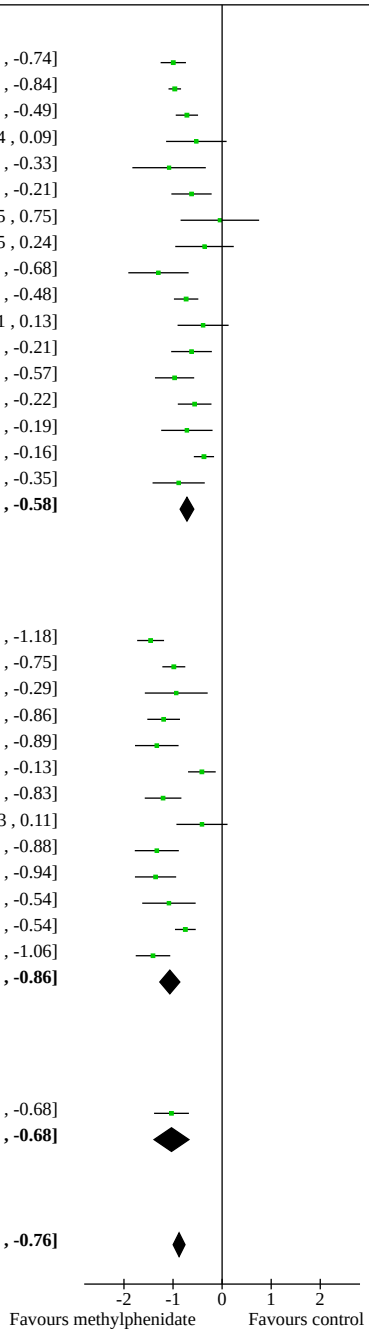
Analysis 2.8. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 8: Cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.8.1 High risk of bias								
Bedard 2008	2.22	2.17	130	6.51	3.54	130	5.8%	-1.46 [-1.73 , -1.18]
Bhat 2020	30	23.5	526	55.9	29.8	526	7.0%	-0.96 [-1.09 , -0.84]
Brams 2012	-4.47	9.1005	158	4.5	9.088	158	6.2%	-0.98 [-1.22 , -0.75]
Chronis 2003	3.3	1.7	21	5.8	3.3	21	2.9%	-0.93 [-1.57 , -0.29]
Döpfner 2004	0.374	0.366	82	1.081	0.751	82	5.2%	-1.19 [-1.52 , -0.86]
Douglas 1986	0.47	0.42	16	1.07	0.64	16	2.4%	-1.08 [-1.83 , -0.33]
Fabiano 2007	2.3	1.5	48	6	3.6	48	4.3%	-1.33 [-1.77 , -0.89]
Huang 2021	3.1	2.9	99	4.3	2.9	99	5.7%	-0.41 [-0.69 , -0.13]
Kent 1995	2.7	2.3	12	2.8	1.9	12	2.2%	-0.05 [-0.85 , 0.75]
Murray 2011	8.7	7.7761	67	18.1	7.76	64	4.9%	-1.20 [-1.58 , -0.83]
NCT02536105	20.07	12.6	67	33.48	13.23	72	5.0%	-1.03 [-1.39 , -0.68]
Pelham 1990a	4.81	3.2	22	6.3	4.8	22	3.2%	-0.36 [-0.95 , 0.24]
Pelham 1999	2.6	1.4	25	5.6	2.9	25	3.1%	-1.30 [-1.91 , -0.68]
Pelham 2002	3	1.4	133	4.4	2.3	133	6.0%	-0.73 [-0.98 , -0.48]
Pelham 2005	5.1	3.8	29	6.9	4.8	29	3.7%	-0.41 [-0.93 , 0.11]
Pelham 2014	2.3	1.5	47	6	3.6	47	4.2%	-1.33 [-1.78 , -0.88]
Silva 2005a	0.67	0.58	54	1.94	1.18	54	4.5%	-1.36 [-1.78 , -0.94]
Silva 2008	2.24	9.8542	68	7.77	9.7965	68	5.2%	-0.56 [-0.90 , -0.22]
Solanto 2009	15.21	9.21	30	26.58	11.39	30	3.5%	-1.08 [-1.63 , -0.54]
Swanson 2004b	12.62	11	184	22.11	14.1	184	6.4%	-0.75 [-0.96 , -0.54]
Wigal 2011	9.8	7.7719	78	20.8	7.7719	78	5.1%	-1.41 [-1.76 , -1.06]
Wilens 2010	14.76	14.48	30	28.33	15.75	30	3.6%	-0.89 [-1.42 , -0.35]
Subtotal (95% CI)			**1926**			**1928**	**100.0%**	**-0.97 [-1.11 , -0.83]**
Heterogeneity: Tau² = 0.07; Chi² = 72.83, df = 21 (P < 0.00001); I² = 71%								
Test for overall effect: Z = 13.51 (P < 0.00001)								
Total (95% CI)			**1926**			**1928**	**100.0%**	**-0.97 [-1.11 , -0.83]**
Heterogeneity: Tau² = 0.07; Chi² = 72.83, df = 21 (P < 0.00001); I² = 71%								
Test for overall effect: Z = 13.51 (P < 0.00001)								
Test for subgroup differences: Not applicable								



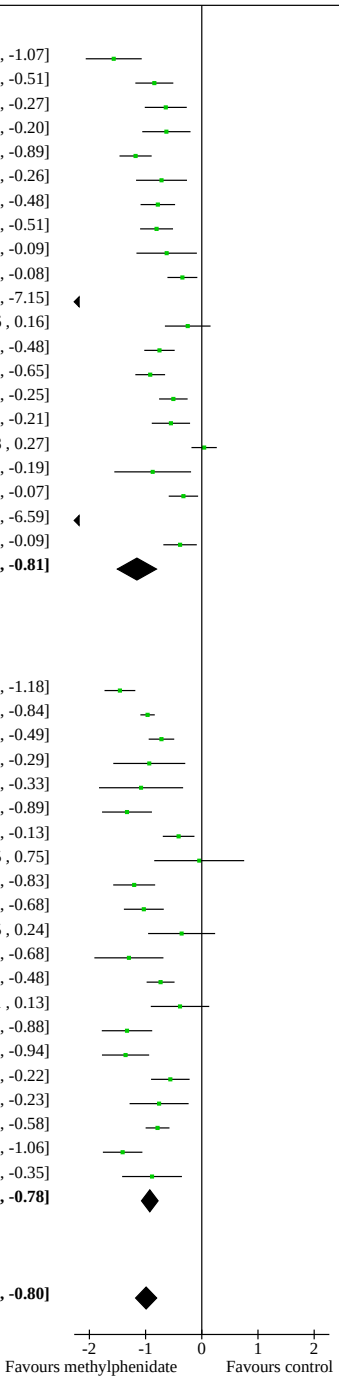
Analysis 2.9. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 9: Subgroup analysis: cross-over trials (endpoint data): dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.9.1 Low dose								
Bedard 2008	3.39	2.65	130	6.51	3.54	130	4.1%	-0.99 [-1.25 , -0.74]
Bhat 2020	30	23.5	526	55.9	29.8	526	4.8%	-0.96 [-1.09 , -0.84]
Brams 2012	-2.02	9.041	159	4.5	9.088	158	4.3%	-0.72 [-0.94 , -0.49]
Chronis 2003	4.3	2.2	21	5.8	3.3	21	2.2%	-0.52 [-1.14 , 0.09]
Douglas 1986	0.47	0.42	16	1.07	0.64	16	1.7%	-1.08 [-1.83 , -0.33]
Fabiano 2007	4	2.7	48	6	3.6	48	3.2%	-0.62 [-1.03 , -0.21]
Kent 1995	2.7	2.3	12	2.8	1.9	12	1.6%	-0.05 [-0.85 , 0.75]
Pelham 1990a	4.81	3.2	22	6.3	4.8	22	2.3%	-0.36 [-0.95 , 0.24]
Pelham 1999	2.6	1.4	25	5.6	2.9	25	2.2%	-1.30 [-1.91 , -0.68]
Pelham 2002	3	1.4	133	4.4	2.3	133	4.2%	-0.73 [-0.98 , -0.48]
Pelham 2005	5.2	3.8	29	6.9	4.8	29	2.6%	-0.39 [-0.91 , 0.13]
Pelham 2014	4	2.7	47	6	3.6	47	3.2%	-0.62 [-1.04 , -0.21]
Silva 2005a	0.99	0.71	54	1.94	1.18	54	3.3%	-0.97 [-1.37 , -0.57]
Silva 2008	2.24	9.8542	68	7.77	9.7965	68	3.6%	-0.56 [-0.90 , -0.22]
Solanto 2009	18.63	10.45	30	26.58	11.39	30	2.6%	-0.72 [-1.24 , -0.19]
Swanson 2004b	16.44	12.43	184	21.47	14.61	184	4.4%	-0.37 [-0.58 , -0.16]
Wilens 2010	14.76	14.48	30	28.33	15.75	30	2.6%	-0.89 [-1.42 , -0.35]
Subtotal (95% CI)			**1534**			**1533**	**52.8%**	**-0.72 [-0.86 , -0.58]**
Heterogeneity: Tau² = 0.04; Chi² = 41.31, df = 16 (P = 0.0005); I² = 61%								
Test for overall effect: Z = 10.08 (P < 0.00001)								
2.9.2 High dose								
Bedard 2008	2.22	2.17	130	6.51	3.54	130	4.0%	-1.46 [-1.73 , -1.18]
Brams 2012	-4.47	9.1005	158	4.5	9.088	158	4.3%	-0.98 [-1.22 , -0.75]
Chronis 2003	3.3	1.7	21	5.8	3.3	21	2.1%	-0.93 [-1.57 , -0.29]
Döpfner 2004	0.374	0.366	82	1.081	0.751	82	3.7%	-1.19 [-1.52 , -0.86]
Fabiano 2007	2.3	1.5	48	6	3.6	48	3.0%	-1.33 [-1.77 , -0.89]
Huang 2021	3.1	2.9	99	4.3	2.9	99	4.0%	-0.41 [-0.69 , -0.13]
Murray 2011	8.7	7.7761	67	18.1	7.76	64	3.4%	-1.20 [-1.58 , -0.83]
Pelham 2005	5.1	3.8	29	6.9	4.8	29	2.6%	-0.41 [-0.93 , 0.11]
Pelham 2014	2.3	1.5	47	6	3.6	47	3.0%	-1.33 [-1.78 , -0.88]
Silva 2005a	0.67	0.58	54	1.94	1.18	54	3.1%	-1.36 [-1.78 , -0.94]
Solanto 2009	15.21	9.21	30	26.58	11.39	30	2.5%	-1.08 [-1.63 , -0.54]
Swanson 2004b	12.62	11	184	22.11	14.1	184	4.4%	-0.75 [-0.96 , -0.54]
Wigal 2011	9.8	7.7719	78	20.8	7.7719	78	3.6%	-1.41 [-1.76 , -1.06]
Subtotal (95% CI)			**1027**			**1024**	**43.7%**	**-1.07 [-1.27 , -0.86]**
Heterogeneity: Tau² = 0.10; Chi² = 52.29, df = 12 (P < 0.00001); I² = 77%								
Test for overall effect: Z = 10.24 (P < 0.00001)								
2.9.3 Unknown dose								
NCT02536105	20.07	12.6	67	33.48	13.23	72	3.5%	-1.03 [-1.39 , -0.68]
Subtotal (95% CI)			**67**			**72**	**3.5%**	**-1.03 [-1.39 , -0.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.70 (P < 0.00001)								
Total (95% CI)			**2628**			**2629**	**100.0%**	**-0.88 [-1.00 , -0.76]**
Heterogeneity: Tau² = 0.07; Chi² = 111.92, df = 30 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 14.24 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.86, df = 2 (P = 0.01), I² = 77.4%								

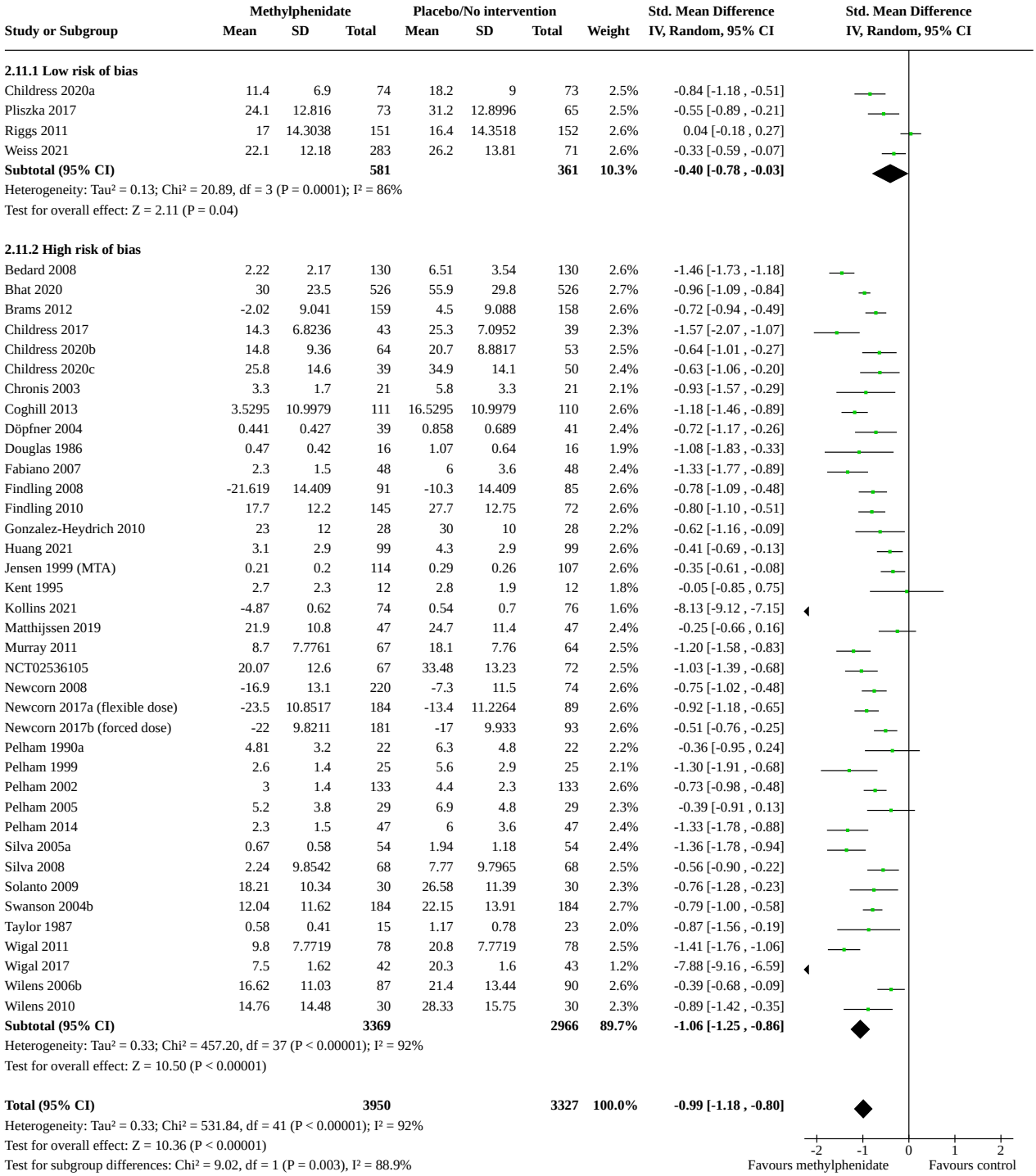


Analysis 2.10. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 10: Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.10.1 All parallel-group trials and first-period cross-over trials								
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	2.3%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	2.5%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	2.5%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	2.4%	-0.63 [-1.06 , -0.20]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	2.6%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	2.4%	-0.72 [-1.17 , -0.26]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	2.6%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	2.6%	-0.80 [-1.10 , -0.51]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	2.2%	-0.62 [-1.16 , -0.09]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	2.6%	-0.35 [-0.61 , -0.08]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	1.6%	-8.13 [-9.12 , -7.15]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	2.4%	-0.25 [-0.66 , 0.16]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	2.6%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	2.6%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	2.6%	-0.51 [-0.76 , -0.25]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	2.5%	-0.55 [-0.89 , -0.21]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	2.6%	0.04 [-0.18 , 0.27]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	2.0%	-0.87 [-1.56 , -0.19]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	2.6%	-0.33 [-0.59 , -0.07]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	1.2%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	2.6%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**2105**			**1481**	**50.1%**	**-1.15 [-1.50 , -0.81]**
Heterogeneity: Tau² = 0.60; Chi² = 432.37, df = 20 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.52 (P < 0.00001)								
2.10.2 Cross-over trials (endpoint data)								
Bedard 2008	2.22	2.17	130	6.51	3.54	130	2.6%	-1.46 [-1.73 , -1.18]
Bhat 2020	30	23.5	526	55.9	29.8	526	2.7%	-0.96 [-1.09 , -0.84]
Brams 2012	-2.02	9.041	159	4.5	9.088	158	2.6%	-0.72 [-0.94 , -0.49]
Chronis 2003	3.3	1.7	21	5.8	3.3	21	2.1%	-0.93 [-1.57 , -0.29]
Douglas 1986	0.47	0.42	16	1.07	0.64	16	1.9%	-1.08 [-1.83 , -0.33]
Fabiano 2007	2.3	1.5	48	6	3.6	48	2.4%	-1.33 [-1.77 , -0.89]
Huang 2021	3.1	2.9	99	4.3	2.9	99	2.6%	-0.41 [-0.69 , -0.13]
Kent 1995	2.7	2.3	12	2.8	1.9	12	1.8%	-0.05 [-0.85 , 0.75]
Murray 2011	8.7	7.7761	67	18.1	7.76	64	2.5%	-1.20 [-1.58 , -0.83]
NCT02536105	20.07	12.6	67	33.48	13.23	72	2.5%	-1.03 [-1.39 , -0.68]
Pelham 1990a	4.81	3.2	22	6.3	4.8	22	2.2%	-0.36 [-0.95 , 0.24]
Pelham 1999	2.6	1.4	25	5.6	2.9	25	2.1%	-1.30 [-1.91 , -0.68]
Pelham 2002	3	1.4	133	4.4	2.3	133	2.6%	-0.73 [-0.98 , -0.48]
Pelham 2005	5.2	3.8	29	6.9	4.8	29	2.3%	-0.39 [-0.91 , 0.13]
Pelham 2014	2.3	1.5	47	6	3.6	47	2.4%	-1.33 [-1.78 , -0.88]
Silva 2005a	0.67	0.58	54	1.94	1.18	54	2.4%	-1.36 [-1.78 , -0.94]
Silva 2008	2.24	9.8542	68	7.77	9.7965	68	2.5%	-0.56 [-0.90 , -0.22]
Solanto 2009	18.21	10.34	30	26.58	11.39	30	2.3%	-0.76 [-1.28 , -0.23]
Swanson 2004b	12.04	11.62	184	22.15	13.91	184	2.7%	-0.79 [-1.00 , -0.58]
Wigal 2011	9.8	7.7719	78	20.8	7.7719	78	2.5%	-1.41 [-1.76 , -1.06]
Wilens 2010	14.76	14.48	30	28.33	15.75	30	2.3%	-0.89 [-1.42 , -0.35]
Subtotal (95% CI)			**1845**			**1846**	**49.9%**	**-0.93 [-1.07 , -0.78]**
Heterogeneity: Tau² = 0.07; Chi² = 73.37, df = 20 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 12.30 (P < 0.00001)								
Total (95% CI)			**3950**			**3327**	**100.0%**	**-0.99 [-1.18 , -0.80]**
Heterogeneity: Tau² = 0.33; Chi² = 531.84, df = 41 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 10.36 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.42, df = 1 (P = 0.23), I² = 29.5%								



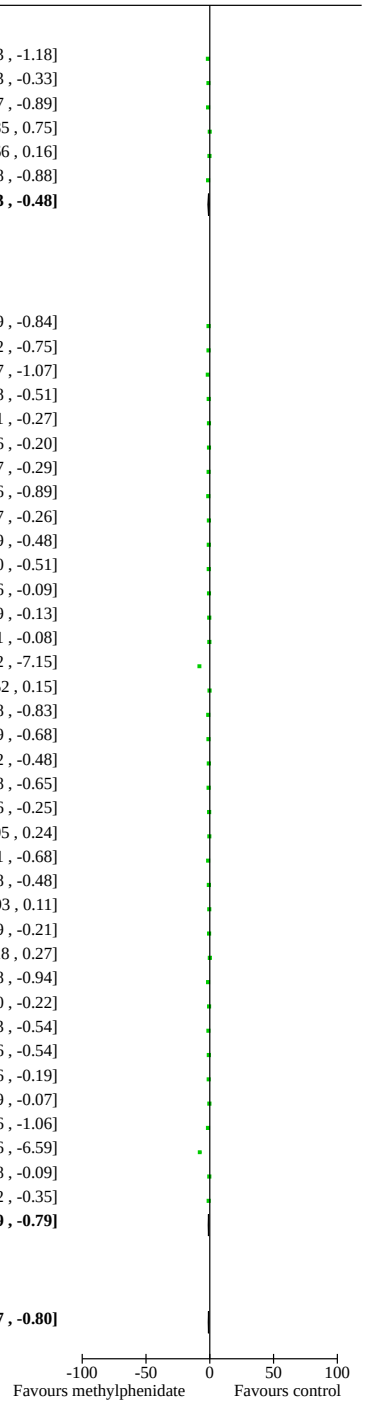
Analysis 2.11. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 11: All parallel-group trials and cross-over trials: risk of bias



Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.11.1 Low risk of bias								
Childress 2020a	11.4	6.9	74	18.2	9	73	2.5%	-0.84 [-1.18 , -0.51]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	2.5%	-0.55 [-0.89 , -0.21]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	2.6%	0.04 [-0.18 , 0.27]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	2.6%	-0.33 [-0.59 , -0.07]
Subtotal (95% CI)			**581**			**361**	**10.3%**	**-0.40 [-0.78 , -0.03]**
Heterogeneity: Tau² = 0.13; Chi² = 20.89, df = 3 (P = 0.0001); I² = 86%								
Test for overall effect: Z = 2.11 (P = 0.04)								
2.11.2 High risk of bias								
Bedard 2008	2.22	2.17	130	6.51	3.54	130	2.6%	-1.46 [-1.73 , -1.18]
Bhat 2020	30	23.5	526	55.9	29.8	526	2.7%	-0.96 [-1.09 , -0.84]
Brams 2012	-2.02	9.041	159	4.5	9.088	158	2.6%	-0.72 [-0.94 , -0.49]
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	2.3%	-1.57 [-2.07 , -1.07]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	2.5%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	2.4%	-0.63 [-1.06 , -0.20]
Chronis 2003	3.3	1.7	21	5.8	3.3	21	2.1%	-0.93 [-1.57 , -0.29]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	2.6%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	2.4%	-0.72 [-1.17 , -0.26]
Douglas 1986	0.47	0.42	16	1.07	0.64	16	1.9%	-1.08 [-1.83 , -0.33]
Fabiano 2007	2.3	1.5	48	6	3.6	48	2.4%	-1.33 [-1.77 , -0.89]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	2.6%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	2.6%	-0.80 [-1.10 , -0.51]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	2.2%	-0.62 [-1.16 , -0.09]
Huang 2021	3.1	2.9	99	4.3	2.9	99	2.6%	-0.41 [-0.69 , -0.13]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	2.6%	-0.35 [-0.61 , -0.08]
Kent 1995	2.7	2.3	12	2.8	1.9	12	1.8%	-0.05 [-0.85 , 0.75]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	1.6%	-8.13 [-9.12 , -7.15]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	2.4%	-0.25 [-0.66 , 0.16]
Murray 2011	8.7	7.7761	67	18.1	7.76	64	2.5%	-1.20 [-1.58 , -0.83]
NCT02536105	20.07	12.6	67	33.48	13.23	72	2.5%	-1.03 [-1.39 , -0.68]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	2.6%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	2.6%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	2.6%	-0.51 [-0.76 , -0.25]
Pelham 1990a	4.81	3.2	22	6.3	4.8	22	2.2%	-0.36 [-0.95 , 0.24]
Pelham 1999	2.6	1.4	25	5.6	2.9	25	2.1%	-1.30 [-1.91 , -0.68]
Pelham 2002	3	1.4	133	4.4	2.3	133	2.6%	-0.73 [-0.98 , -0.48]
Pelham 2005	5.2	3.8	29	6.9	4.8	29	2.3%	-0.39 [-0.91 , 0.13]
Pelham 2014	2.3	1.5	47	6	3.6	47	2.4%	-1.33 [-1.78 , -0.88]
Silva 2005a	0.67	0.58	54	1.94	1.18	54	2.4%	-1.36 [-1.78 , -0.94]
Silva 2008	2.24	9.8542	68	7.77	9.7965	68	2.5%	-0.56 [-0.90 , -0.22]
Solanto 2009	18.21	10.34	30	26.58	11.39	30	2.3%	-0.76 [-1.28 , -0.23]
Swanson 2004b	12.04	11.62	184	22.15	13.91	184	2.7%	-0.79 [-1.00 , -0.58]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	2.0%	-0.87 [-1.56 , -0.19]
Wigal 2011	9.8	7.7719	78	20.8	7.7719	78	2.5%	-1.41 [-1.76 , -1.06]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	1.2%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	2.6%	-0.39 [-0.68 , -0.09]
Wilens 2010	14.76	14.48	30	28.33	15.75	30	2.3%	-0.89 [-1.42 , -0.35]
Subtotal (95% CI)			**3369**			**2966**	**89.7%**	**-1.06 [-1.25 , -0.86]**
Heterogeneity: Tau² = 0.33; Chi² = 457.20, df = 37 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 10.50 (P < 0.00001)								
Total (95% CI)			**3950**			**3327**	**100.0%**	**-0.99 [-1.18 , -0.80]**
Heterogeneity: Tau² = 0.33; Chi² = 531.84, df = 41 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 10.36 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.02, df = 1 (P = 0.003), I² = 88.9%								

Analysis 2.12. Comparison 2: Independent assessor-rated ADHD symptoms, Outcome 12: All parallel-group trials and cross-over trials: vested interest

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.12.1 Low risk of vested interest								
Bedard 2008	2.22	2.17	130	6.51	3.54	130	2.5%	-1.46 [-1.73 , -1.18]
Douglas 1986	0.47	0.42	16	1.07	0.64	16	1.9%	-1.08 [-1.83 , -0.33]
Fabiano 2007	2.3	1.5	48	6	3.6	48	2.3%	-1.33 [-1.77 , -0.89]
Kent 1995	2.7	2.3	12	2.8	1.9	12	1.8%	-0.05 [-0.85 , 0.75]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	2.4%	-0.25 [-0.66 , 0.16]
Pelham 2014	2.3	1.5	47	6	3.6	47	2.3%	-1.33 [-1.78 , -0.88]
Subtotal (95% CI)			**300**			**300**	**13.2%**	**-0.96 [-1.43 , -0.48]**
Heterogeneity: Tau² = 0.29; Chi² = 32.08, df = 5 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 3.90 (P < 0.0001)								
2.12.2 High risk or unclear risk of vested interest								
Bhat 2020	30	23.5	526	55.9	29.8	526	2.6%	-0.96 [-1.09 , -0.84]
Brams 2012	-4.47	9.1005	158	4.5	9.088	158	2.6%	-0.98 [-1.22 , -0.75]
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	2.2%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	2.5%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	2.4%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	2.3%	-0.63 [-1.06 , -0.20]
Chronis 2003	3.3	1.7	21	5.8	3.3	21	2.0%	-0.93 [-1.57 , -0.29]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	2.5%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	2.3%	-0.72 [-1.17 , -0.26]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	2.5%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	2.5%	-0.80 [-1.10 , -0.51]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	2.2%	-0.62 [-1.16 , -0.09]
Huang 2021	3.1	2.9	99	4.3	2.9	99	2.5%	-0.41 [-0.69 , -0.13]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	2.5%	-0.35 [-0.61 , -0.08]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	1.5%	-8.13 [-9.12 , -7.15]
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	2.5%	-0.19 [-0.52 , 0.15]
Murray 2011	8.7	7.7761	67	18.1	7.76	64	2.4%	-1.20 [-1.58 , -0.83]
NCT02536105	20.07	12.6	67	33.48	13.23	72	2.4%	-1.03 [-1.39 , -0.68]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	2.5%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	2.5%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	2.6%	-0.51 [-0.76 , -0.25]
Pelham 1990a	4.81	3.2	22	6.3	4.8	22	2.1%	-0.36 [-0.95 , 0.24]
Pelham 1999	2.6	1.4	25	5.6	2.9	25	2.1%	-1.30 [-1.91 , -0.68]
Pelham 2002	3	1.4	133	4.4	2.3	133	2.6%	-0.73 [-0.98 , -0.48]
Pelham 2005	5.1	3.8	29	6.9	4.8	29	2.2%	-0.41 [-0.93 , 0.11]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	2.5%	-0.55 [-0.89 , -0.21]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	2.6%	0.04 [-0.18 , 0.27]
Silva 2005a	0.67	0.58	54	1.94	1.18	54	2.4%	-1.36 [-1.78 , -0.94]
Silva 2008	2.24	9.8542	68	7.77	9.7965	68	2.5%	-0.56 [-0.90 , -0.22]
Solanto 2009	15.21	9.21	30	26.58	11.39	30	2.2%	-1.08 [-1.63 , -0.54]
Swanson 2004b	12.62	11	184	22.11	14.1	184	2.6%	-0.75 [-0.96 , -0.54]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	2.0%	-0.87 [-1.56 , -0.19]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	2.5%	-0.33 [-0.59 , -0.07]
Wigal 2011	9.8	7.7719	78	20.8	7.7719	78	2.4%	-1.41 [-1.76 , -1.06]
Wigal 2017	7.5	1.62	42	20.3	1.6	43	1.2%	-7.88 [-9.16 , -6.59]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	2.5%	-0.39 [-0.68 , -0.09]
Wilens 2010	14.76	14.48	30	28.33	15.75	30	2.2%	-0.89 [-1.42 , -0.35]
Subtotal (95% CI)			**3719**			**3095**	**86.8%**	**-0.99 [-1.19 , -0.79]**
Heterogeneity: Tau² = 0.34; Chi² = 502.28, df = 36 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 9.70 (P < 0.00001)								
Total (95% CI)			**4019**			**3395**	**100.0%**	**-0.98 [-1.17 , -0.80]**
Heterogeneity: Tau² = 0.33; Chi² = 547.60, df = 42 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 10.39 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%								



Comparison 3. Parent-rated ADHD symptoms

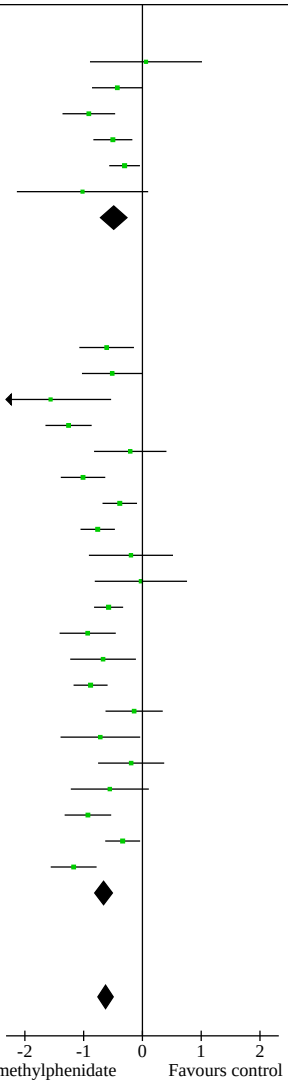
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All parallel-group trials and first-period cross-over trials	27	2927	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.76, -0.50]
3.1.1 Low risk of bias	6	702	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-0.71, -0.26]
3.1.2 High risk of bias	21	2225	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-0.81, -0.51]
3.2 Subgroup analysis: types of scales	27		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2.1 Conners' Parent Rating Scale (CPRS)	8	800	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.80, -0.26]
3.2.2 ADHD Rating Scale - Fourth Edition (ADHD-RS-IV)	5	753	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.53, -0.21]
3.2.3 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)	1	85	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.36, -0.46]
3.2.4 Conners' ADHD/DSM-IV Scales - Parent (CADS-P)	2	195	Std. Mean Difference (IV, Random, 95% CI)	-1.12 [-1.44, -0.81]
3.2.5 CADS-P Inattentive subscale	1	109	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-1.17, -0.39]
3.2.6 CADS-P Hyperactivity subscale	1	109	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.32, -0.53]
3.2.7 Clinican's Manual for the Assesment of Disruptive Behavior Disorders Rating Scale for Parents (Barkley)	1	41	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.82, 0.41]
3.2.8 Abbreviated Conners' Rating Scale (ACRS) - Parent	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.99, -0.25]
3.2.9 Swanson, Nolan, and Pelham, Fourth Edition - Parent (SNAP-IV-Parent) Scale	4	390	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.80, -0.39]
3.2.10 Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale	1	86	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.86, 0.00]
3.2.11 IOWA Conners' Rating Scale - Inattention/Overactivity (IOWA-I/O)	3	352	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-1.35, -0.21]
3.2.12 Parent Vanderbilt ADHD Rating Scale	1	97	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.23, -0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Subgroup analysis: duration of treatment	27	2927	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.76, -0.50]
3.3.1 Short term (up to 6 months)	25	2605	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.78, -0.49]
3.3.2 Long term (over 6 months)	2	322	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.79, -0.34]
3.4 Subgroup analysis: dose	27	3075	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-0.74, -0.48]
3.4.1 Low dose	4	254	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.14, 0.13]
3.4.2 High dose	12	1650	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-0.80, -0.37]
3.4.3 Unknown dose	13	1171	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-0.83, -0.51]
3.5 Subgroup analysis: medication status - medication naive versus not medication naive	11	992	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-0.87, -0.43]
3.5.1 Medication naive	7	544	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-0.84, -0.32]
3.5.2 Not medication naive	4	448	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.16, -0.35]
3.6 Subgroup analysis: trials with enrichment design compared with trials without enrichment design	25	2803	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.77, -0.49]
3.6.1 Trials with enrichment design of all participants	13	2155	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.78, -0.48]
3.6.2 Trials without enrichment design of all participants	12	648	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-0.88, -0.34]
3.7 Subgroup analysis: parallel-group trials compared with first-period cross-over trials	27	2927	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.76, -0.50]
3.7.1 Parallel-group trials	25	2874	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.76, -0.49]
3.7.2 First-period cross-over trials	2	53	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-1.25, -0.11]
3.8 Subgroup analysis: type of control group	27	2927	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.76, -0.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.8.1 Placebo control group	19	2263	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-0.80, -0.48]
3.8.2 No-intervention control group	8	664	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.84, -0.34]
3.9 Cross-over trials (endpoint data)	45	4971	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-0.86, -0.55]
3.9.1 Low risk of bias	8	853	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.72, -0.40]
3.9.2 High risk of bias	37	4118	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.94, -0.57]
3.10 Subgroup analysis: cross-over trials (endpoint data): dose	45	6155	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.76, -0.50]
3.10.1 Low dose	26	3242	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-0.71, -0.45]
3.10.2 High dose	29	2508	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.90, -0.60]
3.10.3 Unknown dose	3	405	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-1.55, 1.93]
3.11 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)	69	7838	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-0.78, -0.56]
3.11.1 All parallel-group trials and first-period cross-over trials	27	2955	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.76, -0.50]
3.11.2 Cross-over trials (endpoint data)	43	4883	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-0.86, -0.55]
3.12 All parallel-group trials and cross-over trials: risk of bias	69	7503	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-0.79, -0.57]
3.12.1 Low risk of bias	12	1234	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.68, -0.39]
3.12.2 High risk of bias	57	6269	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-0.84, -0.58]
3.13 All parallel-group trials and cross-over trials: vested interest	69	7503	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-0.79, -0.57]
3.13.1 Low risk of vested interest	19	1187	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-0.84, -0.54]
3.13.2 High risk or unclear risk of vested interest	50	6316	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-0.82, -0.54]

Analysis 3.1. Comparison 3: Parent-rated ADHD symptoms, Outcome 1: All parallel-group trials and first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Low risk of bias								
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	1.5%	0.06 [-0.89 , 1.01]
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	4.1%	-0.43 [-0.86 , 0.00]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	3.9%	-0.91 [-1.36 , -0.46]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	4.9%	-0.50 [-0.83 , -0.17]
Weiss 2021	23	12.57	283	26.9	13.81	71	5.6%	-0.30 [-0.56 , -0.04]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	1.2%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**470**			**232**	**21.2%**	**-0.49 [-0.71 , -0.26]**
Heterogeneity: Tau² = 0.02; Chi² = 7.49, df = 5 (P = 0.19); I² = 33%								
Test for overall effect: Z = 4.25 (P < 0.0001)								
3.1.2 High risk of bias								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	3.8%	-0.61 [-1.07 , -0.14]
Barragán 2017	24.33	5.09	30	27.77	7.84	30	3.4%	-0.51 [-1.03 , 0.00]
Brown 1985	7.5	2.6	10	13.1	4.1	10	1.3%	-1.56 [-2.59 , -0.53]
Childress 2009	19.6	12.75	57	35.9	13.01	63	4.4%	-1.26 [-1.65 , -0.86]
Duric 2012	23.7	15.153	22	26.7	13.02	19	2.8%	-0.21 [-0.82 , 0.41]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	4.5%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	5.3%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	5.3%	-0.76 [-1.05 , -0.47]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	2.3%	-0.20 [-0.91 , 0.52]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	2.0%	-0.03 [-0.81 , 0.76]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	5.8%	-0.58 [-0.82 , -0.33]
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	3.7%	-0.93 [-1.41 , -0.45]
NCT02293655	17.3	12.3	15	25.2	11.6	82	3.1%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	5.4%	-0.88 [-1.17 , -0.59]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	3.6%	-0.14 [-0.63 , 0.35]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	2.5%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	3.1%	-0.19 [-0.75 , 0.37]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	2.5%	-0.55 [-1.22 , 0.11]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	4.4%	-0.93 [-1.32 , -0.53]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	5.3%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	4.4%	-1.17 [-1.56 , -0.78]
Subtotal (95% CI)			**1238**			**987**	**78.8%**	**-0.66 [-0.81 , -0.51]**
Heterogeneity: Tau² = 0.07; Chi² = 49.42, df = 20 (P = 0.0003); I² = 60%								
Test for overall effect: Z = 8.60 (P < 0.00001)								
Total (95% CI)			**1708**			**1219**	**100.0%**	**-0.63 [-0.76 , -0.50]**
Heterogeneity: Tau² = 0.06; Chi² = 61.62, df = 26 (P = 0.0001); I² = 58%								
Test for overall effect: Z = 9.41 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.56, df = 1 (P = 0.21), I² = 36.0%								

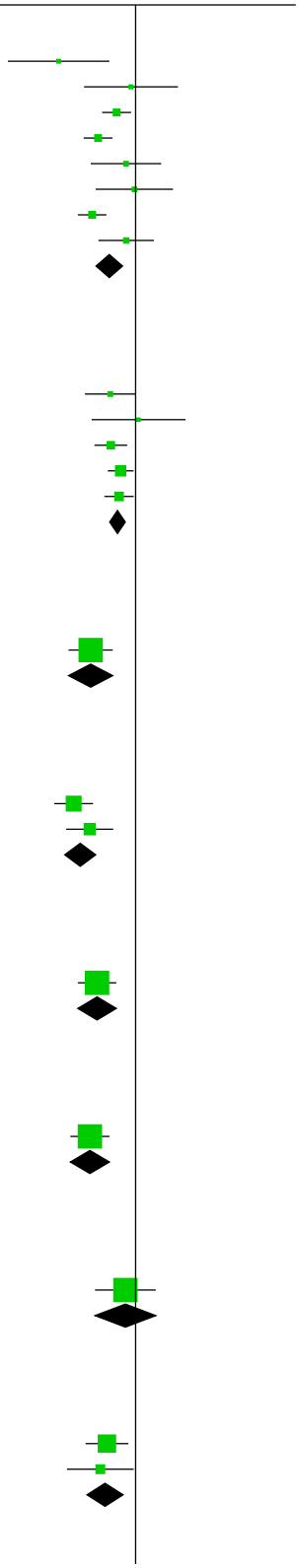


Footnotes

(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 3.2. Comparison 3: Parent-rated ADHD symptoms, Outcome 2: Subgroup analysis: types of scales

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.2.1 Conners' Parent Rating Scale (CPRS)								
Brown 1985	7.5	2.6	10	13.1	4.1	10	5.4%	-1.56 [-2.59 , -0.53]
Carlson 2007	-4.7	24.5	9	-2.9	5.6	8	6.1%	-0.09 [-1.05 , 0.86]
Findling 2008	28.4	21.07	94	37	23.39	88	19.7%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	19.7%	-0.76 [-1.05 , -0.47]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	9.1%	-0.20 [-0.91 , 0.52]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	8.1%	-0.03 [-0.81 , 0.76]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	19.8%	-0.88 [-1.17 , -0.59]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	12.1%	-0.19 [-0.75 , 0.37]
Subtotal (95% CI)			**505**			**295**	**100.0%**	**-0.53 [-0.80 , -0.26]**
Heterogeneity: Tau² = 0.07; Chi² = 16.62, df = 7 (P = 0.02); I² = 58%								
Test for overall effect: Z = 3.89 (P = 0.0001)								
3.2.2 ADHD Rating Scale - Fourth Edition (ADHD-RS-IV)								
Barragán 2017 (1)	24.33	5.09	30	27.77	7.84	30	9.4%	-0.51 [-1.03 , 0.00]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	2.8%	0.06 [-0.89 , 1.01]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	22.7%	-0.50 [-0.83 , -0.17]
Weiss 2021	23	12.57	283	26.9	13.81	71	36.7%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	28.4%	-0.34 [-0.63 , -0.04]
Subtotal (95% CI)			**487**			**266**	**100.0%**	**-0.37 [-0.53 , -0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 2.00, df = 4 (P = 0.74); I² = 0%								
Test for overall effect: Z = 4.56 (P < 0.00001)								
3.2.3 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)								
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	100.0%	-0.91 [-1.36 , -0.46]
Subtotal (95% CI)			**43**			**42**	**100.0%**	**-0.91 [-1.36 , -0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.99 (P < 0.0001)								
3.2.4 Conners' ADHD/DSM-IV Scales - Parent (CADS-P)								
Childress 2009	19.6	12.75	57	35.9	13.01	63	59.1%	-1.26 [-1.65 , -0.86]
NCT00409708 (2)	-17	11.23	38	-7	9.97	37	40.9%	-0.93 [-1.41 , -0.45]
Subtotal (95% CI)			**95**			**100**	**100.0%**	**-1.12 [-1.44 , -0.81]**
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 1 (P = 0.30); I² = 6%								
Test for overall effect: Z = 7.02 (P < 0.00001)								
3.2.5 CADS-P Inattentive subscale								
Tucker 2009	-8.8	6.38	53	-3.8	6.32	56	100.0%	-0.78 [-1.17 , -0.39]
Subtotal (95% CI)			**53**			**56**	**100.0%**	**-0.78 [-1.17 , -0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.93 (P < 0.0001)								
3.2.6 CADS-P Hyperactivity subscale								
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	100.0%	-0.93 [-1.32 , -0.53]
Subtotal (95% CI)			**53**			**56**	**100.0%**	**-0.93 [-1.32 , -0.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.59 (P < 0.00001)								
3.2.7 Clinican's Manual for the Assesment of Disruptive Behavior Disorders Rating Scale for Parents (Barkley)								
Duric 2012	23.7	15.153	22	26.7	13.02	19	100.0%	-0.21 [-0.82 , 0.41]
Subtotal (95% CI)			**22**			**19**	**100.0%**	**-0.21 [-0.82 , 0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
3.2.8 Abbreviated Conners' Rating Scale (ACRS) - Parent								
Lehmkuhl 2002	10	6.5574	43	16	12.9615	42	70.8%	-0.58 [-1.02 , -0.15]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	29.2%	-0.72 [-1.39 , -0.04]
Subtotal (95% CI)			**62**			**59**	**100.0%**	**-0.62 [-0.99 , -0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%								
Test for overall effect: Z = 3.32 (P = 0.0009)								



Analysis 3.2. (Continued)

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)

3.2.9 Swanson, Nolan, and Pelham, Fourth Edition - Parent (SNAP-IV-Parent) Scale

Arnold 2004	0.8	0.7	35	1.3	0.9	40	19.3%	-0.61 [-1.07 , -0.14]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	68.0%	-0.58 [-0.82 , -0.33]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	9.4%	-0.55 [-1.22 , 0.11]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	3.3%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**192**			**198**	**100.0%**	**-0.59 [-0.80 , -0.39]**

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 5.72 (P < 0.00001)

3.2.10 Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale

Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	100.0%	-0.43 [-0.86 , 0.00]
Subtotal (95% CI)			**48**			**38**	**100.0%**	**-0.43 [-0.86 , 0.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)

3.2.11 IOWA Conners' Rating Scale - Inattention/Overactivity (IOWA-I/O)

Findling 2006	5.1	3.0672	120	8.1	3.06	39	34.5%	-0.97 [-1.35 , -0.60]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	31.3%	-0.14 [-0.63 , 0.35]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	34.2%	-1.17 [-1.56 , -0.78]
Subtotal (95% CI)			**238**			**114**	**100.0%**	**-0.78 [-1.35 , -0.21]**

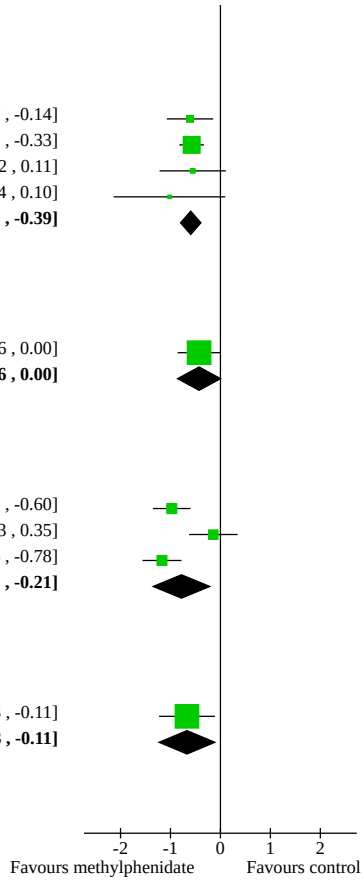
Heterogeneity: Tau² = 0.20; Chi² = 11.15, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 2.70 (P = 0.007)

3.2.12 Parent Vanderbilt ADHD Rating Scale

NCT02293655	17.3	12.3	15	25.2	11.6	82	100.0%	-0.67 [-1.23 , -0.11]
Subtotal (95% CI)			**15**			**82**	**100.0%**	**-0.67 [-1.23 , -0.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)

Test for subgroup differences: Chi² = 0.00, df = 11 (P < 0.00001), I² = 0%

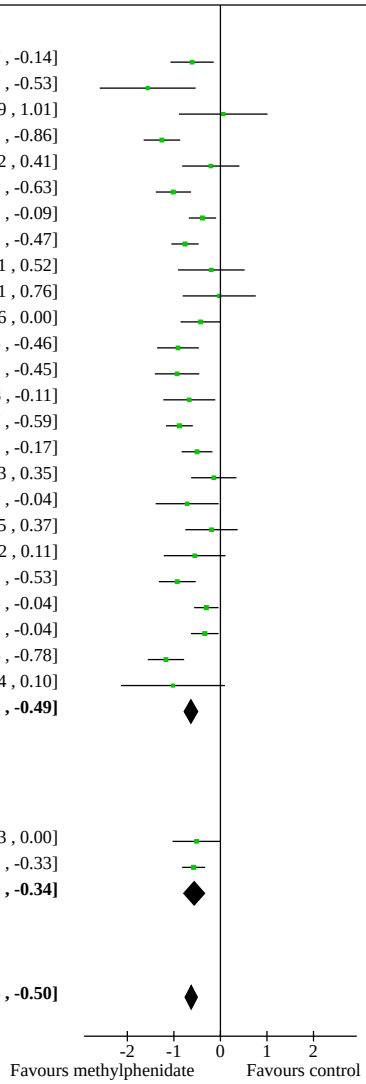


Footnotes

(1) Spanish version of ADHD-RS
(2) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 3.3. Comparison 3: Parent-rated ADHD symptoms, Outcome 3: Subgroup analysis: duration of treatment

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.3.1 Short term (up to 6 months)								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	3.8%	-0.61 [-1.07 , -0.14]
Brown 1985	7.5	2.6	10	13.1	4.1	10	1.3%	-1.56 [-2.59 , -0.53]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	1.5%	0.06 [-0.89 , 1.01]
Childress 2009	19.6	12.75	57	35.9	13.01	63	4.4%	-1.26 [-1.65 , -0.86]
Duric 2012	23.7	15.153	22	26.7	13.02	19	2.8%	-0.21 [-0.82 , 0.41]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	4.5%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	5.3%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	5.3%	-0.76 [-1.05 , -0.47]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	2.3%	-0.20 [-0.91 , 0.52]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	2.0%	-0.03 [-0.81 , 0.76]
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	4.1%	-0.43 [-0.86 , 0.00]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	3.9%	-0.91 [-1.36 , -0.46]
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	3.7%	-0.93 [-1.41 , -0.45]
NCT02293655	17.3	12.3	15	25.2	11.6	82	3.1%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	5.4%	-0.88 [-1.17 , -0.59]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	4.9%	-0.50 [-0.83 , -0.17]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	3.6%	-0.14 [-0.63 , 0.35]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	2.5%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	3.1%	-0.19 [-0.75 , 0.37]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	2.5%	-0.55 [-1.22 , 0.11]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	4.4%	-0.93 [-1.32 , -0.53]
Weiss 2021	23	12.57	283	26.9	13.81	71	5.6%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	5.3%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	4.4%	-1.17 [-1.56 , -0.78]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	1.2%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**1545**			**1060**	**90.8%**	**-0.63 [-0.78 , -0.49]**
Heterogeneity: Tau² = 0.07; Chi² = 61.26, df = 24 (P < 0.0001); I² = 61%								
Test for overall effect: Z = 8.59 (P < 0.00001)								
3.3.2 Long term (over 6 months)								
Barragán 2017	24.33	5.09	30	27.77	7.84	30	3.4%	-0.51 [-1.03 , 0.00]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	5.8%	-0.58 [-0.82 , -0.33]
Subtotal (95% CI)			**163**			**159**	**9.2%**	**-0.56 [-0.79 , -0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 4.96 (P < 0.00001)								
Total (95% CI)			**1708**			**1219**	**100.0%**	**-0.63 [-0.76 , -0.50]**
Heterogeneity: Tau² = 0.06; Chi² = 61.62, df = 26 (P = 0.0001); I² = 58%								
Test for overall effect: Z = 9.41 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%								

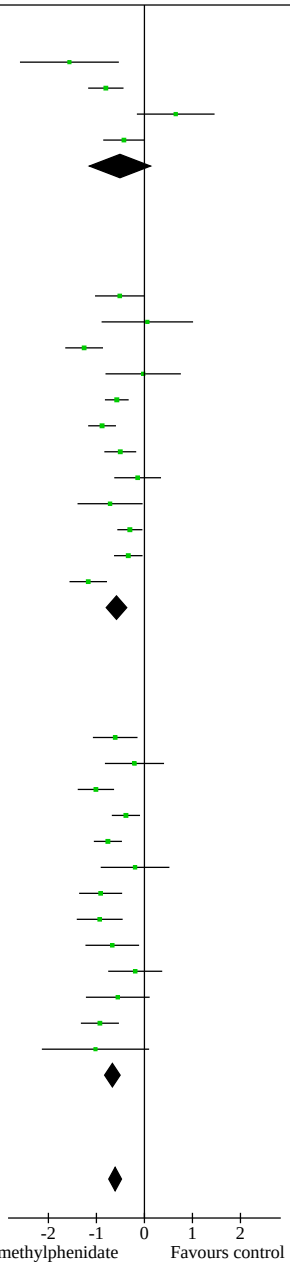


Footnotes

(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 3.4. Comparison 3: Parent-rated ADHD symptoms, Outcome 4: Subgroup analysis: dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.4.1 Low dose								
Brown 1985	7.5	2.6	10	13.1	4.1	10	1.3%	-1.56 [-2.59 , -0.53]
Childress 2009	24.9	14.18	60	35.9	13.03	63	4.3%	-0.80 [-1.17 , -0.44]
Ialongo 1994	12.81	4.35	13	9.9	4.28	12	1.9%	0.65 [-0.16 , 1.46]
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	3.8%	-0.43 [-0.86 , 0.00]
Subtotal (95% CI)			**131**			**123**	**11.3%**	**-0.51 [-1.14 , 0.13]**
Heterogeneity: Tau² = 0.31; Chi² = 14.30, df = 3 (P = 0.003); I² = 79%								
Test for overall effect: Z = 1.57 (P = 0.12)								
3.4.2 High dose								
Barragán 2017	24.33	5.09	30	27.77	7.84	30	3.3%	-0.51 [-1.03 , 0.00]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	1.5%	0.06 [-0.89 , 1.01]
Childress 2009	19.6	12.75	57	35.9	13.03	63	4.1%	-1.26 [-1.65 , -0.86]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	2.0%	-0.03 [-0.81 , 0.76]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	5.2%	-0.58 [-0.82 , -0.33]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	4.9%	-0.88 [-1.17 , -0.59]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	4.6%	-0.50 [-0.83 , -0.17]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	3.4%	-0.14 [-0.63 , 0.35]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	2.4%	-0.72 [-1.39 , -0.04]
Weiss 2021	23	12.57	283	26.9	13.81	71	5.1%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	4.8%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	4.1%	-1.17 [-1.56 , -0.78]
Subtotal (95% CI)			**1022**			**628**	**45.4%**	**-0.58 [-0.80 , -0.37]**
Heterogeneity: Tau² = 0.09; Chi² = 38.40, df = 11 (P < 0.0001); I² = 71%								
Test for overall effect: Z = 5.35 (P < 0.00001)								
3.4.3 Unknown dose								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	3.6%	-0.61 [-1.07 , -0.14]
Duric 2012	23.7	15.153	22	26.7	13.02	19	2.7%	-0.21 [-0.82 , 0.41]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	4.2%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	4.9%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	4.9%	-0.76 [-1.05 , -0.47]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	2.2%	-0.20 [-0.91 , 0.52]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	3.7%	-0.91 [-1.36 , -0.46]
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	3.5%	-0.93 [-1.41 , -0.45]
NCT02293655	17.3	12.3	15	25.2	11.6	82	3.0%	-0.67 [-1.23 , -0.11]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	3.0%	-0.19 [-0.75 , 0.37]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	2.5%	-0.55 [-1.22 , 0.11]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	4.1%	-0.93 [-1.32 , -0.53]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	1.2%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**628**			**543**	**43.3%**	**-0.67 [-0.83 , -0.51]**
Heterogeneity: Tau² = 0.03; Chi² = 18.19, df = 12 (P = 0.11); I² = 34%								
Test for overall effect: Z = 8.11 (P < 0.00001)								
Total (95% CI)			**1781**			**1294**	**100.0%**	**-0.61 [-0.74 , -0.48]**
Heterogeneity: Tau² = 0.07; Chi² = 72.05, df = 28 (P < 0.00001); I² = 61%								
Test for overall effect: Z = 9.02 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.54, df = 2 (P = 0.76), I² = 0%								

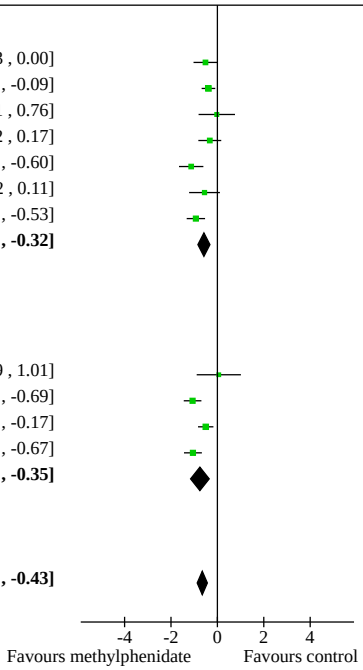


Footnotes

(1) Ritalin LA plus behaviour therapy versus behaviour therapy

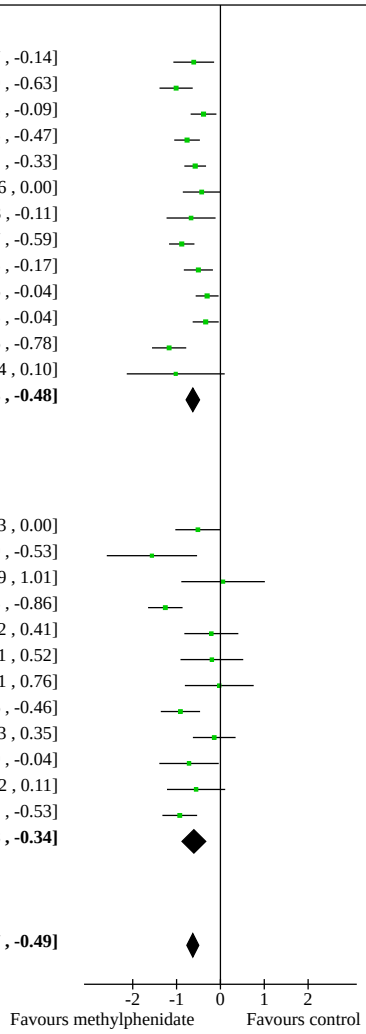
Analysis 3.5. Comparison 3: Parent-rated ADHD symptoms, Outcome 5: Subgroup analysis: medication status - medication naive versus not medication naive

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.5.1 Medication naive								
Barragán 2017	24.33	5.09	30	27.77	7.84	30	8.7%	-0.51 [-1.03 , 0.00]
Findling 2008	28.4	21.07	94	37	23.39	88	12.9%	-0.39 [-0.68 , -0.09]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	5.3%	-0.03 [-0.81 , 0.76]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	9.0%	-0.33 [-0.82 , 0.17]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	8.5%	-1.13 [-1.65 , -0.60]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	6.6%	-0.55 [-1.22 , 0.11]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	10.8%	-0.93 [-1.32 , -0.53]
Subtotal (95% CI)			**274**			**270**	**61.8%**	**-0.58 [-0.84 , -0.32]**
Heterogeneity: Tau² = 0.06; Chi² = 11.83, df = 6 (P = 0.07); I² = 49%								
Test for overall effect: Z = 4.39 (P < 0.0001)								
3.5.2 Not medication naive								
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	4.0%	0.06 [-0.89 , 1.01]
Findling 2006	4.3	3.1768	120	7.7	3.1225	39	11.1%	-1.07 [-1.45 , -0.69]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	12.1%	-0.50 [-0.83 , -0.17]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	11.0%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**288**			**160**	**38.2%**	**-0.75 [-1.16 , -0.35]**
Heterogeneity: Tau² = 0.11; Chi² = 9.82, df = 3 (P = 0.02); I² = 69%								
Test for overall effect: Z = 3.69 (P = 0.0002)								
Total (95% CI)			**562**			**430**	**100.0%**	**-0.65 [-0.87 , -0.43]**
Heterogeneity: Tau² = 0.07; Chi² = 24.38, df = 10 (P = 0.007); I² = 59%								
Test for overall effect: Z = 5.83 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.48), I² = 0%								



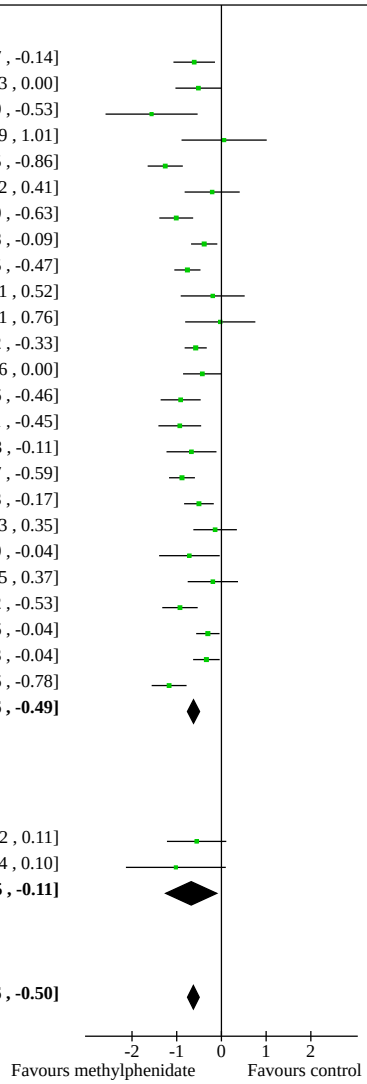
Analysis 3.6. Comparison 3: Parent-rated ADHD symptoms, Outcome 6: Subgroup analysis: trials with enrichment design compared with trials without enrichment design

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.6.1 Trials with enrichment design of all participants								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	4.1%	-0.61 [-1.07 , -0.14]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	4.8%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	5.7%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	5.7%	-0.76 [-1.05 , -0.47]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	6.2%	-0.58 [-0.82 , -0.33]
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	4.4%	-0.43 [-0.86 , 0.00]
NCT02293655	17.3	12.3	15	25.2	11.6	82	3.3%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	5.7%	-0.88 [-1.17 , -0.59]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	5.3%	-0.50 [-0.83 , -0.17]
Weiss 2021	23	12.57	283	26.9	13.81	71	6.0%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	5.7%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	4.7%	-1.17 [-1.56 , -0.78]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	1.2%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**1321**			**834**	**62.9%**	**-0.63 [-0.78 , -0.48]**
Heterogeneity: Tau² = 0.04; Chi² = 29.16, df = 12 (P = 0.004); I² = 59%								
Test for overall effect: Z = 8.07 (P < 0.00001)								
3.6.2 Trials without enrichment design of all participants								
Barragán 2017	24.33	5.09	30	27.77	7.84	30	3.7%	-0.51 [-1.03 , 0.00]
Brown 1985	7.5	2.6	10	13.1	4.1	10	1.4%	-1.56 [-2.59 , -0.53]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	1.6%	0.06 [-0.89 , 1.01]
Childress 2009	19.6	12.75	57	35.9	13.01	63	4.7%	-1.26 [-1.65 , -0.86]
Duric 2012	23.7	15.153	22	26.7	13.02	19	3.0%	-0.21 [-0.82 , 0.41]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	2.5%	-0.20 [-0.91 , 0.52]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	2.2%	-0.03 [-0.81 , 0.76]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	4.2%	-0.91 [-1.36 , -0.46]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	3.9%	-0.14 [-0.63 , 0.35]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	2.6%	-0.72 [-1.39 , -0.04]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	2.7%	-0.55 [-1.22 , 0.11]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	4.7%	-0.93 [-1.32 , -0.53]
Subtotal (95% CI)			**326**			**322**	**37.1%**	**-0.61 [-0.88 , -0.34]**
Heterogeneity: Tau² = 0.13; Chi² = 27.90, df = 11 (P = 0.003); I² = 61%								
Test for overall effect: Z = 4.40 (P < 0.0001)								
Total (95% CI)			**1647**			**1156**	**100.0%**	**-0.63 [-0.77 , -0.49]**
Heterogeneity: Tau² = 0.06; Chi² = 57.76, df = 24 (P = 0.0001); I² = 58%								
Test for overall effect: Z = 9.12 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%								



Analysis 3.7. Comparison 3: Parent-rated ADHD symptoms, Outcome 7: Subgroup analysis: parallel-group trials compared with first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.7.1 Parallel-group trials								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	3.8%	-0.61 [-1.07 , -0.14]
Barragán 2017	24.33	5.09	30	27.77	7.84	30	3.4%	-0.51 [-1.03 , 0.00]
Brown 1985	7.5	2.6	10	13.1	4.1	10	1.3%	-1.56 [-2.59 , -0.53]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	1.5%	0.06 [-0.89 , 1.01]
Childress 2009	19.6	12.75	57	35.9	13.01	63	4.4%	-1.26 [-1.65 , -0.86]
Duric 2012	23.7	15.153	22	26.7	13.02	19	2.8%	-0.21 [-0.82 , 0.41]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	4.5%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	5.3%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	5.3%	-0.76 [-1.05 , -0.47]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	2.3%	-0.20 [-0.91 , 0.52]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	2.0%	-0.03 [-0.81 , 0.76]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	5.8%	-0.58 [-0.82 , -0.33]
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	4.1%	-0.43 [-0.86 , 0.00]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	3.9%	-0.91 [-1.36 , -0.46]
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	3.7%	-0.93 [-1.41 , -0.45]
NCT02293655	17.3	12.3	15	25.2	11.6	82	3.1%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	5.4%	-0.88 [-1.17 , -0.59]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	4.9%	-0.50 [-0.83 , -0.17]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	3.6%	-0.14 [-0.63 , 0.35]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	2.5%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	3.1%	-0.19 [-0.75 , 0.37]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	4.4%	-0.93 [-1.32 , -0.53]
Weiss 2021	23	12.57	283	26.9	13.81	71	5.6%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	5.3%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	4.4%	-1.17 [-1.56 , -0.78]
Subtotal (95% CI)			**1684**			**1190**	**96.3%**	**-0.62 [-0.76 , -0.49]**
Heterogeneity: Tau² = 0.07; Chi² = 61.09, df = 24 (P < 0.0001); I² = 61%								
Test for overall effect: Z = 9.02 (P < 0.00001)								
3.7.2 First-period cross-over trials								
Taylor 1987	0.36	0.42	15	0.68	0.64	23	2.5%	-0.55 [-1.22 , 0.11]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	1.2%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**24**			**29**	**3.7%**	**-0.68 [-1.25 , -0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%								
Test for overall effect: Z = 2.32 (P = 0.02)								
Total (95% CI)			**1708**			**1219**	**100.0%**	**-0.63 [-0.76 , -0.50]**
Heterogeneity: Tau² = 0.06; Chi² = 61.62, df = 26 (P = 0.0001); I² = 58%								
Test for overall effect: Z = 9.41 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%								

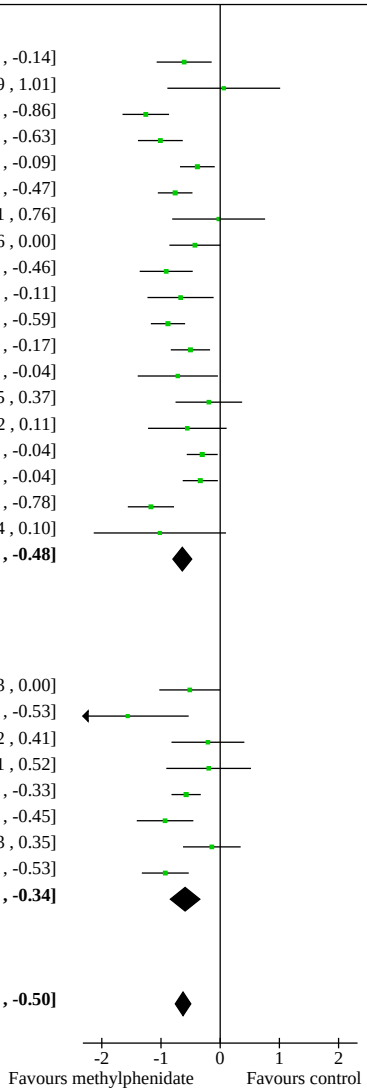


Footnotes

(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 3.8. Comparison 3: Parent-rated ADHD symptoms, Outcome 8: Subgroup analysis: type of control group

Study or Subgroup	Methylphenidate Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.8.1 Placebo control group								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	3.8%	-0.61 [-1.07 , -0.14]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	1.5%	0.06 [-0.89 , 1.01]
Childress 2009	19.6	12.75	57	35.9	13.01	63	4.4%	-1.26 [-1.65 , -0.86]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	4.5%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	5.3%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	5.3%	-0.76 [-1.05 , -0.47]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	2.0%	-0.03 [-0.81 , 0.76]
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	4.1%	-0.43 [-0.86 , 0.00]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	3.9%	-0.91 [-1.36 , -0.46]
NCT02293655	17.3	12.3	15	25.2	11.6	82	3.1%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	5.4%	-0.88 [-1.17 , -0.59]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	4.9%	-0.50 [-0.83 , -0.17]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	2.5%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	3.1%	-0.19 [-0.75 , 0.37]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	2.5%	-0.55 [-1.22 , 0.11]
Weiss 2021	23	12.57	283	26.9	13.81	71	5.6%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	5.3%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	4.4%	-1.17 [-1.56 , -0.78]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	1.2%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**1367**			**896**	**72.8%**	**-0.64 [-0.80 , -0.48]**
Heterogeneity: Tau² = 0.07; Chi² = 47.31, df = 18 (P = 0.0002); I² = 62%								
Test for overall effect: Z = 7.90 (P < 0.00001)								
3.8.2 No-intervention control group								
Barragán 2017	24.33	5.09	30	27.77	7.84	30	3.4%	-0.51 [-1.03 , 0.00]
Brown 1985	7.5	2.6	10	13.1	4.1	10	1.3%	-1.56 [-2.59 , -0.53]
Duric 2012	23.7	15.153	22	26.7	13.02	19	2.8%	-0.21 [-0.82 , 0.41]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	2.3%	-0.20 [-0.91 , 0.52]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	5.8%	-0.58 [-0.82 , -0.33]
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	3.7%	-0.93 [-1.41 , -0.45]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	3.6%	-0.14 [-0.63 , 0.35]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	4.4%	-0.93 [-1.32 , -0.53]
Subtotal (95% CI)			**341**			**323**	**27.2%**	**-0.59 [-0.84 , -0.34]**
Heterogeneity: Tau² = 0.06; Chi² = 14.18, df = 7 (P = 0.05); I² = 51%								
Test for overall effect: Z = 4.68 (P < 0.00001)								
Total (95% CI)			**1708**			**1219**	**100.0%**	**-0.63 [-0.76 , -0.50]**
Heterogeneity: Tau² = 0.06; Chi² = 61.62, df = 26 (P = 0.0001); I² = 58%								
Test for overall effect: Z = 9.41 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%								

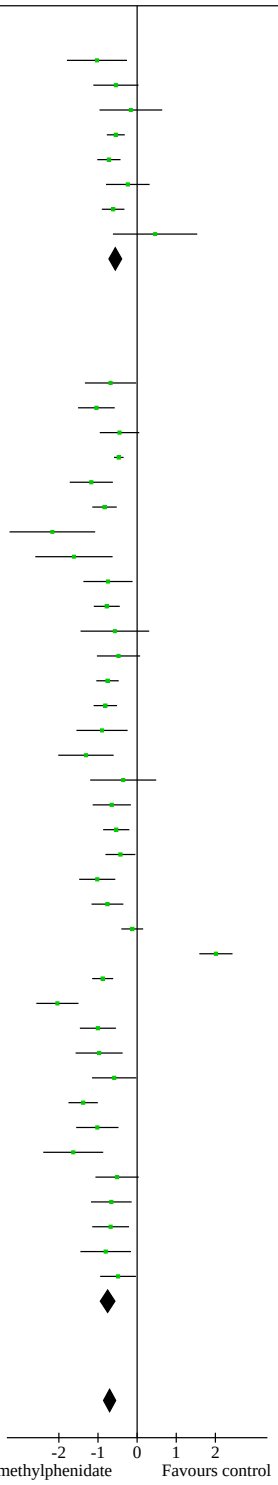


Footnotes

(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 3.9. Comparison 3: Parent-rated ADHD symptoms, Outcome 9: Cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.9.1 Low risk of bias								
Cook 1993	0.41	0.175	15	0.59	0.166	15	1.7%	-1.03 [-1.79 , -0.26]
DuPaul 1996	15.75	9.76	24	21	9.28	24	2.1%	-0.54 [-1.12 , 0.03]
Flapper 2008	13	11.707	12	14.857	10.669	12	1.7%	-0.16 [-0.96 , 0.64]
Kollins 2006 (PATS)	1.09	0.69	142	1.47	0.7	165	2.8%	-0.55 [-0.77 , -0.32]
McGough 2006	20.2	20.3481	93	35.3	21.3125	93	2.7%	-0.72 [-1.02 , -0.42]
Stein 1996	5.5	3.1	25	6.3	3.5	25	2.2%	-0.24 [-0.79 , 0.32]
Stein 2011	20.27	13.557	93	29.12	15.077	101	2.7%	-0.61 [-0.90 , -0.33]
Zeni 2009	1.6267	0.6894	6	1.2625	0.77765	8	1.2%	0.46 [-0.62 , 1.54]
Subtotal (95% CI)			**410**			**443**	**17.2%**	**-0.56 [-0.72 , -0.40]**
Heterogeneity: Tau² = 0.01; Chi² = 8.38, df = 7 (P = 0.30); I² = 16%								
Test for overall effect: Z = 6.72 (P < 0.00001)								
3.9.2 High risk of bias								
Abikoff 2009	0.99	0.55	19	1.4	0.63	19	2.0%	-0.68 [-1.33 , -0.02]
Barkley 1991	14.53	8.2	40	24.88	11.26	40	2.4%	-1.04 [-1.51 , -0.57]
Barkley 2000	16.8	9.7	31	21.9	12.5	31	2.3%	-0.45 [-0.95 , 0.05]
Bhat 2020	56.6	11.6	526	62.5	13.5	526	2.9%	-0.47 [-0.59 , -0.35]
Blum 2011	64.8	26.5	30	89.6	13.1	30	2.2%	-1.17 [-1.72 , -0.62]
Brams 2008	-16.382	14.0495	86	-4.622	14.0495	86	2.7%	-0.83 [-1.15 , -0.52]
Brown 1984a	11	3.49	11	19.55	4.08	11	1.2%	-2.17 [-3.26 , -1.07]
Brown 1988	31.5	5.85	11	39.66	3.61	11	1.4%	-1.61 [-2.60 , -0.63]
Chronis 2003	1.8	1.5	21	3.1	1.9	21	2.0%	-0.75 [-1.37 , -0.12]
Coghill 2007	67	14.8	75	77.2	11.1	75	2.6%	-0.78 [-1.11 , -0.44]
Corkum 2008	62.14	14.11	10	69.38	10.23	11	1.5%	-0.57 [-1.45 , 0.31]
Corkum 2020	62.9	11.6	26	68.2	10.3	26	2.2%	-0.48 [-1.03 , 0.08]
CRIT124US02	-20	13.8	102	-9.7	13.3	99	2.7%	-0.76 [-1.04 , -0.47]
Epstein 2011	19.6	10.09	93	28.26	11.12	93	2.7%	-0.81 [-1.11 , -0.51]
Findling 2007	20.81	9.79	20	32.19	14.61	20	2.0%	-0.90 [-1.55 , -0.24]
Fitzpatrick 1992a	0.96	0.5	19	1.75	0.67	19	1.9%	-1.31 [-2.02 , -0.60]
Gadow 1990	8.3	6.19	11	11	8.24	11	1.6%	-0.36 [-1.20 , 0.49]
Gadow 1995	7.8	4.6	34	11.8	7.3	34	2.3%	-0.65 [-1.14 , -0.16]
Gadow 2007	7.8	4.7	71	11	7	71	2.6%	-0.53 [-0.87 , -0.20]
Gadow 2011	8.6	5.6	54	11.5	7.7	54	2.5%	-0.43 [-0.81 , -0.05]
Gorman 2006	0.72	0.8324	41	1.61	0.8964	41	2.4%	-1.02 [-1.48 , -0.56]
Hoeppner 1997	7.13	6.37	50	12.16	6.78	50	2.5%	-0.76 [-1.17 , -0.35]
Huang 2021	7.6	5.2	99	8.3	6	99	2.7%	-0.12 [-0.40 , 0.15]
Kortekaas-Rijlaarsdam 2017	7.87	17.04	65	-21.98	11.99	65	2.5%	2.01 [1.59 , 2.44]
Manos 1999	10.1	6.71	117	18.61	11.86	117	2.8%	-0.88 [-1.15 , -0.61]
McBride 1988a	6.5	3.9	41	17.4	6.4	41	2.2%	-2.04 [-2.58 , -1.50]
Musten 1997	63.29	13.44	41	77.23	14.1	41	2.4%	-1.00 [-1.46 , -0.54]
Pearson 2013	55.8	9.3	24	66.8	12.7	24	2.1%	-0.97 [-1.57 , -0.37]
Pelham 1999	1.7	1.5	25	3	2.7	25	2.1%	-0.59 [-1.15 , -0.02]
Pelham 2001a	11.41	6.23	68	19.91	6.02	68	2.6%	-1.38 [-1.75 , -1.00]
Pelham 2005	2.3	2.2	30	5.5	3.8	30	2.2%	-1.02 [-1.56 , -0.48]
Schachar 2008	-0.98	2.14	18	3.2	2.82	18	1.7%	-1.63 [-2.40 , -0.87]
Smithee 1998	0.8639	0.4415	26	1.141	0.61022	26	2.2%	-0.51 [-1.07 , 0.04]
Solanto 2009	56.96	12.41	30	65.8	13.98	30	2.2%	-0.66 [-1.18 , -0.14]
Taylor 1987	0.38	0.46	37	0.81	0.76	37	2.4%	-0.68 [-1.15 , -0.21]
Tirosh 1993a	10.75	2.9	20	14	4.8	20	2.0%	-0.80 [-1.45 , -0.16]
Zeiner 1999	3.08	3.7	38	5.25	5.01	38	2.4%	-0.49 [-0.94 , -0.03]
Subtotal (95% CI)			**2060**			**2058**	**82.8%**	**-0.75 [-0.94 , -0.57]**
Heterogeneity: Tau² = 0.26; Chi² = 259.35, df = 36 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 7.94 (P < 0.00001)								
Total (95% CI)			**2470**			**2501**	**100.0%**	**-0.70 [-0.86 , -0.55]**
Heterogeneity: Tau² = 0.21; Chi² = 268.48, df = 44 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 8.85 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.41, df = 1 (P = 0.12), I² = 58.5%								

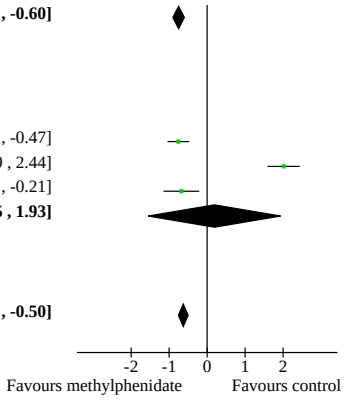


Analysis 3.10. Comparison 3: Parent-rated ADHD symptoms, Outcome 10: Subgroup analysis: cross-over trials (endpoint data): dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.10.1 Low dose								
Barkley 2000	16.8	9.7	31	21.9	12.5	31	1.8%	-0.45 [-0.95 , 0.05]
Bhat 2020	56.6	11.6	526	62.5	13.5	526	2.4%	-0.47 [-0.59 , -0.35]
Brams 2008	-16.382	14.0495	86	-4.622	14.0495	86	2.1%	-0.83 [-1.15 , -0.52]
Brown 1984a	11	3.49	11	19.55	4.08	11	0.9%	-2.17 [-3.26 , -1.07]
Brown 1988	31.5	5.85	11	39.66	3.61	11	1.0%	-1.61 [-2.60 , -0.63]
Chronis 2003	2.6	2	21	3.1	1.9	21	1.6%	-0.25 [-0.86 , 0.36]
Coghill 2007	67.2	13.5	75	77.2	11.1	75	2.1%	-0.81 [-1.14 , -0.47]
Cook 1993	0.41	0.175	15	0.59	0.166	15	1.3%	-1.03 [-1.79 , -0.26]
DuPaul 1996	19.42	9.58	24	21	9.28	24	1.6%	-0.16 [-0.73 , 0.40]
Findling 2007	20.81	9.79	20	32.19	14.61	20	1.5%	-0.90 [-1.55 , -0.24]
Fitzpatrick 1992a	0.96	0.5	19	1.75	0.67	19	1.4%	-1.31 [-2.02 , -0.60]
Flapper 2008	15.75	10.391	12	14.857	10.669	12	1.2%	0.08 [-0.72 , 0.88]
Gadow 1990	9.8	4.51	11	11	8.24	11	1.2%	-0.17 [-1.01 , 0.66]
Gadow 1995	10.2	5.4	34	11.8	7.3	34	1.8%	-0.25 [-0.72 , 0.23]
Gadow 2007	10	5.5	71	11	7	71	2.1%	-0.16 [-0.49 , 0.17]
Gadow 2011	8.6	5.2	54	11.5	7.7	54	2.0%	-0.44 [-0.82 , -0.06]
Hoeppner 1997	7.13	6.37	50	12.16	6.78	50	1.9%	-0.76 [-1.17 , -0.35]
Kollins 2006 (PATS)	1.28	0.73	165	1.47	0.7	165	2.3%	-0.27 [-0.48 , -0.05]
Manos 1999	10.1	6.71	117	18.61	11.86	117	2.2%	-0.88 [-1.15 , -0.61]
McGough 2006	20.2	20.3481	93	35.3	21.3125	93	2.1%	-0.72 [-1.02 , -0.42]
Musten 1997	67.03	15.39	41	77.23	14.1	41	1.9%	-0.68 [-1.13 , -0.24]
Pearson 2013	61.9	11.7	24	66.8	12.7	24	1.6%	-0.39 [-0.97 , 0.18]
Pelham 1999	1.7	1.5	25	3	2.7	25	1.6%	-0.59 [-1.15 , -0.02]
Pelham 2005	2.7	2.2	30	5.5	3.8	30	1.7%	-0.89 [-1.42 , -0.36]
Solanto 2009	61.64	10.39	30	65.8	13.98	30	1.7%	-0.33 [-0.84 , 0.18]
Stein 1996	5.5	3.1	25	6.3	3.5	25	1.7%	-0.24 [-0.79 , 0.32]
Subtotal (95% CI)			**1621**			**1621**	**44.6%**	**-0.58 [-0.71 , -0.45]**
Heterogeneity: Tau² = 0.05; Chi² = 59.00, df = 25 (P = 0.0001); I² = 58%								
Test for overall effect: Z = 8.83 (P < 0.00001)								
3.10.2 High dose								
Abikoff 2009	0.99	0.55	19	1.4	0.63	19	1.5%	-0.68 [-1.33 , -0.02]
Barkley 1991	14.53	8.2	40	24.88	11.26	40	1.8%	-1.04 [-1.51 , -0.57]
Blum 2011	64.8	26.5	30	89.6	13.1	30	1.7%	-1.17 [-1.72 , -0.62]
Chronis 2003	1.8	1.5	21	3.1	1.9	21	1.5%	-0.75 [-1.37 , -0.12]
Coghill 2007	67	14.8	75	77.2	11.1	75	2.1%	-0.78 [-1.11 , -0.44]
Corkum 2008	62.14	14.11	10	69.38	10.23	11	1.1%	-0.57 [-1.45 , 0.31]
Corkum 2020	62.9	11.6	26	68.2	10.3	26	1.7%	-0.48 [-1.03 , 0.08]
DuPaul 1996	15.75	9.76	24	21	9.28	24	1.6%	-0.54 [-1.12 , 0.03]
Epstein 2011	19.6	10.09	93	28.26	11.12	93	2.1%	-0.81 [-1.11 , -0.51]
Flapper 2008	13	11.707	12	14.857	10.669	12	1.2%	-0.16 [-0.96 , 0.64]
Gadow 1990	8.3	6.19	11	11	8.24	11	1.2%	-0.36 [-1.20 , 0.49]
Gadow 1995	7.8	4.6	34	11.8	7.3	34	1.8%	-0.65 [-1.14 , -0.16]
Gadow 2007	7.8	4.7	71	11	7	71	2.1%	-0.53 [-0.87 , -0.20]
Gadow 2011	8.6	5.6	54	11.5	7.7	54	2.0%	-0.43 [-0.81 , -0.05]
Gorman 2006	0.72	0.8324	41	1.61	0.8964	41	1.8%	-1.02 [-1.48 , -0.56]
Huang 2021	7.6	5.2	99	8.3	6	99	2.2%	-0.12 [-0.40 , 0.15]
Kollins 2006 (PATS)	1.09	0.69	142	1.47	0.7	165	2.2%	-0.55 [-0.77 , -0.32]
McBride 1988a	6.5	3.9	41	17.4	6.4	41	1.7%	-2.04 [-2.58 , -1.50]
Musten 1997	63.29	13.44	41	77.23	14.1	41	1.8%	-1.00 [-1.46 , -0.54]
Pearson 2013	55.8	9.3	24	66.8	12.7	24	1.6%	-0.97 [-1.57 , -0.37]
Pelham 2001a	11.41	6.23	68	19.91	6.02	68	2.0%	-1.38 [-1.75 , -1.00]
Pelham 2005	2.3	2.2	30	5.5	3.8	30	1.7%	-1.02 [-1.56 , -0.48]
Schachar 2008	-0.98	2.14	18	3.2	2.82	18	1.3%	-1.63 [-2.40 , -0.87]
Smithee 1998	0.8639	0.4415	26	1.141	0.61022	26	1.7%	-0.51 [-1.07 , 0.04]
Solanto 2009	56.96	12.41	30	65.8	13.98	30	1.7%	-0.66 [-1.18 , -0.14]
Stein 2011	20.27	13.557	93	29.12	15.077	101	2.2%	-0.61 [-0.90 , -0.33]
Tirosh 1993a	10.75	2.9	20	14	4.8	20	1.5%	-0.80 [-1.45 , -0.16]
Zeiner 1999	3.08	3.7	38	5.25	5.01	38	1.8%	-0.49 [-0.94 , -0.03]
Zeni 2009	1.6267	0.6894	6	1.2625	0.77765	8	0.9%	0.46 [-0.62 , 1.54]
Subtotal (95% CI)			**1237**			**1271**	**49.5%**	**-0.75 [-0.90 , -0.60]**
Heterogeneity: Tau² = 0.10; Chi² = 83.92, df = 28 (P < 0.00001); I² = 67%								

Analysis 3.10. (Continued)

Subtotal (95% CI)			**1237**			**1271**	**49.5%**	**-0.75 [-0.90 , -0.60]**
Heterogeneity: Tau² = 0.10; Chi² = 83.92, df = 28 (P < 0.00001); I² = 67%								
Test for overall effect: Z = 9.75 (P < 0.00001)								
3.10.3 Unknown dose								
CRIT124US02	-20	13.8	102	-9.7	13.3	99	2.2%	-0.76 [-1.04 , -0.47]
Kortekaas-Rijlaarsdam 2017	7.87	17.04	65	-21.98	11.99	65	1.9%	2.01 [1.59 , 2.44]
Taylor 1987	0.38	0.46	37	0.81	0.76	37	1.8%	-0.68 [-1.15 , -0.21]
Subtotal (95% CI)			**204**			**201**	**5.9%**	**0.19 [-1.55 , 1.93]**
Heterogeneity: Tau² = 2.33; Chi² = 121.19, df = 2 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 0.21 (P = 0.83)								
Total (95% CI)			**3062**			**3093**	**100.0%**	**-0.63 [-0.76 , -0.50]**
Heterogeneity: Tau² = 0.18; Chi² = 298.62, df = 57 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 9.61 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.81, df = 2 (P = 0.15), I² = 47.5%								

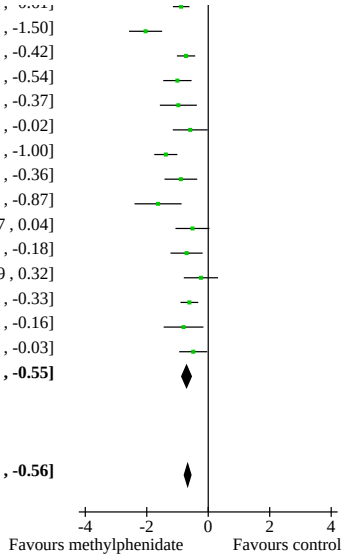


Analysis 3.11. Comparison 3: Parent-rated ADHD symptoms, Outcome 11: Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.11.1 All parallel-group trials and first-period cross-over trials								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	1.5%	-0.61 [-1.07 , -0.14]
Barragán 2017	24.33	5.09	30	27.77	7.84	30	1.4%	-0.51 [-1.03 , 0.00]
Brown 1985	7.5	2.6	10	13.1	4.1	10	0.7%	-1.56 [-2.59 , -0.53]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	0.8%	0.06 [-0.89 , 1.01]
Childress 2009	19.6	12.75	57	35.9	13.01	63	1.6%	-1.26 [-1.65 , -0.86]
Duric 2012	23.7	15.153	22	26.7	13.02	19	1.2%	-0.21 [-0.82 , 0.41]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	1.7%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	1.8%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	1.8%	-0.76 [-1.05 , -0.47]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	1.1%	-0.20 [-0.91 , 0.52]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	1.0%	-0.03 [-0.81 , 0.76]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	1.9%	-0.58 [-0.82 , -0.33]
Kollins 2006 (PATS)	1.09	0.72	61	1.41	0.77	53	1.7%	-0.43 [-0.80 , -0.06]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	1.5%	-0.91 [-1.36 , -0.46]
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	1.5%	-0.93 [-1.41 , -0.45]
NCT02293655	17.3	12.3	15	25.2	11.6	82	1.3%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	1.8%	-0.88 [-1.17 , -0.59]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	1.7%	-0.50 [-0.83 , -0.17]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	1.5%	-0.14 [-0.63 , 0.35]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	1.2%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	1.3%	-0.19 [-0.75 , 0.37]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	1.2%	-0.55 [-1.22 , 0.11]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	1.6%	-0.93 [-1.32 , -0.53]
Weiss 2021	23	12.57	283	26.9	13.81	71	1.8%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	1.8%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	1.6%	-1.17 [-1.56 , -0.78]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	0.7%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**1721**			**1234**	**38.8%**	**-0.63 [-0.76 , -0.50]**
Heterogeneity: Tau² = 0.06; Chi² = 61.88, df = 26 (P < 0.0001); I² = 58%								
Test for overall effect: Z = 9.43 (P < 0.00001)								
3.11.2 Cross-over trials (endpoint data)								
Abikoff 2009	0.99	0.55	19	1.4	0.63	19	1.2%	-0.68 [-1.33 , -0.02]
Barkley 1991	14.53	8.2	40	24.88	11.26	40	1.5%	-1.04 [-1.51 , -0.57]
Barkley 2000	16.8	9.7	31	21.9	12.5	31	1.4%	-0.45 [-0.95 , 0.05]
Bhat 2020	56.6	11.6	526	62.5	13.5	526	2.0%	-0.47 [-0.59 , -0.35]
Blum 2011	64.8	26.5	30	89.6	13.1	30	1.4%	-1.17 [-1.72 , -0.62]
Brams 2008	-16.382	14.0495	86	-4.622	14.0495	86	1.8%	-0.83 [-1.15 , -0.52]
Brown 1984a	11	3.49	11	19.55	4.08	11	0.7%	-2.17 [-3.26 , -1.07]
Brown 1988	36.5	3.2	11	39.66	3.61	11	0.9%	-0.89 [-1.78 , -0.01]
Chronis 2003	1.8	1.5	21	3.1	1.9	21	1.2%	-0.75 [-1.37 , -0.12]
Coghill 2007	67	14.8	75	77.2	11.1	75	1.7%	-0.78 [-1.11 , -0.44]
Cook 1993	0.41	0.175	15	0.59	0.166	15	1.0%	-1.03 [-1.79 , -0.26]
Corkum 2008	63.05	13.89	10	69.38	10.23	11	0.9%	-0.50 [-1.37 , 0.37]
Corkum 2020	62.9	11.6	26	68.2	10.3	26	1.4%	-0.48 [-1.03 , 0.08]
CRIT124US02	-20	13.8	102	-9.7	13.3	99	1.8%	-0.76 [-1.04 , -0.47]
DuPaul 1996	15.75	9.76	24	21	9.28	24	1.3%	-0.54 [-1.12 , 0.03]
Epstein 2011	19.6	10.09	93	28.26	11.12	93	1.8%	-0.81 [-1.11 , -0.51]
Findling 2007	20.81	9.79	20	32.19	14.61	20	1.2%	-0.90 [-1.55 , -0.24]
Fitzpatrick 1992a	0.96	0.5	19	1.75	0.67	19	1.1%	-1.31 [-2.02 , -0.60]
Flapper 2008	13	11.707	12	14.857	10.669	12	1.0%	-0.16 [-0.96 , 0.64]
Gadow 1990	8.3	6.1	11	11	8.24	11	0.9%	-0.36 [-1.20 , 0.49]
Gadow 1995	7.8	4.6	34	11.8	7.3	34	1.5%	-0.65 [-1.14 , -0.16]
Gadow 2007	7.8	4.7	71	11	7	71	1.7%	-0.53 [-0.87 , -0.20]
Gadow 2011	8.6	5.6	54	11.5	7.7	54	1.7%	-0.43 [-0.81 , -0.05]
Gorman 2006	0.72	0.8324	41	1.61	0.8964	41	1.5%	-1.02 [-1.48 , -0.56]
Hoeppner 1997	7.13	6.37	50	12.16	6.78	50	1.6%	-0.76 [-1.17 , -0.35]
Huang 2021	7.6	5.2	99	8.3	6	99	1.8%	-0.12 [-0.40 , 0.15]
Kollins 2006 (PATS)	1.09	0.69	142	1.47	0.7	165	1.9%	-0.55 [-0.77 , -0.32]
Kortekaas-Rijlaarsdam 2017	7.87	17.04	65	-21.98	11.99	65	1.6%	2.01 [1.59 , 2.44]
Manos 1999	10.1	6.71	117	18.61	11.86	117	1.8%	-0.88 [-1.15 , -0.61]
McBride 1988a	6.5	3.9	41	17.4	6.4	41	1.4%	-2.04 [-2.58 , -1.50]
McGough 2006	20.2	20.3481	93	35.3	21.3125	93	1.8%	-0.72 [-1.02 , -0.42]

Analysis 3.11. (Continued)

McBride 1988a	6.5	3.9	41	17.4	6.4	41	1.4%	-2.04 [-2.58 , -1.50]
McGough 2006	20.2	20.3481	93	35.3	21.3125	93	1.8%	-0.72 [-1.02 , -0.42]
Musten 1997	63.29	13.44	41	77.23	14.1	41	1.5%	-1.00 [-1.46 , -0.54]
Pearson 2013	55.8	9.3	24	66.8	12.7	24	1.3%	-0.97 [-1.57 , -0.37]
Pelham 1999	1.7	1.5	25	3	2.7	25	1.3%	-0.59 [-1.15 , -0.02]
Pelham 2001a	11.41	6.23	68	19.91	6.02	68	1.7%	-1.38 [-1.75 , -1.00]
Pelham 2005	2.7	2.2	30	5.5	3.8	30	1.4%	-0.89 [-1.42 , -0.36]
Schachar 2008	-0.98	2.14	18	3.2	2.82	18	1.0%	-1.63 [-2.40 , -0.87]
Smithee 1998	0.8639	0.4415	26	1.141	0.61022	26	1.4%	-0.51 [-1.07 , 0.04]
Solanto 2009	56.96	10.57	30	65.8	13.98	30	1.4%	-0.70 [-1.23 , -0.18]
Stein 1996	5.5	3.1	25	6.3	3.5	25	1.3%	-0.24 [-0.79 , 0.32]
Stein 2011	20.27	13.557	93	29.12	15.077	101	1.8%	-0.61 [-0.90 , -0.33]
Tirosh 1993a	10.75	2.9	20	14	4.8	20	1.2%	-0.80 [-1.45 , -0.16]
Zeiner 1999	3.08	3.7	38	5.25	5.01	38	1.5%	-0.49 [-0.94 , -0.03]
Subtotal (95% CI)			**2427**			**2456**	**61.2%**	**-0.71 [-0.86 , -0.55]**
Heterogeneity: Tau² = 0.21; Chi² = 260.07, df = 42 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 8.77 (P < 0.00001)								
Total (95% CI)			**4148**			**3690**	**100.0%**	**-0.67 [-0.78 , -0.56]**
Heterogeneity: Tau² = 0.15; Chi² = 321.95, df = 69 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 12.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.45), I² = 0%								



Footnotes

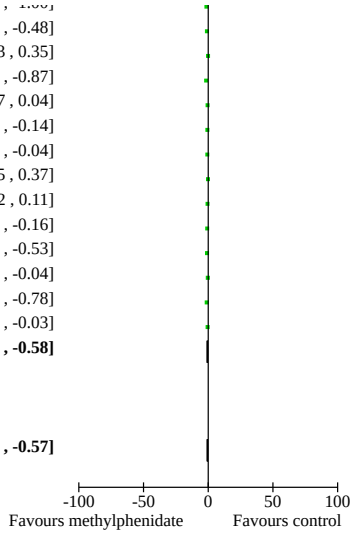
(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 3.12. Comparison 3: Parent-rated ADHD symptoms, Outcome 12: All parallel-group trials and cross-over trials: risk of bias

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
3.12.1 Low risk of bias									
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	0.8%	0.06 [-0.89 , 1.01]	
Cook 1993	0.41	0.175	15	0.59	0.166	15	1.1%	-1.03 [-1.79 , -0.26]	
DuPaul 1996	15.75	9.76	24	21	9.28	24	1.3%	-0.54 [-1.12 , 0.03]	
Flapper 2008	13	11.707	12	14.857	10.669	12	1.0%	-0.16 [-0.96 , 0.64]	
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	1.6%	-0.43 [-0.86 , 0.00]	
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	1.6%	-0.91 [-1.36 , -0.46]	
McGough 2006	20.2	20.3481	93	35.3	21.3125	93	1.8%	-0.72 [-1.02 , -0.42]	
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	1.8%	-0.50 [-0.83 , -0.17]	
Stein 1996	5.5	3.1	25	6.3	3.5	25	1.4%	-0.24 [-0.79 , 0.32]	
Stein 2011	20.27	13.557	93	29.12	15.077	101	1.8%	-0.61 [-0.90 , -0.33]	
Weiss 2021	23	12.57	283	26.9	13.81	71	1.9%	-0.30 [-0.56 , -0.04]	
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	0.7%	-1.02 [-2.14 , 0.10]	
Subtotal (95% CI)			**732**			**502**	**16.8%**	**-0.53 [-0.68 , -0.39]**	
Heterogeneity: Tau² = 0.01; Chi² = 13.55, df = 11 (P = 0.26); I² = 19%									
Test for overall effect: Z = 7.41 (P < 0.00001)									
3.12.2 High risk of bias									
Abikoff 2009	0.99	0.55	19	1.4	0.63	19	1.2%	-0.68 [-1.33 , -0.02]	
Arnold 2004	0.8	0.7	35	1.3	0.9	40	1.5%	-0.61 [-1.07 , -0.14]	
Barkley 1991	14.53	8.2	40	24.88	11.26	40	1.5%	-1.04 [-1.51 , -0.57]	
Barkley 2000	16.8	9.7	31	21.9	12.5	31	1.5%	-0.45 [-0.95 , 0.05]	
Barragán 2017	24.33	5.09	30	27.77	7.84	30	1.5%	-0.51 [-1.03 , 0.00]	
Bhat 2020	56.6	11.6	526	62.5	13.5	526	2.0%	-0.47 [-0.59 , -0.35]	
Blum 2011	64.8	26.5	30	89.6	13.1	30	1.4%	-1.17 [-1.72 , -0.62]	
Brams 2008	-16.382	14.0495	86	-4.622	14.0495	86	1.8%	-0.83 [-1.15 , -0.52]	
Brown 1984a	11	3.49	11	19.55	4.08	11	0.7%	-2.17 [-3.26 , -1.07]	
Brown 1985	7.5	2.6	10	13.1	4.1	10	0.8%	-1.56 [-2.59 , -0.53]	
Brown 1988	31.5	5.85	11	39.66	3.61	11	0.8%	-1.61 [-2.60 , -0.63]	
Childress 2009	19.6	12.75	57	35.9	13.01	63	1.7%	-1.26 [-1.65 , -0.86]	
Chronis 2003	1.8	1.5	21	3.1	1.9	21	1.3%	-0.75 [-1.37 , -0.12]	
Coghill 2007	67	14.8	75	77.2	11.1	75	1.8%	-0.78 [-1.11 , -0.44]	
Corkum 2008	62.14	14.11	10	69.38	10.23	11	0.9%	-0.57 [-1.45 , 0.31]	
Corkum 2020	62.9	11.6	26	68.2	10.3	26	1.4%	-0.48 [-1.03 , 0.08]	
CRIT124US02	-20	13.8	102	-9.7	13.3	99	1.8%	-0.76 [-1.04 , -0.47]	
Duric 2012	23.7	15.153	22	26.7	13.02	19	1.3%	-0.21 [-0.82 , 0.41]	
Epstein 2011	19.6	10.09	93	28.26	11.12	93	1.8%	-0.81 [-1.11 , -0.51]	
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	1.7%	-1.01 [-1.39 , -0.63]	
Findling 2007	20.81	9.79	20	32.19	14.61	20	1.2%	-0.90 [-1.55 , -0.24]	
Findling 2008	28.4	21.07	94	37	23.39	88	1.8%	-0.39 [-0.68 , -0.09]	
Findling 2010	36.52	17.6537	143	50	17.6537	72	1.8%	-0.76 [-1.05 , -0.47]	
Firestone 1981	13.5	7.26	18	14.9	6.58	13	1.1%	-0.20 [-0.91 , 0.52]	
Fitzpatrick 1992a	0.96	0.5	19	1.75	0.67	19	1.1%	-1.31 [-2.02 , -0.60]	
Gadow 1990	8.3	6.19	11	11	8.24	11	1.0%	-0.36 [-1.20 , 0.49]	
Gadow 1995	7.8	4.6	34	11.8	7.3	34	1.5%	-0.65 [-1.14 , -0.16]	
Gadow 2007	7.8	4.7	71	11	7	71	1.8%	-0.53 [-0.87 , -0.20]	
Gadow 2011	8.6	5.6	54	11.5	7.7	54	1.7%	-0.43 [-0.81 , -0.05]	
Gorman 2006	0.72	0.8324	41	1.61	0.8964	41	1.5%	-1.02 [-1.48 , -0.56]	
Hoeppner 1997	7.13	6.37	50	12.16	6.78	50	1.6%	-0.76 [-1.17 , -0.35]	
Huang 2021	7.6	5.2	99	8.3	6	99	1.8%	-0.12 [-0.40 , 0.15]	
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	1.0%	-0.03 [-0.81 , 0.76]	
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	1.9%	-0.58 [-0.82 , -0.33]	
Kortekaas-Rijlaarsdam 2017	7.87	17.04	65	-21.98	11.99	65	1.6%	2.01 [1.59 , 2.44]	
Manos 1999	10.1	6.71	117	18.61	11.86	117	1.9%	-0.88 [-1.15 , -0.61]	
McBride 1988a	6.5	3.9	41	17.4	6.4	41	1.4%	-2.04 [-2.58 , -1.50]	
Musten 1997	63.29	13.44	41	77.23	14.1	41	1.5%	-1.00 [-1.46 , -0.54]	
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	1.5%	-0.93 [-1.41 , -0.45]	
NCT02293655	17.3	12.3	15	25.2	11.6	82	1.4%	-0.67 [-1.23 , -0.11]	
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	1.8%	-0.88 [-1.17 , -0.59]	
Pearson 2013	55.8	9.3	24	66.8	12.7	24	1.3%	-0.97 [-1.57 , -0.37]	
Pelham 1999	1.7	1.5	25	3	2.7	25	1.4%	-0.59 [-1.15 , -0.02]	
Pelham 2001a	11.41	6.23	68	19.91	6.02	68	1.7%	-1.38 [-1.75 , -1.00]	
Pelham 2005	2.3	2.2	30	5.5	3.8	30	1.4%	-1.02 [-1.56 , -0.48]	
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	1.5%	-0.14 [-0.63 , 0.35]	

Analysis 3.12. (Continued)

Pelham 2005	2.3	2.2	30	5.5	3.8	30	1.4%	-1.02 [-1.56 , -0.48]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	1.5%	-0.14 [-0.63 , 0.35]
Schachar 2008	-0.98	2.14	18	3.2	2.82	18	1.1%	-1.63 [-2.40 , -0.87]
Smithee 1998	0.8639	0.4415	26	1.141	0.61022	26	1.4%	-0.51 [-1.07 , 0.04]
Solanto 2009	56.96	12.41	30	65.8	13.98	30	1.4%	-0.66 [-1.18 , -0.14]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	1.2%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	1.4%	-0.19 [-0.75 , 0.37]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	1.2%	-0.55 [-1.22 , 0.11]
Tirosh 1993a	10.75	2.9	20	14	4.8	20	1.2%	-0.80 [-1.45 , -0.16]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	1.7%	-0.93 [-1.32 , -0.53]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	1.8%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	1.7%	-1.17 [-1.56 , -0.78]
Zeiner 1999	3.08	3.7	38	5.25	5.01	38	1.5%	-0.49 [-0.94 , -0.03]
Subtotal (95% CI)			**3261**			**3008**	**83.2%**	**-0.71 [-0.84 , -0.58]**
Heterogeneity: Tau² = 0.19; Chi² = 309.17, df = 56 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 10.58 (P < 0.00001)								
Total (95% CI)			**3993**			**3510**	**100.0%**	**-0.68 [-0.79 , -0.57]**
Heterogeneity: Tau² = 0.16; Chi² = 325.68, df = 68 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 11.79 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.24, df = 1 (P = 0.07), I² = 69.1%								



Footnotes

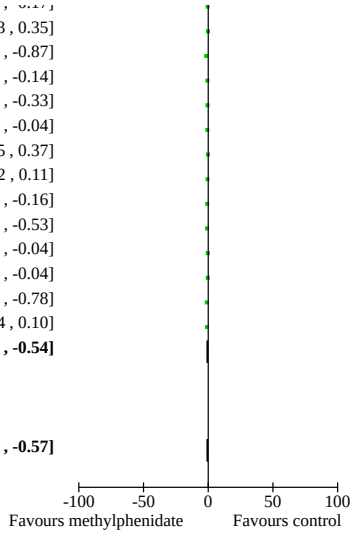
(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 3.13. Comparison 3: Parent-rated ADHD symptoms, Outcome 13: All parallel-group trials and cross-over trials: vested interest

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
3.13.1 Low risk of vested interest									
Barkley 1991	14.53	8.2	40	24.88	11.26	40	1.5%	-1.04 [-1.51 , -0.57]	
Barkley 2000	16.8	9.7	31	21.9	12.5	31	1.5%	-0.45 [-0.95 , 0.05]	
Brown 1988	31.5	5.85	11	39.66	3.61	11	0.8%	-1.61 [-2.60 , -0.63]	
Cook 1993	0.41	0.175	15	0.59	0.166	15	1.1%	-1.03 [-1.79 , -0.26]	
Corkum 2008	62.14	14.11	10	69.38	10.23	11	0.9%	-0.57 [-1.45 , 0.31]	
Corkum 2020	62.9	11.6	26	68.2	10.3	26	1.4%	-0.48 [-1.03 , 0.08]	
Duric 2012	23.7	15.153	22	26.7	13.02	19	1.3%	-0.21 [-0.82 , 0.41]	
Epstein 2011	19.6	10.09	93	28.26	11.12	93	1.8%	-0.81 [-1.11 , -0.51]	
Firestone 1981	13.5	7.26	18	14.9	6.58	13	1.1%	-0.20 [-0.91 , 0.52]	
Fitzpatrick 1992a	0.96	0.5	19	1.75	0.67	19	1.1%	-1.31 [-2.02 , -0.60]	
Flapper 2008	13	11.707	12	14.857	10.669	12	1.0%	-0.16 [-0.96 , 0.64]	
Gadow 1995	7.8	4.6	34	11.8	7.3	34	1.5%	-0.65 [-1.14 , -0.16]	
Gadow 2007	7.8	4.7	71	11	7	71	1.8%	-0.53 [-0.87 , -0.20]	
Gorman 2006	0.72	0.8324	41	1.61	0.8964	41	1.5%	-1.02 [-1.48 , -0.56]	
Musten 1997	63.29	13.44	41	77.23	14.1	41	1.5%	-1.00 [-1.46 , -0.54]	
Pearson 2013	55.8	9.3	24	66.8	12.7	24	1.3%	-0.97 [-1.57 , -0.37]	
Smithee 1998	0.8639	0.4415	26	1.141	0.61022	26	1.4%	-0.51 [-1.07 , 0.04]	
Stein 1996	5.5	3.1	25	6.3	3.5	25	1.4%	-0.24 [-0.79 , 0.32]	
Zeiner 1999	3.08	3.7	38	5.25	5.01	38	1.5%	-0.49 [-0.94 , -0.03]	
Subtotal (95% CI)			**597**			**590**	**25.5%**	**-0.69 [-0.84 , -0.54]**	
Heterogeneity: Tau² = 0.03; Chi² = 26.35, df = 18 (P = 0.09); I² = 32%									
Test for overall effect: Z = 9.01 (P < 0.00001)									
3.13.2 High risk or unclear risk of vested interest									
Abikoff 2009	0.99	0.55	19	1.4	0.63	19	1.2%	-0.68 [-1.33 , -0.02]	
Arnold 2004	0.8	0.7	35	1.3	0.9	40	1.5%	-0.61 [-1.07 , -0.14]	
Barragán 2017	24.33	5.09	30	27.77	7.84	30	1.5%	-0.51 [-1.03 , 0.00]	
Bhat 2020	56.6	11.6	526	62.5	13.5	526	2.0%	-0.47 [-0.59 , -0.35]	
Blum 2011	64.8	26.5	30	89.6	13.1	30	1.4%	-1.17 [-1.72 , -0.62]	
Brams 2008	-16.382	14.0495	86	-4.622	14.0495	86	1.8%	-0.83 [-1.15 , -0.52]	
Brown 1984a	11	3.49	11	19.55	4.08	11	0.7%	-2.17 [-3.26 , -1.07]	
Brown 1985	7.5	2.6	10	13.1	4.1	10	0.8%	-1.56 [-2.59 , -0.53]	
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	0.8%	0.06 [-0.89 , 1.01]	
Childress 2009	19.6	12.75	57	35.9	13.01	63	1.7%	-1.26 [-1.65 , -0.86]	
Chronis 2003	1.8	1.5	21	3.1	1.9	21	1.3%	-0.75 [-1.37 , -0.12]	
Coghill 2007	67	14.8	75	77.2	11.1	75	1.8%	-0.78 [-1.11 , -0.44]	
CRIT124US02	-20	13.8	102	-9.7	13.3	99	1.8%	-0.76 [-1.04 , -0.47]	
DuPaul 1996	15.75	9.76	24	21	9.28	24	1.3%	-0.54 [-1.12 , 0.03]	
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	1.7%	-1.01 [-1.39 , -0.63]	
Findling 2007	20.81	9.79	20	32.19	14.61	20	1.2%	-0.90 [-1.55 , -0.24]	
Findling 2008	28.4	21.07	94	37	23.39	88	1.8%	-0.39 [-0.68 , -0.09]	
Findling 2010	36.52	17.6537	143	50	17.6537	72	1.8%	-0.76 [-1.05 , -0.47]	
Gadow 1990	8.3	6.19	11	11	8.24	11	1.0%	-0.36 [-1.20 , 0.49]	
Gadow 2011	8.6	5.6	54	11.5	7.7	54	1.7%	-0.43 [-0.81 , -0.05]	
Hoeppner 1997	7.13	6.37	50	12.16	6.78	50	1.6%	-0.76 [-1.17 , -0.35]	
Huang 2021	7.6	5.2	99	8.3	6	99	1.8%	-0.12 [-0.40 , 0.15]	
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	1.0%	-0.03 [-0.81 , 0.76]	
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	1.9%	-0.58 [-0.82 , -0.33]	
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	1.6%	-0.43 [-0.86 , 0.00]	
Kortekaas-Rijlaarsdam 2017	7.87	17.04	65	-21.98	11.99	65	1.6%	2.01 [1.59 , 2.44]	
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	1.6%	-0.91 [-1.36 , -0.46]	
Manos 1999	10.1	6.71	117	18.61	11.86	117	1.9%	-0.88 [-1.15 , -0.61]	
McBride 1988a	6.5	3.9	41	17.4	6.4	41	1.4%	-2.04 [-2.58 , -1.50]	
McGough 2006	20.2	20.3481	93	35.3	21.3125	93	1.8%	-0.72 [-1.02 , -0.42]	
NCT00409708 (1)	-17	11.23	38	-7	9.97	37	1.5%	-0.93 [-1.41 , -0.45]	
NCT02293655	17.3	12.3	15	25.2	11.6	82	1.4%	-0.67 [-1.23 , -0.11]	
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	1.8%	-0.88 [-1.17 , -0.59]	
Pelham 1999	1.7	1.5	25	3	2.7	25	1.4%	-0.59 [-1.15 , -0.02]	
Pelham 2001a	11.41	6.23	68	19.91	6.02	68	1.7%	-1.38 [-1.75 , -1.00]	
Pelham 2005	2.3	2.2	30	5.5	3.8	30	1.4%	-1.02 [-1.56 , -0.48]	
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	1.8%	-0.50 [-0.83 , -0.17]	
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	1.5%	-0.14 [-0.63 , 0.35]	
Schachar 2008	-0.98	2.14	18	3.2	2.82	18	1.1%	-1.63 [-2.40 , -0.87]	

Analysis 3.13. (Continued)

Schachar 1997a	1.2	0.7	37	1.3	0.7	29	1.5%	-0.14 [-0.63 , 0.35]
Schachar 2008	-0.98	2.14	18	3.2	2.82	18	1.1%	-1.63 [-2.40 , -0.87]
Solanto 2009	56.96	12.41	30	65.8	13.98	30	1.4%	-0.66 [-1.18 , -0.14]
Stein 2011	20.27	13.557	93	29.12	15.077	101	1.8%	-0.61 [-0.90 , -0.33]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	1.2%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	1.4%	-0.19 [-0.75 , 0.37]
Taylor 1987	0.36	0.42	15	0.68	0.64	23	1.2%	-0.55 [-1.22 , 0.11]
Tirosh 1993a	10.75	2.9	20	14	4.8	20	1.2%	-0.80 [-1.45 , -0.16]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	1.7%	-0.93 [-1.32 , -0.53]
Weiss 2021	23	12.57	283	26.9	13.81	71	1.9%	-0.30 [-0.56 , -0.04]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	1.8%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	1.7%	-1.17 [-1.56 , -0.78]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	0.7%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**3396**			**2920**	**74.5%**	**-0.68 [-0.82 , -0.54]**
Heterogeneity: Tau² = 0.19; Chi² = 298.02, df = 49 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 9.57 (P < 0.00001)								
Total (95% CI)			**3993**			**3510**	**100.0%**	**-0.68 [-0.79 , -0.57]**
Heterogeneity: Tau² = 0.16; Chi² = 325.68, df = 68 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 11.79 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%								



Footnotes

(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Comparison 4. Additional subgroup analyses of ADHD symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Parallel-group trials and first-period cross-over trials: comparison of raters	46	7965	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-0.85, -0.60]
4.1.1 Teacher-rated	21	1759	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.90, -0.60]
4.1.2 Independent assessor-rated	20	3601	Std. Mean Difference (IV, Random, 95% CI)	-0.88 [-1.18, -0.58]
4.1.3 Parent-rated	26	2605	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-0.77, -0.51]
4.2 Parallel-group trials and first-period cross-over trials: age	13	2374	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.35, -0.50]
4.2.1 2 to 6 years	2	153	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.82, -0.18]
4.2.2 7 to 11 years	5	623	Std. Mean Difference (IV, Random, 95% CI)	-1.77 [-3.24, -0.29]
4.2.3 12 to 18 years	6	1598	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.77, -0.19]
4.3 Parallel-group trials and first-period cross-over trials: comorbidity versus no comorbidity	29	3433	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-0.84, -0.54]

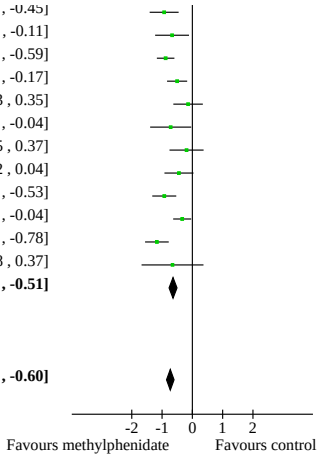
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.1 ADHD with comorbidity	20	2128	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-0.88, -0.47]
4.3.2 ADHD without comorbidity	9	1305	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-0.91, -0.54]
4.4 Parallel-group trials and first-period cross-over trials: subtypes ADHD: ADHD Rating Scale (parent-, teacher- or independent assessor-rated)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.4.1 Combined ADHD	2	559	Std. Mean Difference (IV, Random, 95% CI)	0.65 [-1.30, 2.60]
4.4.2 Inattentive ADHD	1	204	Std. Mean Difference (IV, Random, 95% CI)	-1.31 [-1.61, -1.01]
4.5 Cross-over trials: first-period data versus endpoint data (parent-, independent assessor- and teacher-rated)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.5.1 First-period data	4	191	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-0.93, -0.34]
4.5.2 Endpoint data	4	372	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.18, -0.65]

Analysis 4.1. Comparison 4: Additional subgroup analyses of ADHD symptoms, Outcome 1: Parallel-group trials and first-period cross-over trials: comparison of raters

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Teacher-rated								
Arnold 2004	0.7	0.7	35	1.4	0.9	40	1.5%	-0.85 [-1.33 , -0.38]
Biederman 2003b	16.3	12.12	63	31.3	15.37	71	1.7%	-1.07 [-1.43 , -0.71]
Brown 1985 (1)	15	3.1	10	20.6	2.6	10	0.8%	-1.87 [-2.96 , -0.78]
Butter 1983	30.47	17.3	10	42.7	14.2	10	0.9%	-0.74 [-1.65 , 0.17]
Childress 2009	16.4	13.44	57	30	13.01	63	1.6%	-1.02 [-1.40 , -0.64]
Findling 2006	4.3	3.264	120	7.7	3.1157	39	1.6%	-1.05 [-1.43 , -0.67]
Findling 2008	18.3	17.44	94	31.6	20.07	88	1.7%	-0.71 [-1.01 , -0.41]
Firestone 1981	8.9	4.93	18	11.77	4.83	13	1.2%	-0.57 [-1.30 , 0.16]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	1.0%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	1.8%	-0.47 [-0.72 , -0.22]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	1.5%	-0.33 [-0.82 , 0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	1.5%	-1.06 [-1.52 , -0.61]
Matthijssen 2019	25.1	9.2	40	28.4	9.5	38	1.5%	-0.35 [-0.80 , 0.10]
Moshe 2012	58	10.3	28	64.7	12.5	29	1.4%	-0.58 [-1.11 , -0.05]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	1.4%	-0.28 [-0.79 , 0.23]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	1.2%	-0.89 [-1.56 , -0.22]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	1.4%	-1.13 [-1.65 , -0.60]
Tannock 2018	62	13.6	23	67.9	13.6	26	1.4%	-0.43 [-0.99 , 0.14]
Tourette's Syndrome Study Group 2002	1.315	6.13	37	2.82	6.13	32	1.5%	-0.24 [-0.72 , 0.23]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	1.3%	-0.73 [-1.32 , -0.15]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	1.6%	-1.05 [-1.44 , -0.67]
Subtotal (95% CI)			**948**			**811**	**29.7%**	**-0.75 [-0.90 , -0.60]**
Heterogeneity: Tau² = 0.05; Chi² = 38.48, df = 20 (P = 0.008); I² = 48%								
Test for overall effect: Z = 10.11 (P < 0.00001)								
4.1.2 Independent assessor-rated								
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	1.5%	-1.57 [-2.07 , -1.07]
Childress 2020a	11.4	6.9	74	18.2	9	73	1.7%	-0.84 [-1.18 , -0.51]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	1.6%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	1.6%	-0.63 [-1.06 , -0.20]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	1.7%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	1.5%	-0.72 [-1.17 , -0.26]
Findling 2008	-21.619	14.409	91	-10.3	14.409	85	1.7%	-0.78 [-1.09 , -0.48]
Findling 2010	17.7	12.2	145	27.7	12.75	72	1.7%	-0.80 [-1.10 , -0.51]
Gonzalez-Heydrich 2010	23	12	28	30	10	28	1.4%	-0.62 [-1.16 , -0.09]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	1.8%	-0.35 [-0.61 , -0.08]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	0.9%	-8.13 [-9.12 , -7.15]
Matthijssen 2019	21.9	10.8	47	24.7	11.4	47	1.6%	-0.25 [-0.66 , 0.16]
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	1.7%	-0.19 [-0.52 , 0.15]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	1.8%	-0.75 [-1.02 , -0.48]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	1.8%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	1.8%	-0.51 [-0.76 , -0.25]
Pliszka 2017	24.1	12.816	73	31.2	12.8996	65	1.7%	-0.55 [-0.89 , -0.21]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	1.8%	0.04 [-0.18 , 0.27]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	1.8%	-0.33 [-0.59 , -0.07]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	1.7%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**2118**			**1483**	**32.7%**	**-0.88 [-1.18 , -0.58]**
Heterogeneity: Tau² = 0.42; Chi² = 316.82, df = 19 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 5.81 (P < 0.00001)								
4.1.3 Parent-rated								
Arnold 2004	0.8	0.7	35	1.3	0.9	40	1.5%	-0.61 [-1.07 , -0.14]
Barragán 2017	24.33	5.09	30	27.77	7.84	30	1.4%	-0.51 [-1.03 , 0.00]
Brown 1985	7.5	2.6	10	13.1	4.1	10	0.8%	-1.56 [-2.59 , -0.53]
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	0.9%	0.06 [-0.89 , 1.01]
Childress 2009	19.6	12.75	57	35.9	13.01	63	1.6%	-1.26 [-1.65 , -0.86]
Duric 2012	23.7	15.153	22	26.7	13.02	19	1.3%	-0.21 [-0.82 , 0.41]
Findling 2006	5.1	2.9321	120	8.1	3.0232	39	1.6%	-1.01 [-1.39 , -0.63]
Findling 2008	28.4	21.07	94	37	23.39	88	1.7%	-0.39 [-0.68 , -0.09]
Findling 2010	36.52	17.6537	143	50	17.6537	72	1.7%	-0.76 [-1.05 , -0.47]
Firestone 1981	13.5	7.26	18	14.9	6.58	13	1.2%	-0.20 [-0.91 , 0.52]
Ialongo 1994	9.76	5.94	13	9.9	4.28	12	1.1%	-0.03 [-0.81 , 0.76]
Jensen 1999 (MTA)	0.85	0.63	133	1.24	0.72	129	1.8%	-0.58 [-0.82 , -0.33]
Kollins 2006 (PATS)	1.09	0.72	48	1.41	0.77	38	1.6%	-0.43 [-0.86 , 0.00]
Lehmkuhl 2002	1.1	0.6557	43	1.7	0.6481	42	1.5%	-0.91 [-1.36 , -0.46]
NCT00409708 (2)	-17	11.23	38	-7	9.97	37	1.5%	-0.93 [-1.41 , -0.45]
NCT02293655	17.3	12.3	15	25.2	11.6	82	1.4%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	1.7%	-0.88 [-1.17 , -0.59]

Analysis 4.1. (Continued)

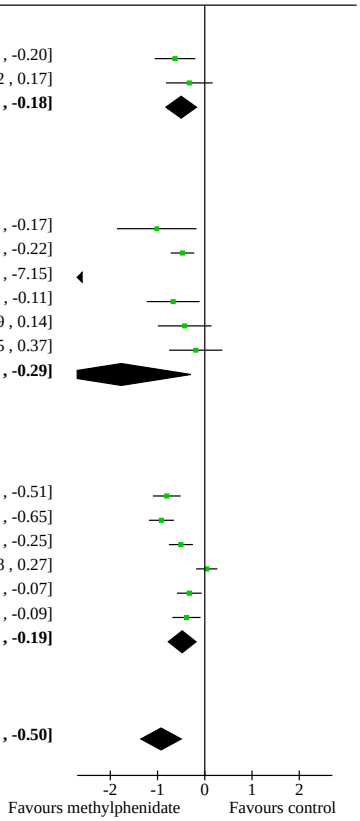
NCT00409708 (2)	-17	11.23	38	-7	9.97	37	1.5%	-0.93 [-1.41 , -0.45]
NCT02293655	17.3	12.3	15	25.2	11.6	82	1.4%	-0.67 [-1.23 , -0.11]
Newcorn 2008	-10.2	9.1	195	-2.3	8.4	66	1.7%	-0.88 [-1.17 , -0.59]
Pliszka 2017	9.4	5.6523	78	12.2	5.4023	67	1.7%	-0.50 [-0.83 , -0.17]
Schachar 1997a	1.2	0.7	37	1.3	0.7	29	1.5%	-0.14 [-0.63 , 0.35]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	1.2%	-0.72 [-1.39 , -0.04]
Tannock 2018	63.4	12.5	23	65.9	13.1	26	1.4%	-0.19 [-0.75 , 0.37]
Tourette's Syndrome Study Group 2002	2.85	7.08	37	6	7.01	32	1.5%	-0.44 [-0.92 , 0.04]
Tucker 2009	-8.2	6.05	53	-3.2	4.6	56	1.6%	-0.93 [-1.32 , -0.53]
Wilens 2006b	16.65	11.07	87	20.84	13.58	90	1.7%	-0.34 [-0.63 , -0.04]
Wolraich 2001	5.44	3.22	81	9.48	3.78	46	1.6%	-1.17 [-1.56 , -0.78]
Zeni 2009	1.2789	0.45518	9	1.7529	0.90373	7	0.8%	-0.65 [-1.68 , 0.37]
Subtotal (95% CI)			**1447**			**1158**	**37.5%**	**-0.64 [-0.77 , -0.51]**
Heterogeneity: Tau² = 0.06; Chi² = 55.51, df = 25 (P = 0.0004); I² = 55%								
Test for overall effect: Z = 9.55 (P < 0.00001)								
Total (95% CI)			**4513**			**3452**	**100.0%**	**-0.73 [-0.85 , -0.60]**
Heterogeneity: Tau² = 0.21; Chi² = 414.82, df = 66 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 11.52 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.73, df = 2 (P = 0.26), I² = 26.7%								



Footnotes
(1) MPH vs waiting list
(2) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 4.2. Comparison 4: Additional subgroup analyses of ADHD symptoms, Outcome 2: Parallel-group trials and first-period cross-over trials: age

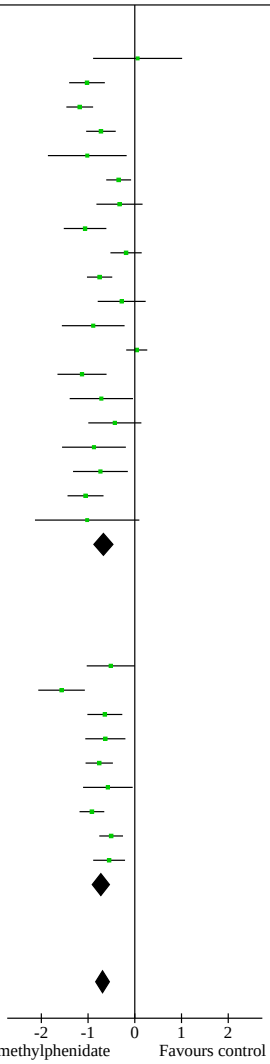
Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.2.1 2 to 6 years								
Childress 2020c	25.8	14.6	39	34.9	14.1	50	7.3%	-0.63 [-1.06 , -0.20]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	7.1%	-0.33 [-0.82 , 0.17]
Subtotal (95% CI)			**71**			**82**	**14.4%**	**-0.50 [-0.82 , -0.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 1 (P = 0.36); I² = 0%								
Test for overall effect: Z = 3.02 (P = 0.003)								
4.2.2 7 to 11 years								
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	6.0%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.75	0.71	134	1.1	0.77	119	7.6%	-0.47 [-0.72 , -0.22]
Kollins 2021	-4.87	0.62	74	0.54	0.7	76	5.5%	-8.13 [-9.12 , -7.15]
NCT02293655	17.3	12.3	15	25.2	11.6	82	6.9%	-0.67 [-1.23 , -0.11]
Tannock 2018 (1)	62	13.6	23	67.9	13.6	26	6.9%	-0.43 [-0.99 , 0.14]
Tannock 2018 (2)	63.4	12.5	23	65.9	13.1	26	6.9%	-0.19 [-0.75 , 0.37]
Subtotal (95% CI)			**282**			**341**	**39.9%**	**-1.77 [-3.24 , -0.29]**
Heterogeneity: Tau² = 3.27; Chi² = 225.55, df = 5 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 2.35 (P = 0.02)								
4.2.3 12 to 18 years								
Findling 2010	17.7	12.2	145	27.7	12.75	72	7.6%	-0.80 [-1.10 , -0.51]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	7.6%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	7.6%	-0.51 [-0.76 , -0.25]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	7.7%	0.04 [-0.18 , 0.27]
Weiss 2021	22.1	12.18	283	26.2	13.81	71	7.6%	-0.33 [-0.59 , -0.07]
Wilens 2006b	16.62	11.03	87	21.4	13.44	90	7.6%	-0.39 [-0.68 , -0.09]
Subtotal (95% CI)			**1031**			**567**	**45.7%**	**-0.48 [-0.77 , -0.19]**
Heterogeneity: Tau² = 0.12; Chi² = 37.15, df = 5 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.20 (P = 0.001)								
Total (95% CI)			**1384**			**990**	**100.0%**	**-0.93 [-1.35 , -0.50]**
Heterogeneity: Tau² = 0.61; Chi² = 272.09, df = 13 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 4.25 (P < 0.0001)								
Test for subgroup differences: Chi² = 2.84, df = 2 (P = 0.24), I² = 29.6%								



Footnotes
(1) Teacher-rated
(2) Parent-rated

Analysis 4.3. Comparison 4: Additional subgroup analyses of ADHD symptoms, Outcome 3: Parallel-group trials and first-period cross-over trials: comorbidity versus no comorbidity

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.3.1 ADHD with comorbidity								
Carlson 2007	-3.3	20.9	9	-4.3	5.2	8	1.6%	0.06 [-0.89 , 1.01]
Childress 2009	16.4	13.44	57	30	13.01	63	3.9%	-1.02 [-1.40 , -0.64]
Coghill 2013	3.5295	10.9979	111	16.5295	10.9979	110	4.4%	-1.18 [-1.46 , -0.89]
Döpfner 2004	0.441	0.427	82	0.858	0.689	82	4.2%	-0.72 [-1.04 , -0.41]
Ialongo 1994	7.53	7.41	13	15.25	7.27	12	1.9%	-1.02 [-1.86 , -0.17]
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	4.5%	-0.35 [-0.61 , -0.08]
Kollins 2006 (PATS)	1.09	0.8	32	1.35	0.77	32	3.3%	-0.33 [-0.82 , 0.17]
Lehmkuhl 2002	0.9	0.6557	43	1.6	0.6481	42	3.5%	-1.06 [-1.52 , -0.61]
McCracken 2016	-10.66	16.6495	70	-7.77	14.0186	68	4.1%	-0.19 [-0.52 , 0.15]
Newcorn 2008	-16.9	13.1	220	-7.3	11.5	74	4.5%	-0.75 [-1.02 , -0.48]
Palumbo 2008	-5.07	6.79	29	-3.2	6.38	30	3.2%	-0.28 [-0.79 , 0.23]
Pliszka 2000	0.81	0.62	20	1.49	0.87	18	2.5%	-0.89 [-1.56 , -0.22]
Riggs 2011	17	14.3038	151	16.4	14.3518	152	4.7%	0.04 [-0.18 , 0.27]
Schachar 1997a	0.9	0.7	37	1.7	0.7	29	3.1%	-1.13 [-1.65 , -0.60]
Szobot 2004	11.9	6.1	19	16.4	6.2	17	2.5%	-0.72 [-1.39 , -0.04]
Tannock 2018 (1)	62	13.6	23	67.9	13.6	26	2.9%	-0.43 [-0.99 , 0.14]
Taylor 1987	0.58	0.41	15	1.17	0.78	23	2.5%	-0.87 [-1.56 , -0.19]
Van der Meere 1999a	73.6	12.7133	24	83.1	12.7133	24	2.9%	-0.73 [-1.32 , -0.15]
Wolraich 2001	5.7	3.84	81	9.87	4.09	46	3.9%	-1.05 [-1.44 , -0.67]
Zeni 2009	1.2022	0.65764	9	1.9317	0.69847	6	1.3%	-1.02 [-2.14 , 0.10]
Subtotal (95% CI)			**1159**			**969**	**65.4%**	**-0.67 [-0.88 , -0.47]**
Heterogeneity: Tau² = 0.15; Chi² = 84.04, df = 19 (P < 0.00001); I² = 77%								
Test for overall effect: Z = 6.45 (P < 0.00001)								
4.3.2 ADHD without comorbidity								
Barragán 2017	24.33	5.09	30	27.77	7.84	30	3.2%	-0.51 [-1.03 , 0.00]
Childress 2017	14.3	6.8236	43	25.3	7.0952	39	3.3%	-1.57 [-2.07 , -1.07]
Childress 2020b	14.8	9.36	64	20.7	8.8817	53	3.9%	-0.64 [-1.01 , -0.27]
Childress 2020c	25.8	14.6	39	34.9	14.1	50	3.6%	-0.63 [-1.06 , -0.20]
Findling 2010	36.52	17.6537	143	50	17.6537	72	4.4%	-0.76 [-1.05 , -0.47]
Moshe 2012	58	10.3	28	64.7	12.5	29	3.1%	-0.58 [-1.11 , -0.05]
Newcorn 2017a (flexible dose)	-23.5	10.8517	184	-13.4	11.2264	89	4.5%	-0.92 [-1.18 , -0.65]
Newcorn 2017b (forced dose)	-22	9.8211	181	-17	9.933	93	4.5%	-0.51 [-0.76 , -0.25]
Pliszka 2017 (2)	24.1	12.816	73	31.2	12.8996	65	4.1%	-0.55 [-0.89 , -0.21]
Subtotal (95% CI)			**785**			**520**	**34.6%**	**-0.73 [-0.91 , -0.54]**
Heterogeneity: Tau² = 0.04; Chi² = 18.26, df = 8 (P = 0.02); I² = 56%								
Test for overall effect: Z = 7.75 (P < 0.00001)								
Total (95% CI)			**1944**			**1489**	**100.0%**	**-0.69 [-0.84 , -0.54]**
Heterogeneity: Tau² = 0.11; Chi² = 104.70, df = 28 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 9.23 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%								



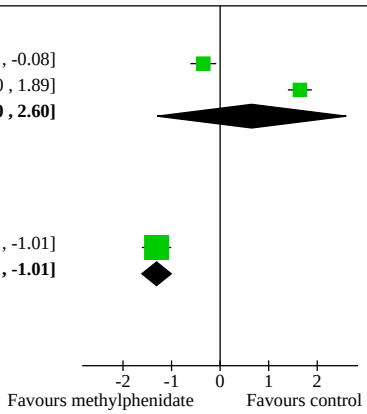
Footnotes

(1) Teacher-rated

(2) Independent assesor-rated

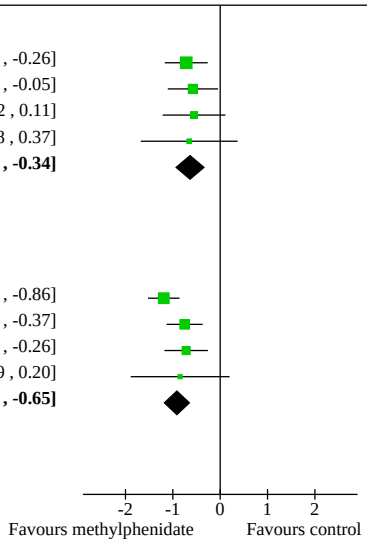
Analysis 4.4. Comparison 4: Additional subgroup analyses of ADHD symptoms, Outcome 4: Parallel-group trials and first-period cross-over trials: subtypes ADHD: ADHD Rating Scale (parent-, teacher- or independent assessor-rated)

Study or Subgroup	Methylphenidate Mean	SD	Total	No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.4.1 Combined ADHD								
Jensen 1999 (MTA)	0.21	0.2	114	0.29	0.26	107	50.0%	-0.35 [-0.61 , -0.08]
Riggs 2011	18.9	1.3	169	16.5	1.6	169	50.0%	1.64 [1.40 , 1.89]
Subtotal (95% CI)			**283**			**276**	**100.0%**	**0.65 [-1.30 , 2.60]**
Heterogeneity: Tau² = 1.96; Chi² = 115.32, df = 1 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 0.65 (P = 0.51)								
4.4.2 Inattentive ADHD								
Riggs 2011	16.8	1.7	102	19.1	1.8	102	100.0%	-1.31 [-1.61 , -1.01]
Subtotal (95% CI)			**102**			**102**	**100.0%**	**-1.31 [-1.61 , -1.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.47 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								



Analysis 4.5. Comparison 4: Additional subgroup analyses of ADHD symptoms, Outcome 5: Cross-over trials: first-period data versus endpoint data (parent-, independent assessor- and teacher-rated)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.5.1 First-period data								
Döpfner 2004	0.441	0.427	39	0.858	0.689	41	41.8%	-0.72 [-1.17 , -0.26]
Moshe 2012	58	10.3	28	64.7	12.5	29	30.5%	-0.58 [-1.11 , -0.05]
Taylor 1987	0.54	1.04	15	1.22	1.3	23	19.5%	-0.55 [-1.22 , 0.11]
Zeni 2009	1.2789	0.45518	9	1.7529	0.90373	7	8.2%	-0.65 [-1.68 , 0.37]
Subtotal (95% CI)			**91**			**100**	**100.0%**	**-0.64 [-0.93 , -0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 3 (P = 0.97); I² = 0%								
Test for overall effect: Z = 4.26 (P < 0.0001)								
4.5.2 Endpoint data								
Döpfner 2004	0.374	0.366	82	1.081	0.751	82	37.7%	-1.19 [-1.52 , -0.86]
Moshe 2012	55.5	9.5	57	62.1	7.9	57	31.8%	-0.75 [-1.13 , -0.37]
Taylor 1987	0.85	1	39	1.59	1.04	39	24.5%	-0.72 [-1.18 , -0.26]
Zeni 2009	0.8911	0.72428	9	1.7	1.0996	7	6.0%	-0.85 [-1.89 , 0.20]
Subtotal (95% CI)			**187**			**185**	**100.0%**	**-0.91 [-1.18 , -0.65]**
Heterogeneity: Tau² = 0.02; Chi² = 4.07, df = 3 (P = 0.25); I² = 26%								
Test for overall effect: Z = 6.80 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								



Comparison 5. Serious adverse events: parallel-group trials and first-period cross-over trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Proportions of participants with serious adverse events (SAE)	26	3673	Risk Ratio (IV, Random, 95% CI)	0.80 [0.39, 1.67]
5.2 Nervous system (including psychiatry)	12	4199	Risk Ratio (IV, Random, 95% CI)	0.70 [0.29, 1.71]

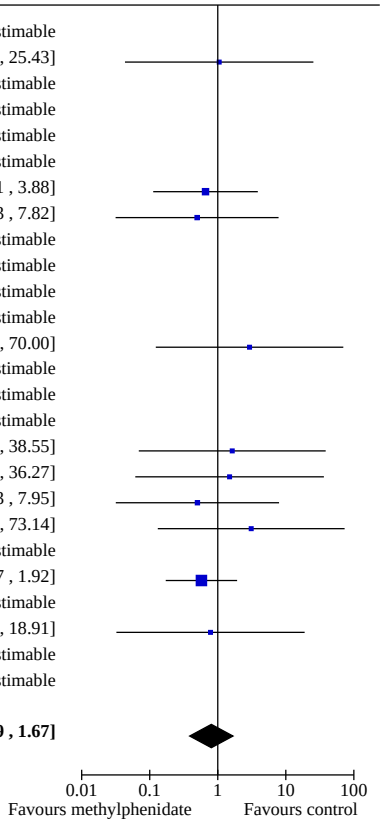
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2.1 Aggression	1	303	Risk Ratio (IV, Random, 95% CI)	0.50 [0.05, 5.49]
5.2.2 Concussion	1	303	Risk Ratio (IV, Random, 95% CI)	0.34 [0.01, 8.17]
5.2.3 Loss of consciousness	1	221	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 8.02]
5.2.4 Psychosis	4	919	Risk Ratio (IV, Random, 95% CI)	0.81 [0.13, 5.12]
5.2.5 Syncope	3	741	Risk Ratio (IV, Random, 95% CI)	1.39 [0.23, 8.47]
5.2.6 Suicidal ideation	6	1032	Risk Ratio (IV, Random, 95% CI)	1.63 [0.07, 38.55]
5.2.7 Suicidal behaviour	2	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
5.2.8 Oppositional behaviour/negativism	1	217	Risk Ratio (IV, Random, 95% CI)	0.17 [0.01, 4.04]
5.2.9 Adjustment disorder	1	230	Risk Ratio (IV, Random, 95% CI)	0.78 [0.03, 18.91]
5.3 Digestive system	2	414	Risk Ratio (IV, Random, 95% CI)	2.11 [0.22, 20.04]
5.3.1 Appendicitis	2	414	Risk Ratio (IV, Random, 95% CI)	2.11 [0.22, 20.04]
5.4 Cardiovascular systems	2	280	Risk Ratio (IV, Random, 95% CI)	1.02 [0.11, 9.65]
5.4.1 Haematoma	1	221	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 8.02]
5.4.2 Tachycardia	1	59	Risk Ratio (IV, Random, 95% CI)	3.10 [0.13, 73.14]
5.5 Respiratory systems	1	606	Risk Ratio (IV, Random, 95% CI)	1.01 [0.11, 9.62]
5.5.1 Bronchitis	1	303	Risk Ratio (IV, Random, 95% CI)	0.34 [0.01, 8.17]
5.5.2 Asthma	1	303	Risk Ratio (IV, Random, 95% CI)	3.02 [0.12, 73.54]
5.6 Urinary system	2	578	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.23, 19.81]
5.6.1 Renal cyst	1	275	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.06, 36.27]
5.6.2 Kidney infection	1	303	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [0.12, 73.54]
5.7 Skeletal and muscular system (including pain)	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
5.7.1 Clavical fracture	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
5.8 Immune system (including infections)	1	303	Risk Ratio (IV, Random, 95% CI)	3.02 [0.12, 73.54]
5.8.1 Cyst rupture	1	303	Risk Ratio (IV, Random, 95% CI)	3.02 [0.12, 73.54]
5.9 Other	2	524	Risk Ratio (IV, Random, 95% CI)	1.00 [0.10, 9.55]
5.9.1 Drug toxicity	1	303	Risk Ratio (IV, Random, 95% CI)	0.34 [0.01, 8.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.9.2 Overdose	1	221	Risk Ratio (IV, Random, 95% CI)	2.97 [0.12, 72.20]

Analysis 5.1. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 1: Proportions of participants with serious adverse events (SAE)

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo/No intervention Events	Placebo/No intervention Total	Weight	Risk Ratio IV, Random, 95% CI
Carlson 2007	0	9	0	8		Not estimable
Childress 2009	1	182	0	63	5.3%	1.05 [0.04 , 25.43]
Childress 2017	0	44	0	41		Not estimable
Childress 2020a	0	74	0	73		Not estimable
Childress 2020b	0	65	0	54		Not estimable
Childress 2020c	0	39	0	50		Not estimable
Coghill 2013	2	111	3	110	17.1%	0.66 [0.11 , 3.88]
Findling 2010 (1)	1	145	1	72	7.1%	0.50 [0.03 , 7.82]
Green 2011	0	22	0	12		Not estimable
Huang 2021	0	50	0	50		Not estimable
Jacobi-Polishook 2009	0	12	0	12		Not estimable
Kollins 2021	0	74	0	76		Not estimable
Lehmkuhl 2002	1	43	0	42	5.3%	2.93 [0.12 , 70.00]
Matthijssen 2019	0	47	0	47		Not estimable
McCracken 2016	0	70	0	68		Not estimable
NCT00409708	0	52	0	52		Not estimable
NCT02293655	0	18	1	92	5.4%	1.63 [0.07 , 38.55]
Newcorn 2017a (flexible dose)	1	184	0	91	5.3%	1.49 [0.06 , 36.27]
Newcorn 2017b (forced dose)	1	219	1	110	7.0%	0.50 [0.03 , 7.95]
Palumbo 2008	1	29	0	30	5.4%	3.10 [0.13 , 73.14]
Pliszka 2017	0	81	0	80		Not estimable
Riggs 2011	4	151	7	152	36.8%	0.58 [0.17 , 1.92]
Schrantee 2016	0	25	0	25		Not estimable
Wigal 2015	1	183	0	47	5.3%	0.78 [0.03 , 18.91]
Wigal 2017	0	42	0	44		Not estimable
Wolraich 2001	0	160	0	41		Not estimable
Total (95% CI)		**2131**		**1542**	**100.0%**	**0.80 [0.39 , 1.67]**
Total events:	13		13			

Heterogeneity: Tau² = 0.00; Chi² = 2.27, df = 9 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable

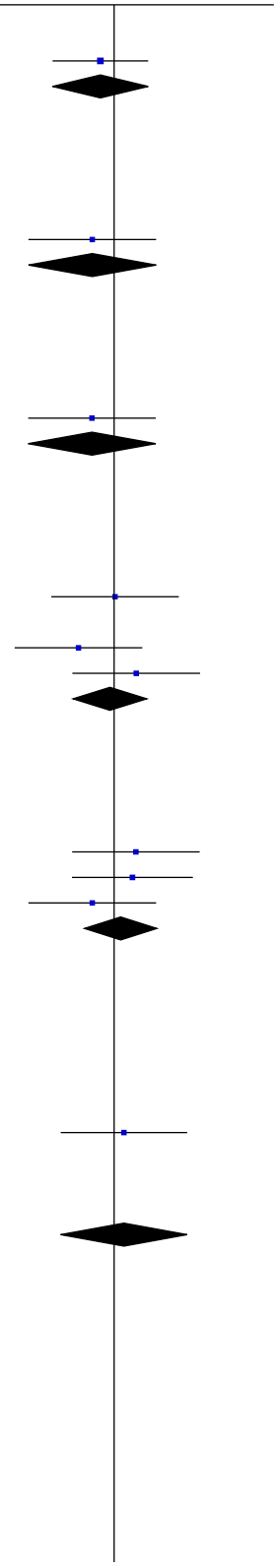


Footnotes

(1) Same patient in Methylphenidate group experienced two syncope events

Analysis 5.2. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 2: Nervous system (including psychiatry)

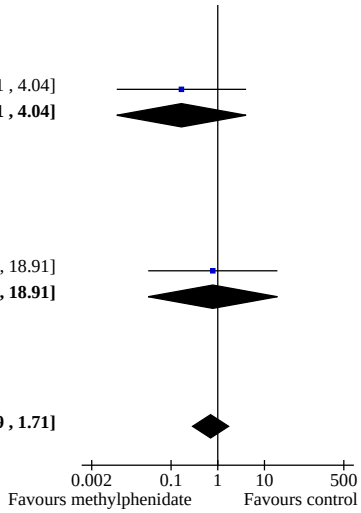
Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
5.2.1 Aggression						
Riggs 2011	1	151	2	152	13.8%	0.50 [0.05 , 5.49]
Subtotal (95% CI)		**151**		**152**	**13.8%**	**0.50 [0.05 , 5.49]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
5.2.2 Concussion						
Riggs 2011	0	151	1	152	7.7%	0.34 [0.01 , 8.17]
Subtotal (95% CI)		**151**		**152**	**7.7%**	**0.34 [0.01 , 8.17]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
5.2.3 Loss of consciousness						
Coghill 2013	0	111	1	110	7.7%	0.33 [0.01 , 8.02]
Subtotal (95% CI)		**111**		**110**	**7.7%**	**0.33 [0.01 , 8.02]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
5.2.4 Psychosis						
Childress 2009	1	188	0	65	7.8%	1.05 [0.04 , 25.40]
Green 2011	0	22	0	12		Not estimable
Newcorn 2017b (forced dose)	0	219	1	110	7.7%	0.17 [0.01 , 4.09]
Riggs 2011	1	151	0	152	7.7%	3.02 [0.12 , 73.54]
Subtotal (95% CI)		**580**		**339**	**23.2%**	**0.81 [0.13 , 5.12]**
Total events:	2		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.82)						
5.2.5 Syncope						
Coghill 2013	1	111	0	110	7.7%	2.97 [0.12 , 72.20]
Findling 2010 (1)	2	145	0	72	8.6%	2.50 [0.12 , 51.40]
Riggs 2011	0	151	1	152	7.7%	0.34 [0.01 , 8.17]
Subtotal (95% CI)		**407**		**334**	**24.1%**	**1.39 [0.23 , 8.47]**
Total events:	3		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
5.2.6 Suicidal ideation						
Childress 2017	0	44	0	41		Not estimable
Childress 2020a	0	74	0	73		Not estimable
NCT02293655	0	18	1	92	7.9%	1.63 [0.07 , 38.55]
Newcorn 2017a (flexible dose)	0	184	0	91		Not estimable
Newcorn 2017b (forced dose)	0	219	0	110		Not estimable
Wigal 2017 (2)	0	42	0	44		Not estimable
Subtotal (95% CI)		**581**		**451**	**7.9%**	**1.63 [0.07 , 38.55]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
5.2.7 Suicidal behaviour						
Childress 2020a	0	74	0	73		Not estimable
Wigal 2017 (2)	0	42	0	44		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.2.8 Oppositional behaviour/negativism						



Analysis 5.2. (Continued)

Test for overall effect: Not applicable

5.2.8 Oppositional behaviour/negativism							
Findling 2010	0	145	1	72	7.8%	0.17 [0.01 , 4.04]	
Subtotal (95% CI)		**145**		**72**	**7.8%**	**0.17 [0.01 , 4.04]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.10 (P = 0.27)							
5.2.9 Adjustment disorder							
Wigal 2015	1	183	0	47	7.8%	0.78 [0.03 , 18.91]	
Subtotal (95% CI)		**183**		**47**	**7.8%**	**0.78 [0.03 , 18.91]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.15 (P = 0.88)							
Total (95% CI)		**2425**		**1774**	**100.0%**	**0.70 [0.29 , 1.71]**	
Total events:	7		8				
Heterogeneity: Tau² = 0.00; Chi² = 4.86, df = 11 (P = 0.94); I² = 0%							
Test for overall effect: Z = 0.78 (P = 0.43)							
Test for subgroup differences: Chi² = 2.12, df = 7 (P = 0.95), I² = 0%							



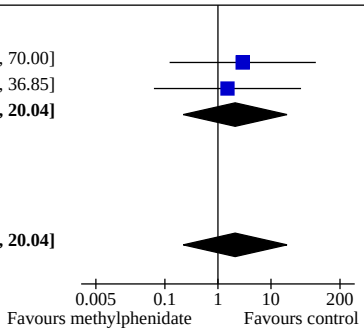
Footnotes

(1) s One patient in Methylphenidate group experienced two syncope events

(2) C-SSRS

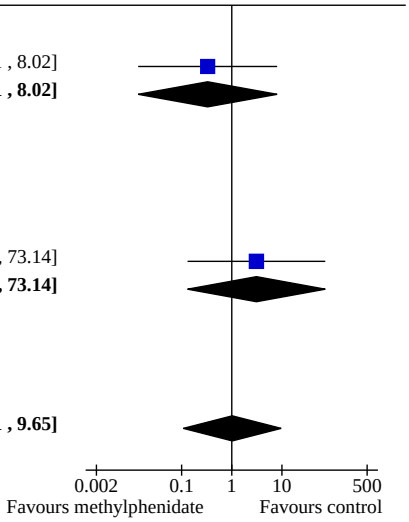
Analysis 5.3. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 3: Digestive system

Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
5.3.1 Appendicitis							
Lehmkuhl 2002	1	43	0	42	50.3%	2.93 [0.12 , 70.00]	
Newcorn 2017b (forced dose)	1	219	0	110	49.7%	1.51 [0.06 , 36.85]	
Subtotal (95% CI)		**262**		**152**	**100.0%**	**2.11 [0.22 , 20.04]**	
Total events:	2		0				
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
Total (95% CI)		**262**		**152**	**100.0%**	**2.11 [0.22 , 20.04]**	
Total events:	2		0				
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
Test for subgroup differences: Not applicable							



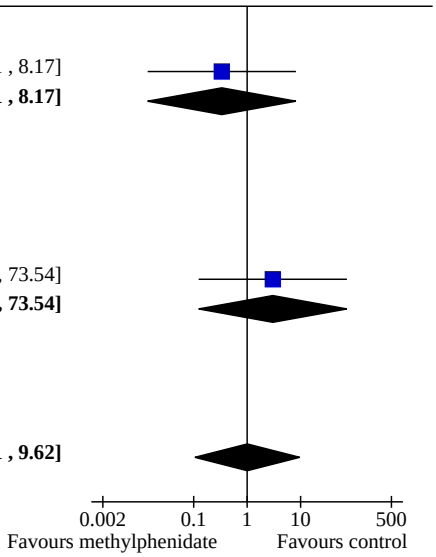
Analysis 5.4. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 4: Cardiovascular systems

Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
5.4.1 Haematoma						
Coghill 2013	0	111	1	110	49.5%	0.33 [0.01 , 8.02]
Subtotal (95% CI)		**111**		**110**	**49.5%**	**0.33 [0.01 , 8.02]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
5.4.2 Tachycardia						
Palumbo 2008	1	29	0	30	50.5%	3.10 [0.13 , 73.14]
Subtotal (95% CI)		**29**		**30**	**50.5%**	**3.10 [0.13 , 73.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**140**		**140**	**100.0%**	**1.02 [0.11 , 9.65]**
Total events:	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%						



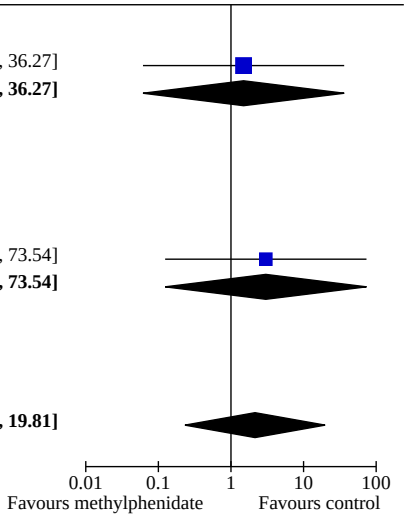
Analysis 5.5. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 5: Respiratory systems

Study or Subgroup	Methylphenidate Events	Total	No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
5.5.1 Bronchitis						
Riggs 2011	0	151	1	152	50.0%	0.34 [0.01 , 8.17]
Subtotal (95% CI)		**151**		**152**	**50.0%**	**0.34 [0.01 , 8.17]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
5.5.2 Asthma						
Riggs 2011	1	151	0	152	50.0%	3.02 [0.12 , 73.54]
Subtotal (95% CI)		**151**		**152**	**50.0%**	**3.02 [0.12 , 73.54]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**302**		**304**	**100.0%**	**1.01 [0.11 , 9.62]**
Total events:	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.01 (P = 1.00)						
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%						



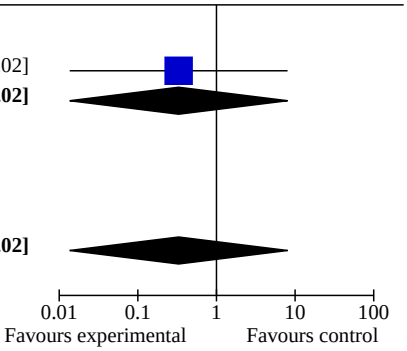
Analysis 5.6. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 6: Urinary system

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	No intervention Events	No intervention Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.6.1 Renal cyst						
Newcorn 2017a (flexible dose)	1	184	0	91	57.3%	1.49 [0.06 , 36.27]
Subtotal (95% CI)		**184**		**91**	**57.3%**	**1.49 [0.06 , 36.27]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.81)						
5.6.2 Kidney infection						
Riggs 2011	1	151	0	152	42.7%	3.02 [0.12 , 73.54]
Subtotal (95% CI)		**151**		**152**	**42.7%**	**3.02 [0.12 , 73.54]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**335**		**243**	**100.0%**	**2.14 [0.23 , 19.81]**
Total events:	2		0			
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%						



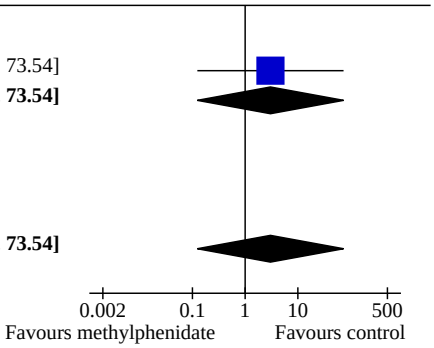
Analysis 5.7. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 7: Skeletal and muscular system (including pain)

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.7.1 Clavical fracture						
Coghill 2013	0	111	1	110	100.0%	0.33 [0.01 , 8.02]
Subtotal (95% CI)		**111**		**110**	**100.0%**	**0.33 [0.01 , 8.02]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**111**		**110**	**100.0%**	**0.33 [0.01 , 8.02]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



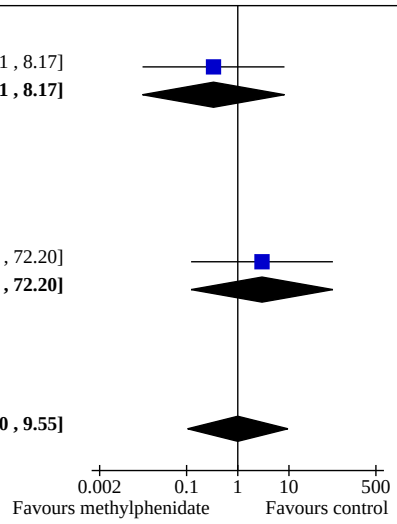
Analysis 5.8. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 8: Immune system (including infections)

Study or Subgroup	Methylphenidate Events	Total	No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
5.8.1 Cyst rupture						
Riggs 2011	1	151	0	152	100.0%	3.02 [0.12 , 73.54]
Subtotal (95% CI)		**151**		**152**	**100.0%**	**3.02 [0.12 , 73.54]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**151**		**152**	**100.0%**	**3.02 [0.12 , 73.54]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



Analysis 5.9. Comparison 5: Serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 9: Other

Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
5.9.1 Drug toxicity						
Riggs 2011	0	151	1	152	50.0%	0.34 [0.01 , 8.17]
Subtotal (95% CI)		**151**		**152**	**50.0%**	**0.34 [0.01 , 8.17]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
5.9.2 Overdose						
Coghill 2013	1	111	0	110	50.0%	2.97 [0.12 , 72.20]
Subtotal (95% CI)		**111**		**110**	**50.0%**	**2.97 [0.12 , 72.20]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**262**		**262**	**100.0%**	**1.00 [0.10 , 9.55]**
Total events:	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%						



Comparison 6. Serious adverse events: cross-over trials (endpoint data)

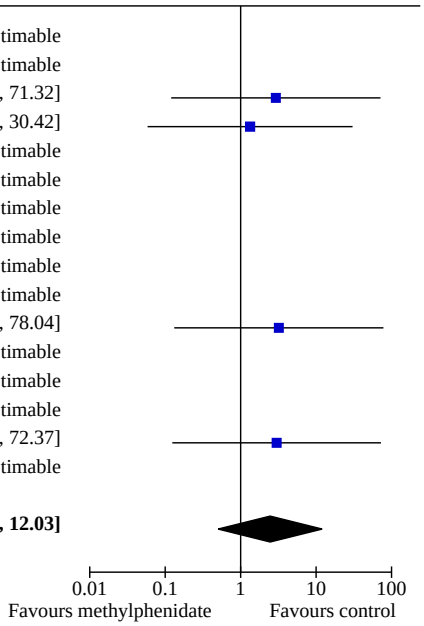
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Proportion of participants with serious adverse events (SAE)	16	3323	Risk Ratio (IV, Random, 95% CI)	2.46 [0.50, 12.03]
6.2 Nervous system (including psychiatry)	2	304	Risk Ratio (IV, Random, 95% CI)	2.05 [0.22, 19.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.1 Hallucinations	1	37	Risk Ratio (IV, Random, 95% CI)	1.33 [0.06, 30.42]
6.2.2 Psychiatric disorder	1	267	Risk Ratio (IV, Random, 95% CI)	3.21 [0.13, 78.04]
6.3 Urinary system	1	136	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.37]
6.3.1 Proteinuria	1	136	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.37]
6.4 Immune system	1	644	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.31, 27.99]
6.4.1 Peritonsillar abscess	1	322	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.32]
6.4.2 Oral bullae	1	322	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 71.32]

Analysis 6.1. Comparison 6: Serious adverse events: cross-over trials (endpoint data), Outcome 1: Proportion of participants with serious adverse events (SAE)

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bhat 2020	0	526	0	526		Not estimable
Brams 2008	0	86	0	86		Not estimable
Brams 2012 (1)	1	163	0	159	24.7%	2.93 [0.12 , 71.32]
Buitelaar 1995	1	26	0	11	25.7%	1.33 [0.06 , 30.42]
Cox 2006	0	35	0	35		Not estimable
CRIT124US02	0	102	0	99		Not estimable
Döpfner 2004	0	82	0	82		Not estimable
Froehlich 2018	0	168	0	168		Not estimable
Gonzalez-Heydrich 2010	0	28	0	28		Not estimable
Hawk 2018	0	80	0	80		Not estimable
NCT02039908	1	129	0	138	24.7%	3.21 [0.13 , 78.04]
NCT02536105	0	80	0	74		Not estimable
Pelham 2005	0	36	0	36		Not estimable
Schachar 2008	0	18	0	18		Not estimable
Silva 2008	1	68	0	68	24.8%	3.00 [0.12 , 72.37]
Wigal 2013	0	44	0	44		Not estimable
Total (95% CI)		**1671**		**1652**	**100.0%**	**2.46 [0.50 , 12.03]**
Total events:	4		0			

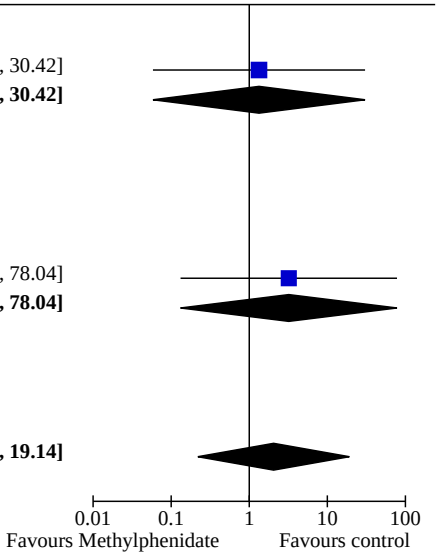
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



Footnotes
(1) One patient in Methylphenidate group experienced two immune system events

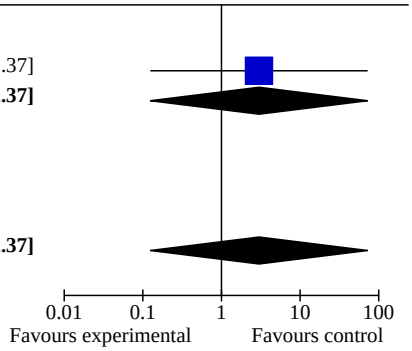
Analysis 6.2. Comparison 6: Serious adverse events: cross-over trials (endpoint data), Outcome 2: Nervous system (including psychiatry)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.2.1 Hallucinations						
Buitelaar 1995	1	26	0	11	51.0%	1.33 [0.06 , 30.42]
Subtotal (95% CI)		**26**		**11**	**51.0%**	**1.33 [0.06 , 30.42]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
6.2.2 Psychiatric disorder						
NCT02039908	1	129	0	138	49.0%	3.21 [0.13 , 78.04]
Subtotal (95% CI)		**129**		**138**	**49.0%**	**3.21 [0.13 , 78.04]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Total (95% CI)		**155**		**149**	**100.0%**	**2.05 [0.22 , 19.14]**
Total events:	2		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						



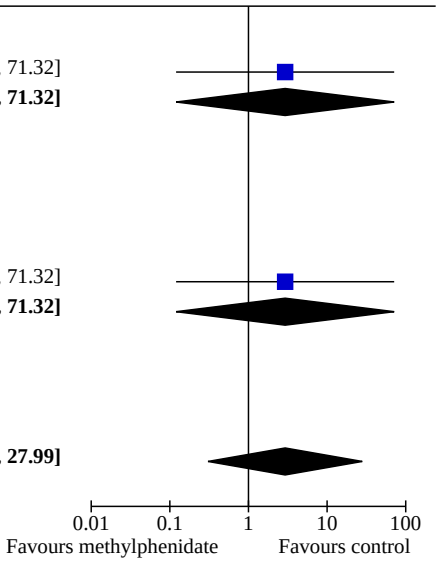
Analysis 6.3. Comparison 6: Serious adverse events: cross-over trials (endpoint data), Outcome 3: Urinary system

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 Proteinuria						
Silva 2008	1	68	0	68	100.0%	3.00 [0.12 , 72.37]
Subtotal (95% CI)		**68**		**68**	**100.0%**	**3.00 [0.12 , 72.37]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**68**		**68**	**100.0%**	**3.00 [0.12 , 72.37]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



Analysis 6.4. Comparison 6: Serious adverse events: cross-over trials (endpoint data), Outcome 4: Immune system

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.4.1 Peritonsillar abscess						
Brams 2012 (1)	1	163	0	159	50.0%	2.93 [0.12 , 71.32]
Subtotal (95% CI)		**163**		**159**	**50.0%**	**2.93 [0.12 , 71.32]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
6.4.2 Oral bullae						
Brams 2012 (1)	1	163	0	159	50.0%	2.93 [0.12 , 71.32]
Subtotal (95% CI)		**163**		**159**	**50.0%**	**2.93 [0.12 , 71.32]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)		**326**		**318**	**100.0%**	**2.93 [0.31 , 27.99]**
Total events:	2		0			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



Footnotes

(1) Same patient in Methylphenidate group experienced two immune system events

Comparison 7. Non-serious adverse events: parallel-group trials and first-period cross-over trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Proportion of participants with non-serious adverse events	35	5342	Risk Ratio (IV, Random, 95% CI)	1.23 [1.11, 1.37]
7.2 Subgroup analysis: proportion of participants with non-serious adverse events according to dose	32	4718	Risk Ratio (IV, Random, 95% CI)	1.24 [1.12, 1.37]
7.2.1 Low dose	3	289	Risk Ratio (IV, Random, 95% CI)	1.02 [0.97, 1.07]
7.2.2 High dose	22	3365	Risk Ratio (IV, Random, 95% CI)	1.23 [1.14, 1.32]
7.2.3 Unknown dose	8	1064	Risk Ratio (IV, Random, 95% CI)	1.37 [0.93, 2.02]
7.3 Nervous system (including psychiatry)	37		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.3.1 Affective	4	456	Risk Ratio (IV, Random, 95% CI)	2.39 [0.48, 11.96]
7.3.2 Aggression	3	503	Risk Ratio (IV, Random, 95% CI)	1.23 [0.30, 5.08]
7.3.3 Apathy	1	59	Risk Ratio (IV, Random, 95% CI)	0.80 [0.19, 3.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3.4 Confusion or confusional state	3	823	Risk Ratio (IV, Random, 95% CI)	0.75 [0.17, 3.24]
7.3.5 Depression	1	59	Risk Ratio (IV, Random, 95% CI)	0.83 [0.22, 3.10]
7.3.6 Dizziness	11	2149	Risk Ratio (IV, Random, 95% CI)	1.77 [0.95, 3.30]
7.3.7 Drowsiness	4	811	Risk Ratio (IV, Random, 95% CI)	1.27 [0.82, 1.98]
7.3.8 Emotional lability	5	624	Risk Ratio (IV, Random, 95% CI)	1.24 [0.54, 2.85]
7.3.9 Fatigue	14	2228	Risk Ratio (IV, Random, 95% CI)	0.67 [0.44, 1.02]
7.3.10 Headache	32	5041	Risk Ratio (IV, Random, 95% CI)	1.33 [1.04, 1.70]
7.3.11 Irritability	20	3290	Risk Ratio (IV, Random, 95% CI)	1.05 [0.82, 1.34]
7.3.12 Nervousness	2	362	Risk Ratio (IV, Random, 95% CI)	2.52 [0.82, 7.76]
7.3.13 Pain	1	132	Risk Ratio (IV, Random, 95% CI)	1.91 [0.21, 17.60]
7.3.14 Picking at skin or fingers, nail biting, lip or cheek chewing	5	686	Risk Ratio (IV, Random, 95% CI)	0.97 [0.60, 1.57]
7.3.15 Sad, tearful or depressed	7	1015	Risk Ratio (IV, Random, 95% CI)	1.47 [0.95, 2.28]
7.3.16 Thirst	2	179	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 71.82]
7.3.17 Dull, tired, listless	1	110	Risk Ratio (IV, Random, 95% CI)	1.70 [0.51, 5.68]
7.3.18 Tics or nervous movements	12	1556	Risk Ratio (IV, Random, 95% CI)	0.77 [0.27, 2.22]
7.3.19 Worried or anxious	3	596	Risk Ratio (IV, Random, 95% CI)	1.37 [0.84, 2.25]
7.3.20 Feeling jittery	1	86	Risk Ratio (IV, Random, 95% CI)	0.52 [0.05, 5.56]
7.3.21 Malaise	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.3.22 Dysgeusia	2	171	Risk Ratio (IV, Random, 95% CI)	0.79 [0.19, 3.30]
7.3.23 Lethargy	2	224	Risk Ratio (IV, Random, 95% CI)	0.69 [0.40, 1.17]
7.3.24 Aphonia	1	86	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.3.25 Psychomotor hyperactivity	3	522	Risk Ratio (IV, Random, 95% CI)	3.67 [0.61, 22.01]
7.3.26 Syncope	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.3.27 Tremor	3	231	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3.28 Social withdrawal	1	110	Risk Ratio (IV, Random, 95% CI)	2.56 [0.24, 26.71]
7.3.29 Sedation	1	138	Risk Ratio (IV, Random, 95% CI)	1.30 [0.66, 2.53]
7.3.30 Mood swings	2	247	Risk Ratio (IV, Random, 95% CI)	2.53 [0.94, 6.82]
7.3.31 Anger	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.3.32 Anxiety	2	180	Risk Ratio (IV, Random, 95% CI)	0.64 [0.08, 5.08]
7.3.33 Change in sustained attention	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.3.34 Emotional poverty	2	175	Risk Ratio (IV, Random, 95% CI)	3.47 [0.37, 32.68]
7.3.35 Trichotillomania	1	85	Risk Ratio (IV, Random, 95% CI)	2.80 [0.12, 66.85]
7.3.36 Stuttering	1	94	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.98]
7.3.37 Emotional disorder	2	174	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 10.16]
7.3.38 Negativism	2	174	Risk Ratio (IV, Random, 95% CI)	3.83 [0.16, 91.41]
7.3.39 Migraine	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.3.40 Tension	1	60	Risk Ratio (IV, Random, 95% CI)	23.00 [1.42, 373.44]
7.4 Digestive system	34	22299	Risk Ratio (IV, Random, 95% CI)	1.81 [1.54, 2.14]
7.4.1 Change in appetite	1	94	Risk Ratio (IV, Random, 95% CI)	0.78 [0.32, 1.92]
7.4.2 Decreased appetite	30	5127	Risk Ratio (IV, Random, 95% CI)	3.35 [2.49, 4.50]
7.4.3 Increased appetite	2	265	Risk Ratio (IV, Random, 95% CI)	0.15 [0.02, 1.34]
7.4.4 Change in weight	1	94	Risk Ratio (IV, Random, 95% CI)	0.40 [0.08, 1.96]
7.4.5 Increased weight	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.4.6 Decreased weight	11	2001	Risk Ratio (IV, Random, 95% CI)	5.44 [2.47, 11.98]
7.4.7 Dyspepsia	5	390	Risk Ratio (IV, Random, 95% CI)	0.71 [0.16, 3.19]
7.4.8 Upper abdominal pain	10	1745	Risk Ratio (IV, Random, 95% CI)	1.25 [0.79, 1.96]
7.4.9 Stomachache (abdominal pain)	18	3069	Risk Ratio (IV, Random, 95% CI)	1.19 [0.94, 1.50]
7.4.10 Vomiting	20	3105	Risk Ratio (IV, Random, 95% CI)	1.26 [0.85, 1.86]
7.4.11 Constipation	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.4.12 Oral pain	2	171	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.4.13 Retching	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.4.14 Diarrhoea	8	1088	Risk Ratio (IV, Random, 95% CI)	0.83 [0.35, 1.94]
7.4.15 Dry mouth	4	1057	Risk Ratio (IV, Random, 95% CI)	3.79 [1.26, 11.39]
7.4.16 Nausea	19	3484	Risk Ratio (IV, Random, 95% CI)	1.40 [1.00, 1.95]
7.4.17 Flatulence	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.4.18 Gastritis	1	89	Risk Ratio (IV, Random, 95% CI)	3.83 [0.16, 91.40]
7.4.19 Gastrointestinal concerns (unspecified)	1	94	Risk Ratio (IV, Random, 95% CI)	1.00 [0.06, 15.52]
7.4.20 Polydipsia	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.5 Cardiovascular system	12	3047	Risk Ratio (IV, Random, 95% CI)	1.41 [0.81, 2.46]
7.5.1 ECG: prolonged QT-interval	2	466	Risk Ratio (IV, Random, 95% CI)	0.81 [0.13, 5.00]
7.5.2 ECG: tachycardia	5	686	Risk Ratio (IV, Random, 95% CI)	0.66 [0.20, 2.22]
7.5.3 Increased diastolic blood pressure	1	119	Risk Ratio (IV, Random, 95% CI)	1.07 [0.43, 2.68]
7.5.4 Increased systolic blood pressure	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.5.5 Increased heart rate	2	422	Risk Ratio (IV, Random, 95% CI)	4.99 [0.86, 28.85]
7.5.6 Supraventricular extrasystoles	1	17	Risk Ratio (IV, Random, 95% CI)	3.00 [0.11, 84.55]
7.5.7 Ventricular arrhythmia	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.5.8 Epistaxis	3	303	Risk Ratio (IV, Random, 95% CI)	1.71 [0.29, 10.07]
7.5.9 Increased blood pressure	2	414	Risk Ratio (IV, Random, 95% CI)	2.72 [0.00, 70377274832184590000000000000
7.5.10 Orthostatic hypotension	1	329	Risk Ratio (IV, Random, 95% CI)	2.72 [0.00, 70377274832184590000000000000
7.5.11 Palpitations	1	60	Risk Ratio (IV, Random, 95% CI)	11.00 [0.64, 190.54]
7.5.12 Pallor	1	60	Risk Ratio (IV, Random, 95% CI)	23.00 [1.42, 373.44]
7.6 Respiratory system	13		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.6.1 Pharyngolaryngeal pain	1	303	Risk Ratio (IV, Random, 95% CI)	1.12 [0.59, 2.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.6.2 Upper respiratory tract infection	3	421	Risk Ratio (IV, Random, 95% CI)	1.14 [0.56, 2.34]
7.6.3 Bronchitis	1	85	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.43]
7.6.4 Oropharyngeal pain	1	86	Risk Ratio (IV, Random, 95% CI)	7.33 [0.39, 137.67]
7.6.5 Rhinorrhoea	1	86	Risk Ratio (IV, Random, 95% CI)	5.23 [0.26, 105.88]
7.6.6 Allergic bronchitis	1	86	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.6.7 Sneezing	1	86	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.6.8 Nasal congestion	3	565	Risk Ratio (IV, Random, 95% CI)	1.24 [0.62, 2.48]
7.6.9 Cough	9	1656	Risk Ratio (IV, Random, 95% CI)	1.31 [0.62, 2.78]
7.6.10 Shortness of breath	2	179	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 71.82]
7.7 Urinary system	1	178	Risk Ratio (M-H, Random, 95% CI)	3.83 [0.41, 36.08]
7.7.1 Pollakiuria	1	89	Risk Ratio (M-H, Random, 95% CI)	3.83 [0.16, 91.40]
7.7.2 Urinary incontinence	1	89	Risk Ratio (M-H, Random, 95% CI)	3.83 [0.16, 91.40]
7.8 Skeletal and muscular systems (including pain)	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.8.1 Arthralgia	2	388	Risk Ratio (IV, Random, 95% CI)	0.67 [0.24, 1.84]
7.8.2 Asthenia	1	177	Risk Ratio (IV, Random, 95% CI)	0.21 [0.01, 4.25]
7.8.3 Back pain	3	474	Risk Ratio (IV, Random, 95% CI)	0.77 [0.38, 1.57]
7.8.4 Myalgia	3	474	Risk Ratio (IV, Random, 95% CI)	0.55 [0.22, 1.35]
7.8.5 Toothache	1	303	Risk Ratio (IV, Random, 95% CI)	1.01 [0.43, 2.35]
7.8.6 Ligament strain	1	85	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.43]
7.8.7 Muscle strain	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.8.8 Fractures	1	94	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 71.82]
7.8.9 Muscle cramps	1	94	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 71.82]
7.8.10 Pain in extremity	1	89	Risk Ratio (IV, Random, 95% CI)	0.26 [0.01, 5.16]
7.8.11 Pain	1	132	Risk Ratio (IV, Random, 95% CI)	1.87 [0.22, 16.19]
7.9 Immune system (including infections)	17		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.9.1 Gastroenteritis	5	606	Risk Ratio (IV, Random, 95% CI)	2.41 [0.66, 8.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.9.2 Influenza	4	709	Risk Ratio (IV, Random, 95% CI)	0.55 [0.23, 1.30]
7.9.3 Nasopharyngitis	10	1623	Risk Ratio (IV, Random, 95% CI)	1.14 [0.76, 1.70]
7.9.4 Otitis media	3	271	Risk Ratio (IV, Random, 95% CI)	0.99 [0.15, 6.61]
7.9.5 Pharyngitis	5	614	Risk Ratio (IV, Random, 95% CI)	2.02 [0.55, 7.35]
7.9.6 Pyrexia	5	678	Risk Ratio (IV, Random, 95% CI)	0.68 [0.12, 3.81]
7.9.7 Rhinitis	1	132	Risk Ratio (IV, Random, 95% CI)	1.28 [0.43, 3.79]
7.9.8 Upper respiratory tract infection - not otherwise specified (NOS)	12	1929	Risk Ratio (IV, Random, 95% CI)	0.95 [0.65, 1.39]
7.9.9 Viral infection NOS	5	1029	Risk Ratio (IV, Random, 95% CI)	0.97 [0.44, 2.14]
7.9.10 Seasonal allergy	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.9.11 Streptococcal impetigo	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.9.12 Sinusitis	1	89	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 10.16]
7.9.13 Cellulitis	1	89	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 10.16]
7.9.14 Pleurisy	1	275	Risk Ratio (IV, Random, 95% CI)	1.49 [0.06, 36.27]
7.10 Integumentary system	7	1455	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.37, 1.58]
7.10.1 Purple spots	1	94	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 71.82]
7.10.2 Skin disorder (rash)	5	460	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.12, 4.96]
7.10.3 Skin laceration	3	474	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.18, 1.22]
7.10.4 Burns second degree	1	85	Risk Ratio (M-H, Random, 95% CI)	2.80 [0.12, 66.85]
7.10.5 Burns first degree	1	86	Risk Ratio (M-H, Random, 95% CI)	3.14 [0.13, 74.98]
7.10.6 Subcutaneous haematoma	1	86	Risk Ratio (M-H, Random, 95% CI)	3.14 [0.13, 74.98]
7.10.7 Periorbital haematoma	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.10.8 Rash maculo-papular	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.11 Sleep variability	29	7308	Risk Ratio (IV, Random, 95% CI)	1.57 [1.23, 2.02]
7.11.1 Somnolence	6	757	Risk Ratio (IV, Random, 95% CI)	0.87 [0.52, 1.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.11.2 Trouble sleeping or sleep problems	15	2620	Risk Ratio (IV, Random, 95% CI)	1.62 [1.18, 2.21]
7.11.3 Insomnia	15	2315	Risk Ratio (IV, Random, 95% CI)	1.90 [1.12, 3.22]
7.11.4 Initial insomnia	5	917	Risk Ratio (IV, Random, 95% CI)	2.25 [0.89, 5.71]
7.11.5 Middle insomnia	2	171	Risk Ratio (IV, Random, 95% CI)	1.05 [0.07, 16.22]
7.11.6 Sleep disorder	2	528	Risk Ratio (IV, Random, 95% CI)	0.67 [0.22, 2.10]
7.12 Sleep variability continuous outcomes	2	943	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.01, 0.06]
7.12.1 Sleep efficiency after treatment discontinuation (percentage)	1	48	Mean Difference (IV, Fixed, 95% CI)	5.42 [0.21, 10.63]
7.12.2 Sleep onset latency (min)	1	48	Mean Difference (IV, Fixed, 95% CI)	-20.16 [-45.74, 5.42]
7.12.3 Total sleep time (min)	1	48	Mean Difference (IV, Fixed, 95% CI)	30.82 [-7.73, 69.37]
7.12.4 Total in-bed time (min)	1	48	Mean Difference (IV, Fixed, 95% CI)	-2.07 [-33.82, 29.68]
7.12.5 Wake after sleep onset (min)	1	48	Mean Difference (IV, Fixed, 95% CI)	-7.89 [-22.87, 7.09]
7.12.6 Number of wake bouts	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-8.38, 7.06]
7.12.7 Mean wake bout time (min)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.47, 0.13]
7.12.8 Interdaily stability	1	48	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.06, 0.12]
7.12.9 Interdaily variability	1	48	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.01, 0.07]
7.12.10 Amount of activity during the 5 hours with the lowest activity	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-1.62, 0.70]
7.12.11 Amount of activity during the 10 hours with the highest activity	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-3.57, 2.39]
7.12.12 Amplitude of sleep-wake rhythm	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-2.87, 2.63]
7.12.13 Pittsburgh Sleep Quality Index (PSQI)	1	367	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.83, 1.03]

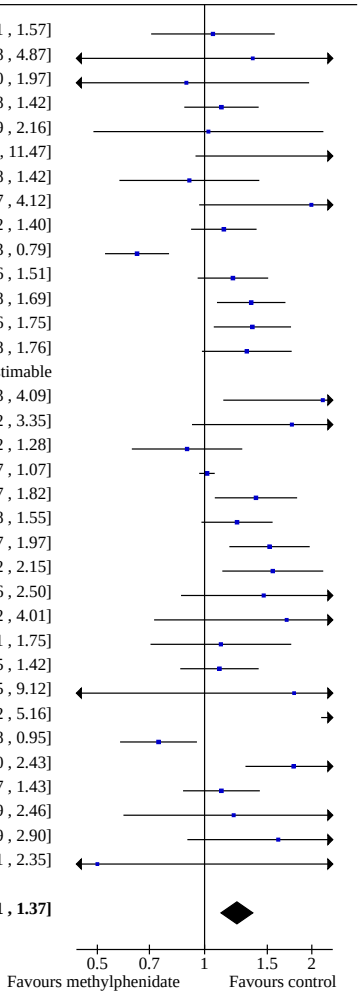
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.13 Vital signs	14	6407	Mean Difference (IV, Random, 95% CI)	2.12 [1.26, 2.98]
7.13.1 Diastolic blood pressure (mmHg)	13	2032	Mean Difference (IV, Random, 95% CI)	1.90 [0.68, 3.11]
7.13.2 Systolic blood pressure (mmHg)	13	2032	Mean Difference (IV, Random, 95% CI)	0.85 [-0.20, 1.89]
7.13.3 Pulse or heart rate (bpm)	13	2205	Mean Difference (IV, Random, 95% CI)	3.86 [2.09, 5.63]
7.13.4 ECG: changes in QTcB	1	138	Mean Difference (IV, Random, 95% CI)	-1.70 [-7.94, 4.54]
7.14 Physical parameters	7	2425	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-1.24, -0.70]
7.14.1 Height	1	215	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.35, 0.22]
7.14.2 Weight	7	1400	Std. Mean Difference (IV, Random, 95% CI)	-1.13 [-1.40, -0.85]
7.14.3 BMI	3	810	Std. Mean Difference (IV, Random, 95% CI)	-1.00 [-1.26, -0.73]
7.15 Other (including drug toxicity)	9	4145	Risk Ratio (IV, Random, 95% CI)	1.13 [0.74, 1.72]
7.15.1 Accidental injury	3	656	Risk Ratio (IV, Random, 95% CI)	0.99 [0.48, 2.07]
7.15.2 Excoriation	2	389	Risk Ratio (IV, Random, 95% CI)	3.22 [1.20, 8.64]
7.15.3 Overdose	1	221	Risk Ratio (IV, Random, 95% CI)	2.97 [0.12, 72.20]
7.15.4 Arthropod-bite	2	171	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.15.5 Contusion	1	86	Risk Ratio (IV, Random, 95% CI)	0.12 [0.01, 2.10]
7.15.6 Wound	2	171	Risk Ratio (IV, Random, 95% CI)	0.73 [0.06, 9.22]
7.15.7 Tinnitus	1	86	Risk Ratio (IV, Random, 95% CI)	5.23 [0.26, 105.89]
7.15.8 Dry eye	2	171	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.15.9 Excessive eye blinking	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.15.10 Occular hyperaemia	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.15.11 Visual impairment	1	86	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.15.12 Red eyes	1	94	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.15.13 Conjunctival abrasion	1	86	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.15.14 Radius fracture	1	86	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.15.15 Snake bite	1	86	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 74.98]
7.15.16 Enuresis	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.15.17 Night sweats	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.15.18 Abnormal liver function test	1	85	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.43]
7.15.19 Alopecia	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.15.20 Nail injury	1	86	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.33]
7.15.21 Itching	2	179	Risk Ratio (IV, Random, 95% CI)	5.00 [0.25, 101.43]
7.15.22 Ear pain	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.15.23 Corneal injury	1	89	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 10.16]
7.15.24 Wrist fracture	1	329	Risk Ratio (IV, Random, 95% CI)	1.51 [0.06, 36.85]
7.15.25 Dysmennorhea	1	329	Risk Ratio (IV, Random, 95% CI)	1.51 [0.06, 36.85]
7.15.26 Myopia	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
7.15.27 Other AEs unspecified	1	60	Risk Ratio (IV, Random, 95% CI)	0.40 [0.08, 1.90]

Analysis 7.1. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 1: Proportion of participants with non-serious adverse events

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo/No intervention Events	Placebo/No intervention Total	Weight	Risk Ratio IV, Random, 95% CI
Barragán 2017	19	30	18	30	3.1%	1.06 [0.71 , 1.57]
Biederman 2003b	5	65	4	71	0.6%	1.37 [0.38 , 4.87]
Carlson 2007	5	9	5	8	1.3%	0.89 [0.40 , 1.97]
Childress 2009	116	182	36	63	4.3%	1.12 [0.88 , 1.42]
Childress 2017	11	44	10	41	1.4%	1.02 [0.49 , 2.16]
Childress 2020a	10	74	3	73	0.6%	3.29 [0.94 , 11.47]
Childress 2020b	24	65	22	54	2.7%	0.91 [0.58 , 1.42]
Childress 2020c	14	39	9	50	1.5%	1.99 [0.97 , 4.12]
Coghill 2013	72	111	63	110	4.6%	1.13 [0.92 , 1.40]
Findling 2006	71	133	38	46	4.6%	0.65 [0.53 , 0.79]
Findling 2008	63	91	49	85	4.4%	1.20 [0.96 , 1.51]
Findling 2010	112	145	40	70	4.5%	1.35 [1.08 , 1.69]
Greenhill 2002	80	155	61	161	4.2%	1.36 [1.06 , 1.75]
Greenhill 2006	40	53	27	47	3.9%	1.31 [0.98 , 1.76]
Jacobi-Polishook 2009	0	12	0	12		Not estimable
Kollins 2021	23	74	11	76	1.8%	2.15 [1.13 , 4.09]
Lehmkuhl 2002	18	43	10	42	1.8%	1.76 [0.92 , 3.35]
Matthijssen 2019 (1)	25	47	28	47	3.4%	0.89 [0.62 , 1.28]
McCracken 2016	69	70	66	68	5.6%	1.02 [0.97 , 1.07]
NCT02293655	15	18	55	92	4.1%	1.39 [1.07 , 1.82]
Newcorn 2008	146	219	40	74	4.4%	1.23 [0.98 , 1.55]
Newcorn 2017a (flexible dose)	120	184	39	91	4.2%	1.52 [1.17 , 1.97]
Newcorn 2017b (forced dose)	99	219	32	110	3.6%	1.55 [1.12 , 2.15]
Palumbo 2008	17	29	12	30	2.2%	1.47 [0.86 , 2.50]
Pliszka 2000	10	20	5	17	1.1%	1.70 [0.72 , 4.01]
Pliszka 2017	27	81	24	80	2.7%	1.11 [0.71 , 1.75]
Riggs 2011	70	151	64	152	4.2%	1.10 [0.85 , 1.42]
Tourette's Syndrome Study Group 2002	4	37	2	33	0.4%	1.78 [0.35 , 9.12]
Tucker 2009	47	53	15	56	2.8%	3.31 [2.12 , 5.16]
Weiss 2021	36	74	192	293	4.3%	0.74 [0.58 , 0.95]
Wigal 2004	80	90	21	42	3.7%	1.78 [1.30 , 2.43]
Wigal 2017	33	42	31	44	4.3%	1.12 [0.87 , 1.43]
Wilens 2006b	14	87	12	90	1.5%	1.21 [0.59 , 2.46]
Wolraich 2001	56	160	10	46	2.0%	1.61 [0.89 , 2.90]
Zeni 2009	2	16	4	16	0.4%	0.50 [0.11 , 2.35]
Total (95% CI)		**2922**		**2420**	**100.0%**	**1.23 [1.11 , 1.37]**
Total events:	1553		1058			

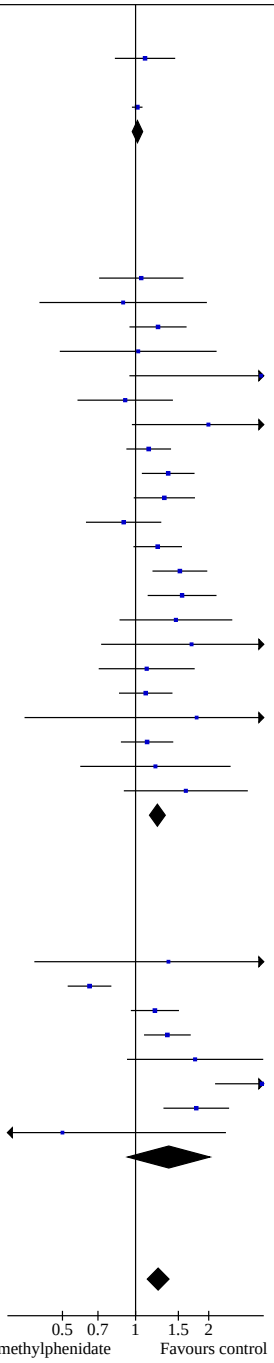
Heterogeneity: Tau² = 0.05; Chi² = 118.99, df = 33 (P < 0.00001); I² = 72%
Test for overall effect: Z = 3.98 (P < 0.0001)
Test for subgroup differences: Not applicable



Footnotes
(1) Discontinuation study

Analysis 7.2. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 2: Subgroup analysis: proportion of participants with non-serious adverse events according to dose

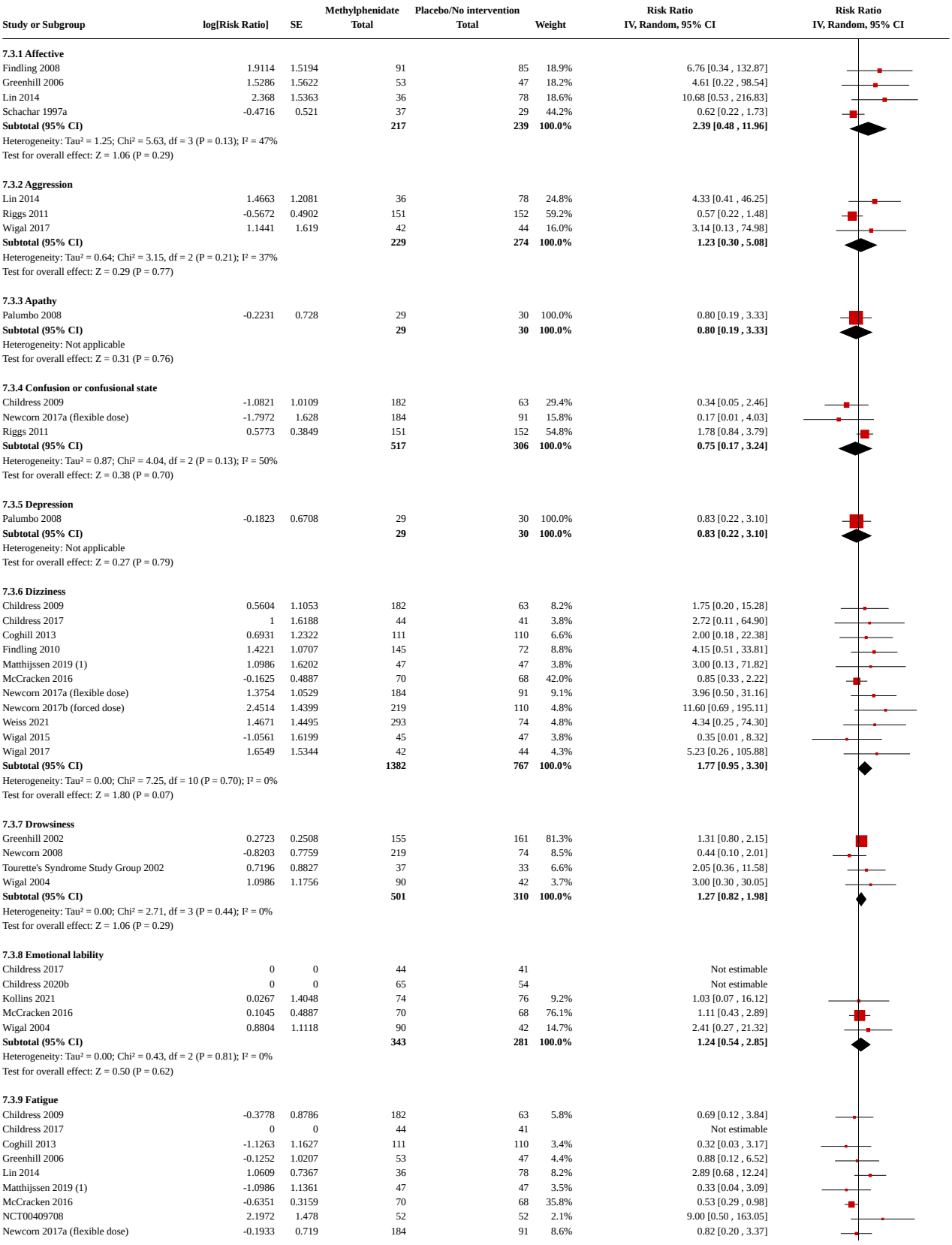
Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
7.2.1 Low dose						
Childress 2009	40	64	36	63	4.2%	1.09 [0.82 , 1.46]
Jacobi-Polishook 2009	0	12	0	12		Not estimable
McCracken 2016	69	70	66	68	6.2%	1.02 [0.97 , 1.07]
Subtotal (95% CI)		**146**		**143**	**10.4%**	**1.02 [0.97 , 1.07]**
Total events:	109		102			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
7.2.2 High dose						
Barragán 2017	19	30	18	30	3.2%	1.06 [0.71 , 1.57]
Carlson 2007	5	9	5	8	1.3%	0.89 [0.40 , 1.97]
Childress 2009	41	58	36	63	4.4%	1.24 [0.94 , 1.62]
Childress 2017	11	44	10	41	1.5%	1.02 [0.49 , 2.16]
Childress 2020a	10	74	3	73	0.6%	3.29 [0.94 , 11.47]
Childress 2020b	24	65	22	54	2.8%	0.91 [0.58 , 1.42]
Childress 2020c	14	39	9	50	1.5%	1.99 [0.97 , 4.12]
Coghill 2013	72	111	63	110	5.0%	1.13 [0.92 , 1.40]
Greenhill 2002	80	155	61	161	4.6%	1.36 [1.06 , 1.75]
Greenhill 2006	40	53	27	47	4.2%	1.31 [0.98 , 1.76]
Matthijssen 2019 (1)	25	47	28	47	3.6%	0.89 [0.62 , 1.28]
Newcorn 2008	146	219	40	74	4.8%	1.23 [0.98 , 1.55]
Newcorn 2017a (flexible dose)	120	184	39	91	4.5%	1.52 [1.17 , 1.97]
Newcorn 2017b (forced dose)	99	219	32	110	3.8%	1.55 [1.12 , 2.15]
Palumbo 2008	17	29	12	30	2.3%	1.47 [0.86 , 2.50]
Pliszka 2000	10	20	5	17	1.2%	1.70 [0.72 , 4.01]
Pliszka 2017	27	81	24	80	2.8%	1.11 [0.71 , 1.75]
Riggs 2011	70	151	64	152	4.5%	1.10 [0.85 , 1.42]
Tourette's Syndrome Study Group 2002	4	37	2	33	0.4%	1.78 [0.35 , 9.12]
Wigal 2017	33	42	31	44	4.6%	1.12 [0.87 , 1.43]
Wilens 2006b	14	87	12	90	1.6%	1.21 [0.59 , 2.46]
Wolraich 2001	56	160	10	46	2.1%	1.61 [0.89 , 2.90]
Subtotal (95% CI)		**1914**		**1451**	**65.2%**	**1.23 [1.14 , 1.32]**
Total events:	937		553			
Heterogeneity: Tau² = 0.00; Chi² = 19.85, df = 21 (P = 0.53); I² = 0%						
Test for overall effect: Z = 5.41 (P < 0.00001)						
7.2.3 Unknown dose						
Biederman 2003b	5	65	4	71	0.6%	1.37 [0.38 , 4.87]
Findling 2006	71	133	38	46	5.0%	0.65 [0.53 , 0.79]
Findling 2008	63	91	49	85	4.8%	1.20 [0.96 , 1.51]
Findling 2010	112	145	40	70	4.9%	1.35 [1.08 , 1.69]
Lehmkuhl 2002	18	43	10	42	1.8%	1.76 [0.92 , 3.35]
Tucker 2009	47	53	15	56	2.9%	3.31 [2.12 , 5.16]
Wigal 2004	80	90	21	42	4.0%	1.78 [1.30 , 2.43]
Zeni 2009	2	16	4	16	0.4%	0.50 [0.11 , 2.35]
Subtotal (95% CI)		**636**		**428**	**24.4%**	**1.37 [0.93 , 2.02]**
Total events:	398		181			
Heterogeneity: Tau² = 0.23; Chi² = 64.12, df = 7 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Total (95% CI)		**2696**		**2022**	**100.0%**	**1.24 [1.12 , 1.37]**
Total events:	1444		836			
Heterogeneity: Tau² = 0.04; Chi² = 103.12, df = 31 (P < 0.00001); I² = 70%						
Test for overall effect: Z = 4.08 (P < 0.0001)						
Test for subgroup differences: Chi² = 18.52, df = 2 (P < 0.0001), I² = 89.2%						



Footnotes

(1) Discontinuation study

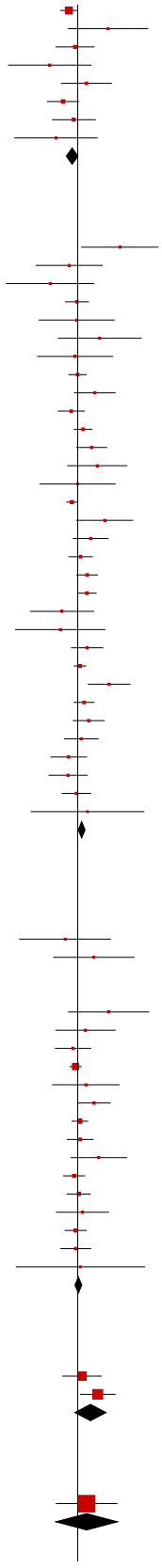
Analysis 7.3. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 3: Nervous system (including psychiatry)



Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo/No intervention Total	Weight	Risk Ratio IV, Random, 95% CI
7.3.1 Affective						
Findling 2008	1.9114	1.5194	91	85	18.9%	6.76 [0.34 , 132.87]
Greenhill 2006	1.5286	1.5622	53	47	18.2%	4.61 [0.22 , 98.54]
Lin 2014	2.368	1.5363	36	78	18.6%	10.68 [0.53 , 216.83]
Schachar 1997a	-0.4716	0.521	37	29	44.2%	0.62 [0.22 , 1.73]
Subtotal (95% CI)			**217**	**239**	**100.0%**	**2.39 [0.48 , 11.96]**
Heterogeneity: Tau² = 1.25; Chi² = 5.63, df = 3 (P = 0.13); I² = 47%						
Test for overall effect: Z = 1.06 (P = 0.29)						
7.3.2 Aggression						
Lin 2014	1.4663	1.2081	36	78	24.8%	4.33 [0.41 , 46.25]
Riggs 2011	-0.5672	0.4902	151	152	59.2%	0.57 [0.22 , 1.48]
Wigal 2017	1.1441	1.619	42	44	16.0%	3.14 [0.13 , 74.98]
Subtotal (95% CI)			**229**	**274**	**100.0%**	**1.23 [0.30 , 5.08]**
Heterogeneity: Tau² = 0.64; Chi² = 3.15, df = 2 (P = 0.21); I² = 37%						
Test for overall effect: Z = 0.29 (P = 0.77)						
7.3.3 Apathy						
Palumbo 2008	-0.2231	0.728	29	30	100.0%	0.80 [0.19 , 3.33]
Subtotal (95% CI)			**29**	**30**	**100.0%**	**0.80 [0.19 , 3.33]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
7.3.4 Confusion or confusional state						
Childress 2009	-1.0821	1.0109	182	63	29.4%	0.34 [0.05 , 2.46]
Newcorn 2017a (flexible dose)	-1.7972	1.628	184	91	15.8%	0.17 [0.01 , 4.03]
Riggs 2011	0.5773	0.3849	151	152	54.8%	1.78 [0.84 , 3.79]
Subtotal (95% CI)			**517**	**306**	**100.0%**	**0.75 [0.17 , 3.24]**
Heterogeneity: Tau² = 0.87; Chi² = 4.04, df = 2 (P = 0.13); I² = 50%						
Test for overall effect: Z = 0.38 (P = 0.70)						
7.3.5 Depression						
Palumbo 2008	-0.1823	0.6708	29	30	100.0%	0.83 [0.22 , 3.10]
Subtotal (95% CI)			**29**	**30**	**100.0%**	**0.83 [0.22 , 3.10]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
7.3.6 Dizziness						
Childress 2009	0.5604	1.1053	182	63	8.2%	1.75 [0.20 , 15.28]
Childress 2017	1	1.6188	44	41	3.8%	2.72 [0.11 , 64.90]
Coghill 2013	0.6931	1.2322	111	110	6.6%	2.00 [0.18 , 22.38]
Findling 2010	1.4221	1.0707	145	72	8.8%	4.15 [0.51 , 33.81]
Matthijssen 2019 (1)	1.0986	1.6202	47	47	3.8%	3.00 [0.13 , 71.82]
McCracken 2016	-0.1625	0.4887	70	68	42.0%	0.85 [0.33 , 2.22]
Newcorn 2017a (flexible dose)	1.3754	1.0529	184	91	9.1%	3.96 [0.50 , 31.16]
Newcorn 2017b (forced dose)	2.4514	1.4399	219	110	4.8%	11.60 [0.69 , 195.11]
Weiss 2021	1.4671	1.4495	293	74	4.8%	4.34 [0.25 , 74.30]
Wigal 2015	-1.0561	1.6199	45	47	3.8%	0.35 [0.01 , 8.32]
Wigal 2017	1.6549	1.5344	42	44	4.3%	5.23 [0.26 , 105.88]
Subtotal (95% CI)			**1382**	**767**	**100.0%**	**1.77 [0.95 , 3.30]**
Heterogeneity: Tau² = 0.00; Chi² = 7.25, df = 10 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
7.3.7 Drowsiness						
Greenhill 2002	0.2723	0.2508	155	161	81.3%	1.31 [0.80 , 2.15]
Newcorn 2008	-0.8203	0.7759	219	74	8.5%	0.44 [0.10 , 2.01]
Tourette's Syndrome Study Group 2002	0.7196	0.8827	37	33	6.6%	2.05 [0.36 , 11.58]
Wigal 2004	1.0986	1.1756	90	42	3.7%	3.00 [0.30 , 30.05]
Subtotal (95% CI)			**501**	**310**	**100.0%**	**1.27 [0.82 , 1.98]**
Heterogeneity: Tau² = 0.00; Chi² = 2.71, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						
7.3.8 Emotional lability						
Childress 2017	0	0	44	41		Not estimable
Childress 2020b	0	0	65	54		Not estimable
Kollins 2021	0.0267	1.4048	74	76	9.2%	1.03 [0.07 , 16.12]
McCracken 2016	0.1045	0.4887	70	68	76.1%	1.11 [0.43 , 2.89]
Wigal 2004	0.8804	1.1118	90	42	14.7%	2.41 [0.27 , 21.32]
Subtotal (95% CI)			**343**	**281**	**100.0%**	**1.24 [0.54 , 2.85]**
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
7.3.9 Fatigue						
Childress 2009	-0.3778	0.8786	182	63	5.8%	0.69 [0.12 , 3.84]
Childress 2017	0	0	44	41		Not estimable
Coghill 2013	-1.1263	1.1627	111	110	3.4%	0.32 [0.03 , 3.17]
Greenhill 2006	-0.1252	1.0207	53	47	4.4%	0.88 [0.12 , 6.52]
Lin 2014	1.0609	0.7367	36	78	8.2%	2.89 [0.68 , 12.24]
Matthijssen 2019 (1)	-1.0986	1.1361	47	47	3.5%	0.33 [0.04 , 3.09]
McCracken 2016	-0.6351	0.3159	70	68	35.8%	0.53 [0.29 , 0.98]
NCT00409708	2.1972	1.478	52	52	2.1%	9.00 [0.50 , 163.05]
Newcorn 2017a (flexible dose)	-0.1933	0.719	184	91	8.6%	0.82 [0.20 , 3.37]

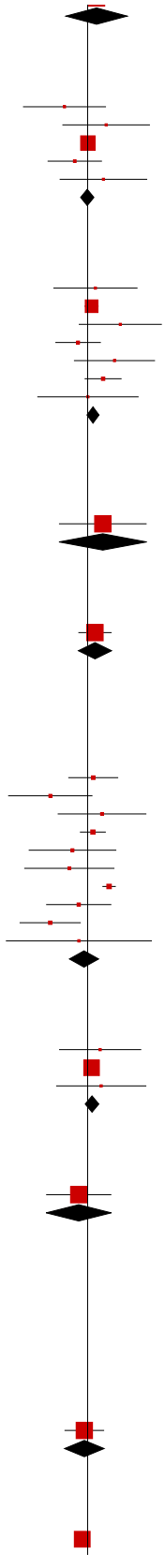
Analysis 7.3. (Continued)

McCracken 2016	-0.6351	0.3159	70	68	35.8%	0.53 [0.29 , 0.98]
NCT00409708	2.1972	1.478	52	52	2.1%	9.00 [0.50 , 163.05]
Newcorn 2017a (flexible dose)	-0.1933	0.719	184	91	8.6%	0.82 [0.20 , 3.37]
Palumbo 2008	-2.0161	1.5349	29	30	2.0%	0.13 [0.01 , 2.70]
Pliszka 2000	0.6286	0.9376	20	17	5.2%	1.87 [0.30 , 11.78]
Riggs 2011	-1.0533	0.5957	151	152	12.2%	0.35 [0.11 , 1.12]
Weiss 2021	-0.2775	0.8061	293	74	6.9%	0.76 [0.16 , 3.68]
Wigal 2017	-1.564	1.5344	42	44	2.0%	0.21 [0.01 , 4.23]
Subtotal (95% CI)			**1314**	**914**	**100.0%**	**0.67 [0.44 , 1.02]**
Heterogeneity: Tau² = 0.03; Chi² = 12.60, df = 12 (P = 0.40); I² = 5%						
Test for overall effect: Z = 1.85 (P = 0.06)						
7.3.10 Headache						
Barragán 2017	3.0445	1.425	30	30	0.7%	21.00 [1.29 , 342.90]
Biederman 2003b	-0.6179	1.237	65	71	0.9%	0.54 [0.05 , 6.09]
Carlson 2007	-1.9889	1.6307	9	8	0.6%	0.14 [0.01 , 3.34]
Childress 2009	-0.0562	0.4415	182	63	4.9%	0.95 [0.40 , 2.25]
Childress 2017	-0.0706	1.3975	44	41	0.8%	0.93 [0.06 , 14.42]
Childress 2020a	1.596	1.5405	74	73	0.6%	4.93 [0.24 , 101.02]
Childress 2020b	-0.1854	1.4022	65	54	0.7%	0.83 [0.05 , 12.97]
Coghill 2013	-0.0113	0.3369	111	110	6.5%	0.99 [0.51 , 1.91]
Findling 2006	1.2365	0.7661	133	46	2.2%	3.44 [0.77 , 15.46]
Findling 2010	-0.4599	0.4983	109	53	4.2%	0.63 [0.24 , 1.68]
Greenhill 2002	0.3893	0.3418	155	161	6.4%	1.48 [0.76 , 2.88]
Greenhill 2006	1.0043	0.5707	53	47	3.5%	2.73 [0.89 , 8.35]
Kollins 2021	1.413	1.106	74	76	1.2%	4.11 [0.47 , 35.90]
Matthijssen 2019	0	1.3991	47	47	0.8%	1.00 [0.06 , 15.52]
McCracken 2016	-0.4199	0.2095	70	68	9.1%	0.66 [0.44 , 0.99]
NCT00409708	1.9459	1.0509	52	52	1.3%	7.00 [0.89 , 54.91]
NCT02293655	0.9383	0.6585	18	92	2.8%	2.56 [0.70 , 9.29]
Newcorn 2008	0.2098	0.4505	219	74	4.7%	1.23 [0.51 , 2.98]
Newcorn 2017a (flexible dose)	0.6822	0.4027	184	91	5.4%	1.98 [0.90 , 4.36]
Newcorn 2017b (forced dose)	0.6695	0.355	219	110	6.2%	1.95 [0.97 , 3.92]
Palumbo 2008	-1.135	1.1858	29	30	1.0%	0.32 [0.03 , 3.28]
Pliszka 2000	-1.257	1.665	20	17	0.5%	0.28 [0.01 , 7.44]
Pliszka 2017	0.6807	0.5917	81	80	3.3%	1.98 [0.62 , 6.30]
Riggs 2011	0.1725	0.2316	151	152	8.6%	1.19 [0.75 , 1.87]
Tucker 2009	2.2713	0.7846	53	56	2.1%	9.69 [2.08 , 45.11]
Weiss 2021	0.4622	0.3856	293	74	5.7%	1.59 [0.75 , 3.38]
Wigal 2004	0.794	0.5906	90	42	3.3%	2.21 [0.70 , 7.04]
Wigal 2015	0.2666	0.6376	45	47	2.9%	1.31 [0.37 , 4.56]
Wigal 2017	-0.6466	0.6734	42	44	2.7%	0.52 [0.14 , 1.96]
Wilens 2006b	-0.6931	0.7237	87	90	2.4%	0.50 [0.12 , 2.07]
Wolraich 2001	-0.0931	0.5421	160	46	3.7%	0.91 [0.31 , 2.64]
Zeni 2009	0.7075	2.0897	16	16	0.3%	2.03 [0.03 , 121.90]
Subtotal (95% CI)			**2980**	**2061**	**100.0%**	**1.33 [1.04 , 1.70]**
Heterogeneity: Tau² = 0.13; Chi² = 45.55, df = 31 (P = 0.04); I² = 32%						
Test for overall effect: Z = 2.29 (P = 0.02)						
7.3.11 Irritability						
Barragán 2017	0	0	30	30		Not estimable
Carlson 2007	-0.9076	1.6908	9	12	0.5%	0.40 [0.01 , 11.09]
Childress 2009	1.1637	1.4979	182	63	0.7%	3.20 [0.17 , 60.31]
Childress 2017	0	0	44	41		Not estimable
Childress 2020b	0	0	65	54		Not estimable
Coghill 2013	2.2247	1.4969	111	110	0.7%	9.25 [0.49 , 173.92]
Findling 2006	0.5641	1.1091	133	46	1.3%	1.76 [0.20 , 15.45]
Findling 2010	-0.3374	0.6684	109	53	3.5%	0.71 [0.19 , 2.64]
Greenhill 2002	-0.1569	0.2256	155	161	30.5%	0.85 [0.55 , 1.33]
Greenhill 2006	0.59	1.2415	53	47	1.0%	1.80 [0.16 , 20.56]
Lin 2014	1.1787	0.6132	36	78	4.1%	3.25 [0.98 , 10.81]
McCracken 2016	0.1533	0.3053	70	68	16.6%	1.17 [0.64 , 2.12]
NCT02293655	0.1845	0.4923	18	92	6.4%	1.20 [0.46 , 3.16]
Newcorn 2008	1.5275	1.0466	219	74	1.4%	4.61 [0.59 , 35.83]
Newcorn 2017a (flexible dose)	-0.2622	0.4076	184	91	9.3%	0.77 [0.35 , 1.71]
Newcorn 2017b (forced dose)	0.0735	0.4426	219	110	7.9%	1.08 [0.45 , 2.56]
Pliszka 2000	0.3448	0.9771	20	18	1.6%	1.41 [0.21 , 9.58]
Weiss 2021	-0.144	0.4094	293	74	9.3%	0.87 [0.39 , 1.93]
Wigal 2017	-0.1358	0.5658	42	44	4.8%	0.87 [0.29 , 2.65]
Zeni 2009	0.1995	2.382	16	16	0.3%	1.22 [0.01 , 130.08]
Subtotal (95% CI)			**2008**	**1282**	**100.0%**	**1.05 [0.82 , 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 11.15, df = 16 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
7.3.12 Nervousness						
Palumbo 2008	0.3032	0.7281	29	30	46.3%	1.35 [0.33 , 5.64]
Riggs 2011	1.4558	0.6562	151	152	53.7%	4.29 [1.18 , 15.52]
Subtotal (95% CI)			**180**	**182**	**100.0%**	**2.52 [0.82 , 7.76]**
Heterogeneity: Tau² = 0.18; Chi² = 1.38, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 1.61 (P = 0.11)						
7.3.13 Pain						
Wigal 2004	0.6455	1.134	90	42	100.0%	1.91 [0.21 , 17.60]
Subtotal (95% CI)			**90**	**42**	**100.0%**	**1.91 [0.21 , 17.60]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						

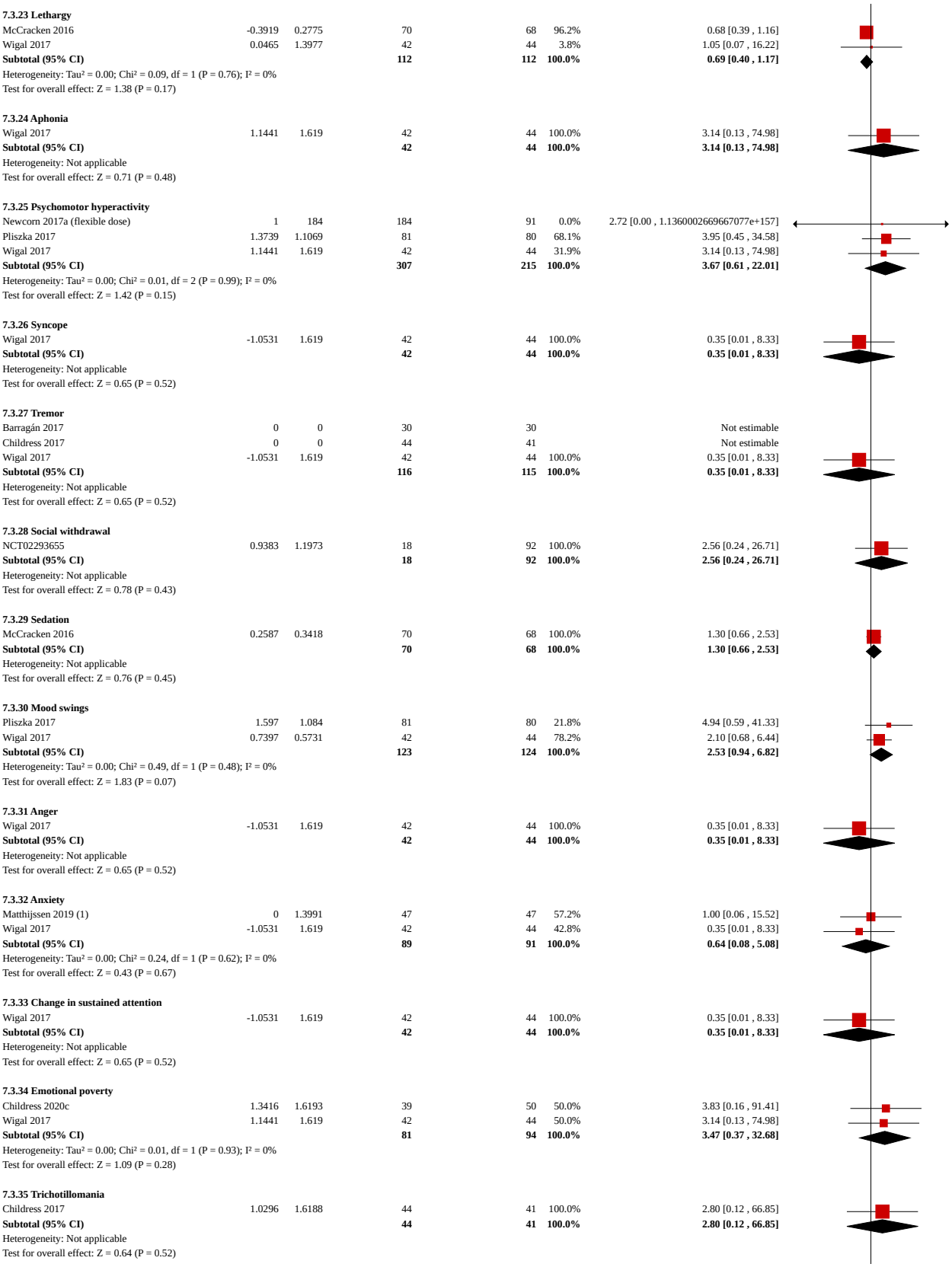


Analysis 7.3. (Continued)

Subtotal (95% CI)			**90**	**42**	**100.0%**	**1.91 [0.21 , 17.60]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
7.3.14 Picking at skin or fingers, nail biting, lip or cheek chewing						
Childress 2017	-1.6784	1.5343	44	41	2.6%	0.19 [0.01 , 3.78]
Childress 2020c (2)	1.3416	1.6193	39	50	2.3%	3.83 [0.16 , 91.41]
Greenhill 2002	0.0148	0.2645	155	161	86.8%	1.01 [0.60 , 1.70]
NCT02293655	-0.9335	1.0052	18	92	6.0%	0.39 [0.05 , 2.82]
Wigal 2017 (2)	1.1441	1.619	42	44	2.3%	3.14 [0.13 , 74.98]
Subtotal (95% CI)			**298**	**388**	**100.0%**	**0.97 [0.60 , 1.57]**
Heterogeneity: Tau² = 0.00; Chi² = 3.23, df = 4 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
7.3.15 Sad, tearful or depressed						
Childress 2009	0.5647	1.556	182	63	2.1%	1.76 [0.08 , 37.13]
Greenhill 2002	0.284	0.2585	155	161	74.5%	1.33 [0.80 , 2.20]
Lin 2014	2.368	1.5363	36	78	2.1%	10.68 [0.53 , 216.83]
Matthijssen 2019 (3)	-0.6931	0.8411	47	47	7.0%	0.50 [0.10 , 2.60]
NCT00409708 (4)	1.9459	1.4993	52	52	2.2%	7.00 [0.37 , 132.22]
NCT02293655	1.1206	0.6833	18	92	10.7%	3.07 [0.80 , 11.70]
Zeni 2009	0.0219	1.873	16	16	1.4%	1.02 [0.03 , 40.16]
Subtotal (95% CI)			**506**	**509**	**100.0%**	**1.47 [0.95 , 2.28]**
Heterogeneity: Tau² = 0.00; Chi² = 5.76, df = 6 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.74 (P = 0.08)						
7.3.16 Thirst						
Childress 2017	0	0	44	41		Not estimable
Matthijssen 2019	1.0986	1.6202	47	47	100.0%	3.00 [0.13 , 71.82]
Subtotal (95% CI)			**91**	**88**	**100.0%**	**3.00 [0.13 , 71.82]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
7.3.17 Dull, tired, listless						
NCT02293655	0.5328	0.6148	18	92	100.0%	1.70 [0.51 , 5.68]
Subtotal (95% CI)			**18**	**92**	**100.0%**	**1.70 [0.51 , 5.68]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
7.3.18 Tics or nervous movements						
Barragán 2017	0	0	30	30		Not estimable
Childress 2017	0	0	44	41		Not estimable
Coghill 2013	0.4055	0.923	111	110	12.4%	1.50 [0.25 , 9.16]
Findling 2006	-2.7081	1.5588	133	46	7.4%	0.07 [0.00 , 1.41]
Findling 2008	1.0418	1.6399	91	85	7.0%	2.83 [0.11 , 70.52]
Greenhill 2002	0.3791	0.4789	155	161	16.9%	1.46 [0.57 , 3.73]
Matthijssen 2019 (1)	-1.0986	1.6202	47	47	7.1%	0.33 [0.01 , 7.98]
Pliszka 2000	-1.3282	1.6681	19	16	6.8%	0.26 [0.01 , 6.97]
Schachar 1997a	1.554	0.2474	37	29	18.7%	4.73 [2.91 , 7.68]
Wigal 2017	-0.6466	1.2056	42	44	9.9%	0.52 [0.05 , 5.56]
Wolraich 2001	-2.7175	1.1314	160	46	10.5%	0.07 [0.01 , 0.61]
Zeni 2009	-0.6349	2.7003	16	16	3.3%	0.53 [0.00 , 105.38]
Subtotal (95% CI)			**885**	**671**	**100.0%**	**0.77 [0.27 , 2.22]**
Heterogeneity: Tau² = 1.51; Chi² = 29.30, df = 9 (P = 0.0006); I² = 69%						
Test for overall effect: Z = 0.49 (P = 0.63)						
7.3.19 Worried or anxious						
Childress 2009	0.9068	1.5189	182	63	2.8%	2.48 [0.13 , 48.61]
Greenhill 2002	0.284	0.2585	155	161	95.0%	1.33 [0.80 , 2.20]
Pliszka 2000	0.9842	1.6677	19	16	2.3%	2.68 [0.10 , 70.30]
Subtotal (95% CI)			**356**	**240**	**100.0%**	**1.37 [0.84 , 2.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
7.3.20 Feeling jittery						
Wigal 2017	-0.6466	1.2056	42	44	100.0%	0.52 [0.05 , 5.56]
Subtotal (95% CI)			**42**	**44**	**100.0%**	**0.52 [0.05 , 5.56]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
7.3.21 Malaise						
Wigal 2017	0	0	42	44		Not estimable
Subtotal (95% CI)			**0**	**0**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.3.22 Dysgeusia						
Childress 2017	0	0	44	41		Not estimable
Wigal 2017	-0.2412	0.7327	42	44	100.0%	0.79 [0.19 , 3.30]
Subtotal (95% CI)			**86**	**85**	**100.0%**	**0.79 [0.19 , 3.30]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
7.3.23 Lethargy						
McCracken 2016	-0.3919	0.2775	70	68	96.2%	0.68 [0.39 , 1.16]
Wigal 2017	0.0465	1.3977	42	44	3.8%	1.05 [0.07 , 16.22]



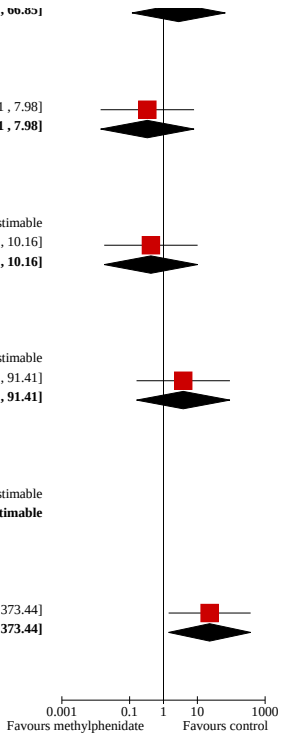
Analysis 7.3. (Continued)



Analysis 7.3. (Continued)

Subtotal (95% CI)			**44**	**41**	**100.0%**	**2.80 [0.12 , 66.85]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
7.3.36 Stuttering						
Matthijssen 2019 (1)	-1.0986	1.6202	47	47	100.0%	0.33 [0.01 , 7.98]
Subtotal (95% CI)			**47**	**47**	**100.0%**	**0.33 [0.01 , 7.98]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
7.3.37 Emotional disorder						
Childress 2017	0	0	44	41		Not estimable
Childress 2020c	-0.8557	1.6193	39	50	100.0%	0.42 [0.02 , 10.16]
Subtotal (95% CI)			**83**	**91**	**100.0%**	**0.42 [0.02 , 10.16]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
7.3.38 Negativism						
Childress 2017	0	0	44	41		Not estimable
Childress 2020c	1.3416	1.6193	39	50	100.0%	3.83 [0.16 , 91.41]
Subtotal (95% CI)			**83**	**91**	**100.0%**	**3.83 [0.16 , 91.41]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
7.3.39 Migraine						
Childress 2017	0	0	44	41		Not estimable
Subtotal (95% CI)			**0**	**0**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.3.40 Tension						
Barragán 2017	3.1355	1.4221	30	30	100.0%	23.00 [1.42 , 373.44]
Subtotal (95% CI)			**30**	**30**	**100.0%**	**23.00 [1.42 , 373.44]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						

Test for subgroup differences: Chi² = 0.00, df = 37 (P < 0.00001), I² = 0%

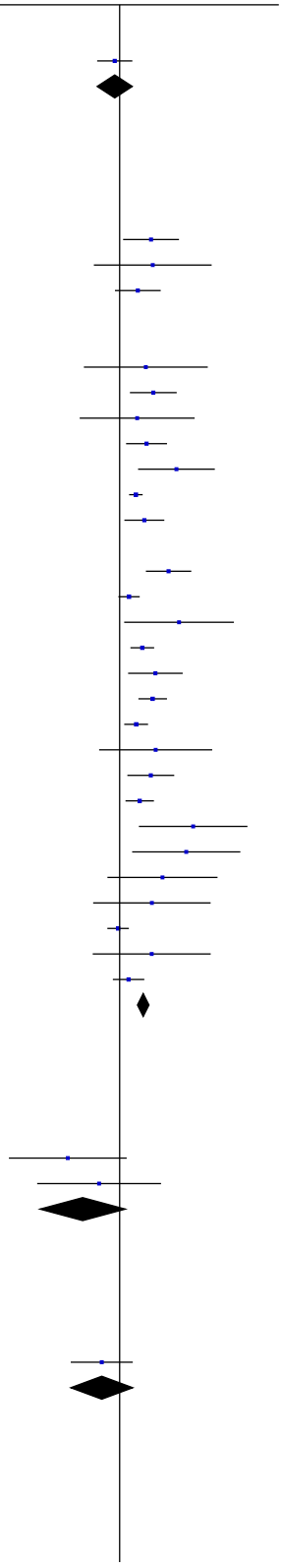


Footnotes

(1) Discontinuation study
(2) Onychophagia
(3) Discontinuation study (moodiness)
(4) Ritalin LA plus behaviour therapy versus behaviour therapy

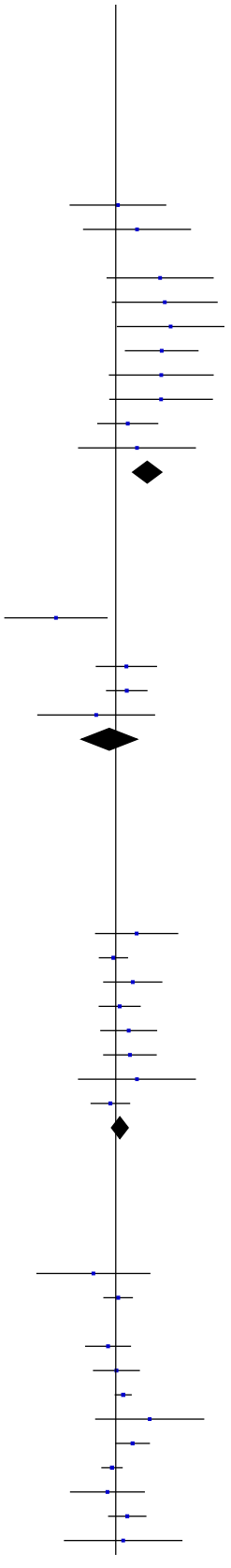
Analysis 7.4. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 4: Digestive system

Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
7.4.1 Change in appetite						
Matthijssen 2019 (1)	7	47	9	47	1.7%	0.78 [0.32 , 1.92]
Subtotal (95% CI)		**47**		**47**	**1.7%**	**0.78 [0.32 , 1.92]**
Total events:	7		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
7.4.2 Decreased appetite						
Barragán 2017	10	30	2	30	0.9%	5.00 [1.19 , 20.92]
Biederman 2003b	2	65	0	71	0.3%	5.45 [0.27 , 111.54]
Childress 2009	22	182	3	63	1.2%	2.54 [0.79 , 8.19]
Childress 2017	0	44	0	41		Not estimable
Childress 2020b	0	65	0	54		Not estimable
Childress 2020c	1	39	0	50	0.2%	3.83 [0.16 , 91.40]
Coghill 2013	17	111	3	110	1.2%	5.62 [1.69 , 18.62]
Findling 2006	3	133	0	46	0.3%	2.46 [0.13 , 46.65]
Findling 2008	17	91	4	85	1.4%	3.97 [1.39 , 11.32]
Findling 2010	37	145	1	72	0.6%	18.37 [2.57 , 131.23]
Greenhill 2002	73	155	33	161	2.9%	2.30 [1.62 , 3.25]
Greenhill 2006	16	53	4	47	1.5%	3.55 [1.28 , 9.87]
Kollins 2021	0	74	0	76		Not estimable
Lin 2014	17	36	3	78	1.3%	12.28 [3.84 , 39.25]
McCracken 2016	25	70	15	68	2.5%	1.62 [0.94 , 2.80]
NCT00409708	10	52	0	52	0.3%	21.00 [1.26 , 349.29]
NCT02293655	10	18	16	92	2.3%	3.19 [1.74 , 5.86]
Newcorn 2008	37	219	2	74	1.0%	6.25 [1.54 , 25.31]
Newcorn 2017a (flexible dose)	77	184	7	91	2.0%	5.44 [2.62 , 11.31]
Newcorn 2017b (forced dose)	51	219	11	110	2.3%	2.33 [1.27 , 4.29]
Pliszka 2000	3	20	0	18	0.3%	6.33 [0.35 , 114.81]
Pliszka 2017	15	81	3	80	1.2%	4.94 [1.49 , 16.40]
Riggs 2011	25	151	9	152	2.0%	2.80 [1.35 , 5.79]
Tucker 2009	20	53	0	56	0.3%	43.28 [2.68 , 698.02]
Weiss 2021	59	293	0	74	0.3%	30.36 [1.90 , 485.36]
Wigal 2004	9	90	0	42	0.3%	8.98 [0.53 , 150.71]
Wigal 2015	2	45	0	47	0.3%	5.22 [0.26 , 105.77]
Wigal 2017	15	42	17	44	2.4%	0.92 [0.53 , 1.60]
Wilens 2006b	2	87	0	90	0.3%	5.17 [0.25 , 106.18]
Wolraich 2001	33	160	6	46	1.9%	1.58 [0.71 , 3.54]
Subtotal (95% CI)		**3007**		**2120**	**31.5%**	**3.35 [2.49 , 4.50]**
Total events:	608		139			
Heterogeneity: Tau² = 0.22; Chi² = 50.37, df = 26 (P = 0.003); I² = 48%						
Test for overall effect: Z = 8.00 (P < 0.00001)						
7.4.3 Increased appetite						
Findling 2006	0	133	2	46	0.3%	0.07 [0.00 , 1.43]
Wigal 2017	0	42	1	44	0.2%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**175**		**90**	**0.5%**	**0.15 [0.02 , 1.34]**
Total events:	0		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.70 (P = 0.09)						
7.4.4 Change in weight						
Matthijssen 2019	2	47	5	47	0.8%	0.40 [0.08 , 1.96]
Subtotal (95% CI)		**47**		**47**	**0.8%**	**0.40 [0.08 , 1.96]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
7.4.5 Increased weight						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**



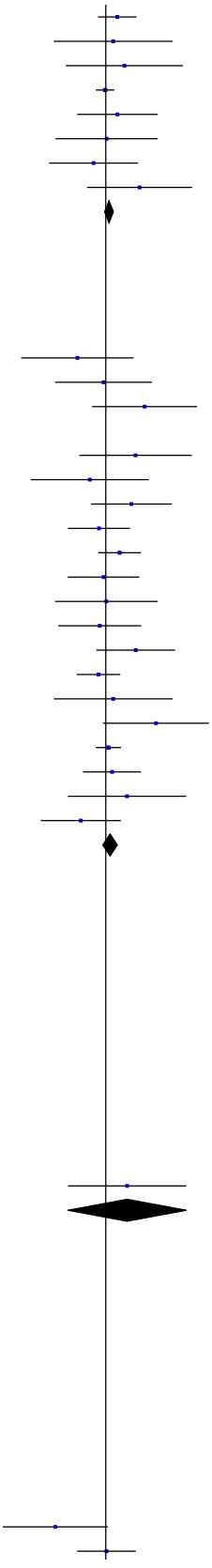
Analysis 7.4. (Continued)

7.4.5 Increased weight						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.4.6 Decreased weight						
Carlson 2007	1	8	1	9	0.4%	1.13 [0.08 , 15.19]
Childress 2009	4	182	0	63	0.3%	3.15 [0.17 , 57.65]
Childress 2017	0	44	0	41		Not estimable
Coghill 2013	5	111	0	110	0.3%	10.90 [0.61 , 194.82]
Findling 2008	7	91	0	85	0.3%	14.02 [0.81 , 241.82]
Lin 2014	4	36	0	78	0.3%	19.22 [1.06 , 347.68]
Newcorn 2017a (flexible dose)	24	184	1	91	0.6%	11.87 [1.63 , 86.36]
Newcorn 2017b (forced dose)	11	219	0	110	0.3%	11.60 [0.69 , 195.12]
Weiss 2021	22	293	0	74	0.3%	11.48 [0.70 , 187.08]
Wigal 2004	4	44	2	42	0.8%	1.91 [0.37 , 9.88]
Wigal 2017	1	42	0	44	0.2%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**1254**		**747**	**3.7%**	**5.44 [2.47 , 11.98]**
Total events:	83		4			
Heterogeneity: Tau² = 0.00; Chi² = 5.74, df = 9 (P = 0.77); I² = 0%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
7.4.7 Dyspepsia						
Barragán 2017	0	30	12	30	0.3%	0.04 [0.00 , 0.65]
Childress 2017	0	44	0	41		Not estimable
Greenhill 2006	4	53	2	47	0.8%	1.77 [0.34 , 9.25]
Palumbo 2008	7	29	4	30	1.3%	1.81 [0.59 , 5.53]
Wigal 2017	0	42	1	44	0.2%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**198**		**192**	**2.6%**	**0.71 [0.16 , 3.19]**
Total events:	11		19			
Heterogeneity: Tau² = 1.28; Chi² = 7.04, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 0.45 (P = 0.65)						
7.4.8 Upper abdominal pain						
Childress 2017	0	44	0	41		Not estimable
Childress 2020b	0	65	0	54		Not estimable
Kollins 2021	3	74	1	76	0.5%	3.08 [0.33 , 28.95]
McCracken 2016	10	70	11	68	1.9%	0.88 [0.40 , 1.94]
NCT00409708 (2)	5	52	2	52	0.8%	2.50 [0.51 , 12.31]
Newcorn 2017a (flexible dose)	10	184	4	91	1.3%	1.24 [0.40 , 3.84]
Newcorn 2017b (forced dose)	8	219	2	110	0.9%	2.01 [0.43 , 9.30]
Weiss 2021	17	293	2	74	0.9%	2.15 [0.51 , 9.09]
Wigal 2015	1	45	0	47	0.2%	3.13 [0.13 , 74.90]
Wigal 2017	5	42	7	44	1.4%	0.75 [0.26 , 2.17]
Subtotal (95% CI)		**1088**		**657**	**7.9%**	**1.25 [0.79 , 1.96]**
Total events:	59		29			
Heterogeneity: Tau² = 0.00; Chi² = 4.21, df = 7 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
7.4.9 Stomachache (abdominal pain)						
Carlson 2007	0	9	1	8	0.3%	0.30 [0.01 , 6.47]
Childress 2009	23	182	7	63	1.9%	1.14 [0.51 , 2.52]
Childress 2020b	0	65	0	54		Not estimable
Coghill 2013	4	111	6	110	1.2%	0.66 [0.19 , 2.28]
Findling 2006	9	133	3	46	1.1%	1.04 [0.29 , 3.67]
Greenhill 2002	36	155	25	161	2.7%	1.50 [0.94 , 2.37]
Greenhill 2006	3	53	0	47	0.3%	6.22 [0.33 , 117.41]
Lin 2014	8	36	7	78	1.6%	2.48 [0.97 , 6.30]
McCracken 2016	16	70	19	68	2.4%	0.82 [0.46 , 1.45]
NCT02293655	1	18	8	92	0.6%	0.64 [0.09 , 4.80]
Newcorn 2008	22	219	4	74	1.4%	1.86 [0.66 , 5.22]
Newcorn 2017a (flexible dose)	1	184	0	91	0.2%	1.49 [0.06 , 36.27]



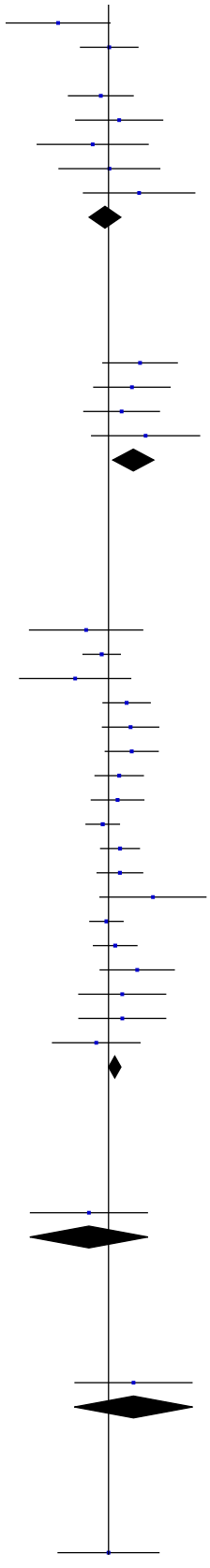
Analysis 7.4. (Continued)

Newcorn 2008	22	219	4	74	1.4%	1.86 [0.66 , 5.22]
Newcorn 2017a (flexible dose)	1	184	0	91	0.2%	1.49 [0.06 , 36.27]
Pliszka 2000	1	20	0	18	0.3%	2.71 [0.12 , 62.70]
Riggs 2011	25	151	26	152	2.6%	0.97 [0.59 , 1.60]
Wigal 2004	4	90	1	42	0.5%	1.87 [0.22 , 16.19]
Wigal 2017	1	42	1	44	0.3%	1.05 [0.07 , 16.21]
Wilens 2006b	1	87	2	90	0.4%	0.52 [0.05 , 5.60]
Wolraich 2001	10	160	0	46	0.3%	6.13 [0.37 , 102.68]
Subtotal (95% CI)		**1785**		**1284**	**18.0%**	**1.19 [0.94 , 1.50]**
Total events:	165		110			
Heterogeneity: Tau² = 0.00; Chi² = 11.82, df = 16 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
7.4.10 Vomiting						
Biederman 2003b	0	65	2	71	0.3%	0.22 [0.01 , 4.46]
Carlson 2007	1	9	1	8	0.4%	0.89 [0.07 , 12.00]
Childress 2009	11	182	0	63	0.3%	8.04 [0.48 , 134.55]
Childress 2017	0	44	0	41		Not estimable
Childress 2020a	2	74	0	73	0.3%	4.93 [0.24 , 101.02]
Childress 2020c	0	39	1	50	0.2%	0.42 [0.02 , 10.16]
Coghill 2013	4	111	1	110	0.5%	3.96 [0.45 , 34.90]
Findling 2006	4	133	2	46	0.8%	0.69 [0.13 , 3.65]
Findling 2008	9	91	4	85	1.3%	2.10 [0.67 , 6.57]
Greenhill 2006	2	53	2	47	0.6%	0.89 [0.13 , 6.05]
Kollins 2021	1	74	1	76	0.3%	1.03 [0.07 , 16.12]
Lin 2014	1	36	3	78	0.5%	0.72 [0.08 , 6.71]
NCT00409708 (2)	5	52	1	52	0.5%	5.00 [0.60 , 41.34]
Newcorn 2008	8	219	4	74	1.2%	0.68 [0.21 , 2.18]
Newcorn 2017a (flexible dose)	1	184	0	91	0.2%	1.49 [0.06 , 36.27]
Pliszka 2017	7	81	0	80	0.3%	14.82 [0.86 , 255.18]
Riggs 2011	16	151	14	152	2.1%	1.15 [0.58 , 2.27]
Wigal 2004	6	90	2	42	0.8%	1.40 [0.29 , 6.65]
Wigal 2015	1	45	0	47	0.2%	3.13 [0.13 , 74.90]
Wigal 2017	1	42	4	44	0.5%	0.26 [0.03 , 2.25]
Subtotal (95% CI)		**1775**		**1330**	**11.4%**	**1.26 [0.85 , 1.86]**
Total events:	80		42			
Heterogeneity: Tau² = 0.00; Chi² = 15.06, df = 18 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
7.4.11 Constipation						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.4.12 Oral pain						
Childress 2017	0	44	0	41		Not estimable
Wigal 2017 (3)	1	42	0	44	0.2%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**86**		**85**	**0.2%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.4.13 Retching						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.4.14 Diarrhoea						
Barragán 2017	0	30	7	30	0.3%	0.07 [0.00 , 1.12]
Childress 2009	6	182	2	63	0.8%	1.04 [0.22 , 5.01]



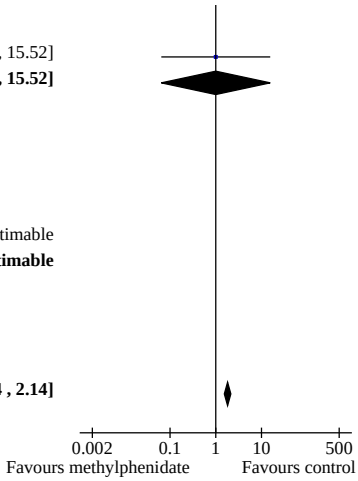
Analysis 7.4. (Continued)

Barragán 2017	0	30	7	30	0.3%	0.07 [0.00 , 1.12]
Childress 2009	6	182	2	63	0.8%	1.04 [0.22 , 5.01]
Childress 2017	0	44	0	41		Not estimable
Coghill 2013	2	111	3	110	0.7%	0.66 [0.11 , 3.88]
Greenhill 2006	2	53	1	47	0.4%	1.77 [0.17 , 18.94]
Lin 2014	0	36	2	78	0.3%	0.43 [0.02 , 8.67]
Wigal 2017	1	42	1	44	0.3%	1.05 [0.07 , 16.21]
Wilens 2006b	2	87	0	90	0.3%	5.17 [0.25 , 106.18]
Subtotal (95% CI)		**585**		**503**	**3.1%**	**0.83 [0.35 , 1.94]**
Total events:	13		16			
Heterogeneity: Tau² = 0.00; Chi² = 5.23, df = 6 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
7.4.15 Dry mouth						
Newcorn 2017a (flexible dose)	11	184	1	91	0.5%	5.44 [0.71 , 41.49]
Newcorn 2017b (forced dose)	7	219	1	110	0.5%	3.52 [0.44 , 28.22]
Weiss 2021	8	293	1	74	0.5%	2.02 [0.26 , 15.90]
Wigal 2017	3	42	0	44	0.3%	7.33 [0.39 , 137.68]
Subtotal (95% CI)		**738**		**319**	**1.9%**	**3.79 [1.26 , 11.39]**
Total events:	29		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.37 (P = 0.02)						
7.4.16 Nausea						
Barragán 2017	0	30	0	30		Not estimable
Carlson 2007	0	9	1	8	0.3%	0.30 [0.01 , 6.47]
Childress 2009	10	182	5	63	1.4%	0.69 [0.25 , 1.95]
Childress 2020b	0	65	2	54	0.3%	0.17 [0.01 , 3.40]
Coghill 2013	8	111	3	110	1.1%	2.64 [0.72 , 9.70]
Findling 2008	7	91	2	85	0.8%	3.27 [0.70 , 15.30]
Findling 2010	14	145	2	72	0.9%	3.48 [0.81 , 14.88]
Greenhill 2006	6	53	3	47	1.0%	1.77 [0.47 , 6.70]
Lin 2014	3	36	4	78	0.9%	1.63 [0.38 , 6.89]
Newcorn 2008	13	219	6	74	1.6%	0.73 [0.29 , 1.86]
Newcorn 2017a (flexible dose)	15	184	4	91	1.4%	1.85 [0.63 , 5.43]
Newcorn 2017b (forced dose)	11	219	3	110	1.1%	1.84 [0.52 , 6.47]
Pliszka 2017	5	81	0	80	0.3%	10.87 [0.61 , 193.32]
Riggs 2011	8	151	9	152	1.6%	0.89 [0.35 , 2.26]
Weiss 2021	17	293	3	74	1.2%	1.43 [0.43 , 4.75]
Wigal 2004	10	90	1	42	0.5%	4.67 [0.62 , 35.28]
Wigal 2015	2	45	1	47	0.4%	2.09 [0.20 , 22.24]
Wigal 2017	2	42	1	44	0.4%	2.10 [0.20 , 22.26]
Wilens 2006b	1	87	2	90	0.4%	0.52 [0.05 , 5.60]
Subtotal (95% CI)		**2133**		**1351**	**15.9%**	**1.40 [1.00 , 1.95]**
Total events:	132		52			
Heterogeneity: Tau² = 0.00; Chi² = 15.81, df = 17 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.98 (P = 0.05)						
7.4.17 Flatulence						
Wigal 2017	0	42	1	44	0.2%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**0.2%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.4.18 Gastritis						
Childress 2020c	1	39	0	50	0.2%	3.83 [0.16 , 91.40]
Subtotal (95% CI)		**39**		**50**	**0.2%**	**3.83 [0.16 , 91.40]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
7.4.19 Gastrointestinal concerns (unspecified)						
Matthiissen 2019	1	47	1	47	0.3%	1.00 [0.06 , 15.52]



Analysis 7.4. (Continued)

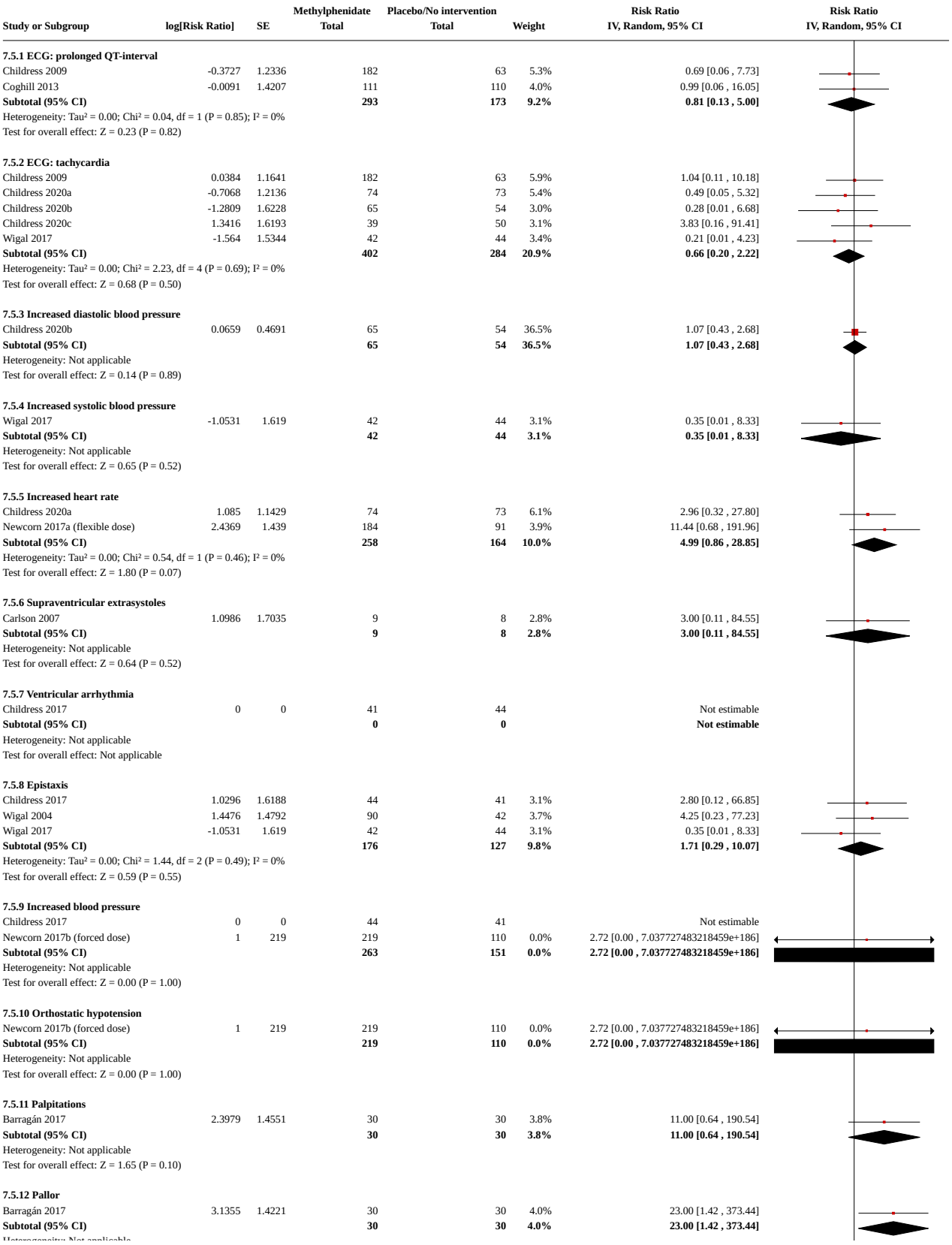
7.4.19 Gastrointestinal concerns (unspecified)						
Matthijssen 2019	1	47	1	47	0.3%	1.00 [0.06 , 15.52]
Subtotal (95% CI)		**47**		**47**	**0.3%**	**1.00 [0.06 , 15.52]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
7.4.20 Polydipsia						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**13222**		**9077**	**100.0%**	**1.81 [1.54 , 2.14]**
Total events:	1192		433			
Heterogeneity: Tau² = 0.21; Chi² = 181.52, df = 121 (P = 0.0003); I² = 33%						
Test for overall effect: Z = 7.12 (P < 0.00001)						
Test for subgroup differences: Chi² = 59.46, df = 15 (P < 0.00001), I² = 74.8%						



Footnotes

(1) Discontinuation study
(2) Ritalin LA plus behaviour therapy versus behaviour therapy
(3) Gingival pain

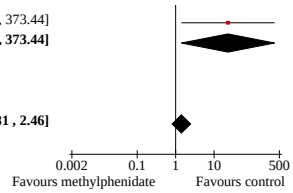
Analysis 7.5. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 5: Cardiovascular system



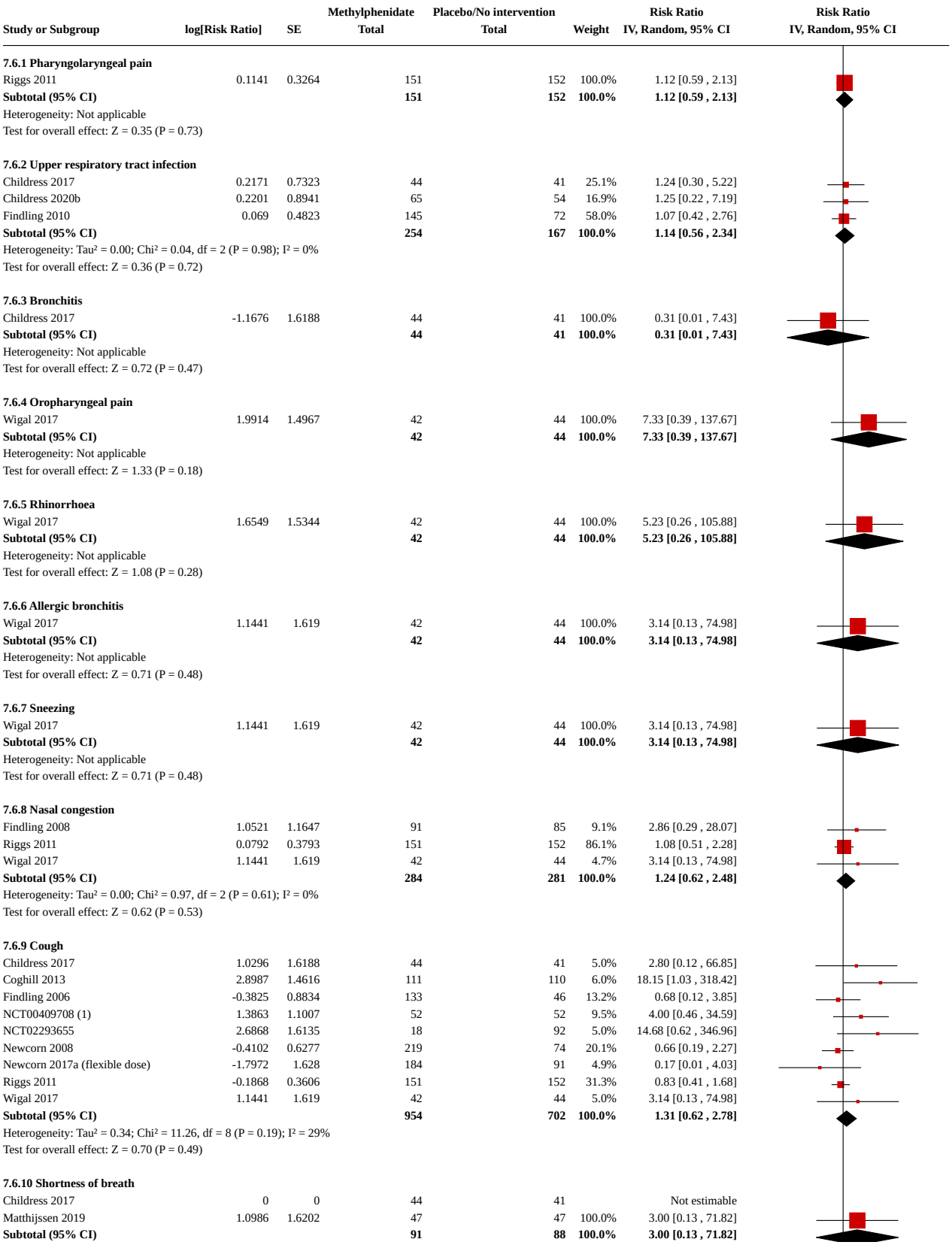
Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo/No intervention Total	Weight	Risk Ratio IV, Random, 95% CI
7.5.1 ECG: prolonged QT-interval						
Childress 2009	-0.3727	1.2336	182	63	5.3%	0.69 [0.06 , 7.73]
Coghill 2013	-0.0091	1.4207	111	110	4.0%	0.99 [0.06 , 16.05]
Subtotal (95% CI)			**293**	**173**	**9.2%**	**0.81 [0.13 , 5.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
7.5.2 ECG: tachycardia						
Childress 2009	0.0384	1.1641	182	63	5.9%	1.04 [0.11 , 10.18]
Childress 2020a	-0.7068	1.2136	74	73	5.4%	0.49 [0.05 , 5.32]
Childress 2020b	-1.2809	1.6228	65	54	3.0%	0.28 [0.01 , 6.68]
Childress 2020c	1.3416	1.6193	39	50	3.1%	3.83 [0.16 , 91.41]
Wigal 2017	-1.564	1.5344	42	44	3.4%	0.21 [0.01 , 4.23]
Subtotal (95% CI)			**402**	**284**	**20.9%**	**0.66 [0.20 , 2.22]**
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 4 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
7.5.3 Increased diastolic blood pressure						
Childress 2020b	0.0659	0.4691	65	54	36.5%	1.07 [0.43 , 2.68]
Subtotal (95% CI)			**65**	**54**	**36.5%**	**1.07 [0.43 , 2.68]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
7.5.4 Increased systolic blood pressure						
Wigal 2017	-1.0531	1.619	42	44	3.1%	0.35 [0.01 , 8.33]
Subtotal (95% CI)			**42**	**44**	**3.1%**	**0.35 [0.01 , 8.33]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.5.5 Increased heart rate						
Childress 2020a	1.085	1.1429	74	73	6.1%	2.96 [0.32 , 27.80]
Newcorn 2017a (flexible dose)	2.4369	1.439	184	91	3.9%	11.44 [0.68 , 191.96]
Subtotal (95% CI)			**258**	**164**	**10.0%**	**4.99 [0.86 , 28.85]**
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
7.5.6 Supraventricular extrasystoles						
Carlson 2007	1.0986	1.7035	9	8	2.8%	3.00 [0.11 , 84.55]
Subtotal (95% CI)			**9**	**8**	**2.8%**	**3.00 [0.11 , 84.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
7.5.7 Ventricular arrhythmia						
Childress 2017	0	0	41	44		Not estimable
Subtotal (95% CI)			**0**	**0**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.5.8 Epistaxis						
Childress 2017	1.0296	1.6188	44	41	3.1%	2.80 [0.12 , 66.85]
Wigal 2004	1.4476	1.4792	90	42	3.7%	4.25 [0.23 , 77.23]
Wigal 2017	-1.0531	1.619	42	44	3.1%	0.35 [0.01 , 8.33]
Subtotal (95% CI)			**176**	**127**	**9.8%**	**1.71 [0.29 , 10.07]**
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.55)						
7.5.9 Increased blood pressure						
Childress 2017	0	0	44	41		Not estimable
Newcorn 2017b (forced dose)	1	219	219	110	0.0%	2.72 [0.00 , 7.037727483218459e+186]
Subtotal (95% CI)			**263**	**151**	**0.0%**	**2.72 [0.00 , 7.037727483218459e+186]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
7.5.10 Orthostatic hypotension						
Newcorn 2017b (forced dose)	1	219	219	110	0.0%	2.72 [0.00 , 7.037727483218459e+186]
Subtotal (95% CI)			**219**	**110**	**0.0%**	**2.72 [0.00 , 7.037727483218459e+186]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
7.5.11 Palpitations						
Barragán 2017	2.3979	1.4551	30	30	3.8%	11.00 [0.64 , 190.54]
Subtotal (95% CI)			**30**	**30**	**3.8%**	**11.00 [0.64 , 190.54]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
7.5.12 Pallor						
Barragán 2017	3.1355	1.4221	30	30	4.0%	23.00 [1.42 , 373.44]
Subtotal (95% CI)			**30**	**30**	**4.0%**	**23.00 [1.42 , 373.44]**

Analysis 7.5. (Continued)

Barragán 2017	3.1355	1.4221	30	30	4.0%	23.00 [1.42 , 373.44]
Subtotal (95% CI)			**30**	**30**	**4.0%**	**23.00 [1.42 , 373.44]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)			**1828**	**1219**	**100.0%**	**1.41 [0.81 , 2.46]**
Heterogeneity: Tau² = 0.00; Chi² = 15.30, df = 18 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 11.05, df = 10 (P = 0.35), I² = 9.5%						



Analysis 7.6. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 6: Respiratory system



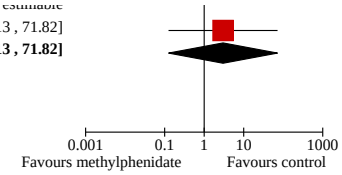
Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo/No intervention Total	Weight	Risk Ratio IV, Random, 95% CI
7.6.1 Pharyngolaryngeal pain						
Riggs 2011	0.1141	0.3264	151	152	100.0%	1.12 [0.59 , 2.13]
Subtotal (95% CI)			**151**	**152**	**100.0%**	**1.12 [0.59 , 2.13]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
7.6.2 Upper respiratory tract infection						
Childress 2017	0.2171	0.7323	44	41	25.1%	1.24 [0.30 , 5.22]
Childress 2020b	0.2201	0.8941	65	54	16.9%	1.25 [0.22 , 7.19]
Findling 2010	0.069	0.4823	145	72	58.0%	1.07 [0.42 , 2.76]
Subtotal (95% CI)			**254**	**167**	**100.0%**	**1.14 [0.56 , 2.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
7.6.3 Bronchitis						
Childress 2017	-1.1676	1.6188	44	41	100.0%	0.31 [0.01 , 7.43]
Subtotal (95% CI)			**44**	**41**	**100.0%**	**0.31 [0.01 , 7.43]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
7.6.4 Oropharyngeal pain						
Wigal 2017	1.9914	1.4967	42	44	100.0%	7.33 [0.39 , 137.67]
Subtotal (95% CI)			**42**	**44**	**100.0%**	**7.33 [0.39 , 137.67]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
7.6.5 Rhinorrhoea						
Wigal 2017	1.6549	1.5344	42	44	100.0%	5.23 [0.26 , 105.88]
Subtotal (95% CI)			**42**	**44**	**100.0%**	**5.23 [0.26 , 105.88]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
7.6.6 Allergic bronchitis						
Wigal 2017	1.1441	1.619	42	44	100.0%	3.14 [0.13 , 74.98]
Subtotal (95% CI)			**42**	**44**	**100.0%**	**3.14 [0.13 , 74.98]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.6.7 Sneezing						
Wigal 2017	1.1441	1.619	42	44	100.0%	3.14 [0.13 , 74.98]
Subtotal (95% CI)			**42**	**44**	**100.0%**	**3.14 [0.13 , 74.98]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.6.8 Nasal congestion						
Findling 2008	1.0521	1.1647	91	85	9.1%	2.86 [0.29 , 28.07]
Riggs 2011	0.0792	0.3793	151	152	86.1%	1.08 [0.51 , 2.28]
Wigal 2017	1.1441	1.619	42	44	4.7%	3.14 [0.13 , 74.98]
Subtotal (95% CI)			**284**	**281**	**100.0%**	**1.24 [0.62 , 2.48]**
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.53)						
7.6.9 Cough						
Childress 2017	1.0296	1.6188	44	41	5.0%	2.80 [0.12 , 66.85]
Coghill 2013	2.8987	1.4616	111	110	6.0%	18.15 [1.03 , 318.42]
Findling 2006	-0.3825	0.8834	133	46	13.2%	0.68 [0.12 , 3.85]
NCT00409708 (1)	1.3863	1.1007	52	52	9.5%	4.00 [0.46 , 34.59]
NCT02293655	2.6868	1.6135	18	92	5.0%	14.68 [0.62 , 346.96]
Newcorn 2008	-0.4102	0.6277	219	74	20.1%	0.66 [0.19 , 2.27]
Newcorn 2017a (flexible dose)	-1.7972	1.628	184	91	4.9%	0.17 [0.01 , 4.03]
Riggs 2011	-0.1868	0.3606	151	152	31.3%	0.83 [0.41 , 1.68]
Wigal 2017	1.1441	1.619	42	44	5.0%	3.14 [0.13 , 74.98]
Subtotal (95% CI)			**954**	**702**	**100.0%**	**1.31 [0.62 , 2.78]**
Heterogeneity: Tau² = 0.34; Chi² = 11.26, df = 8 (P = 0.19); I² = 29%						
Test for overall effect: Z = 0.70 (P = 0.49)						
7.6.10 Shortness of breath						
Childress 2017	0	0	44	41		Not estimable
Matthijssen 2019	1.0986	1.6202	47	47	100.0%	3.00 [0.13 , 71.82]
Subtotal (95% CI)			**91**	**88**	**100.0%**	**3.00 [0.13 , 71.82]**

Analysis 7.6. (Continued)

Childress 2017	0	0	44	41			Not estimable
Matthijssen 2019	1.0986	1.6202	47	47	100.0%	3.00 [0.13 , 71.82]	
Subtotal (95% CI)			**91**	**88**	**100.0%**	**3.00 [0.13 , 71.82]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Chi² = 0.00, df = 9 (P < 0.00001), I² = 0%

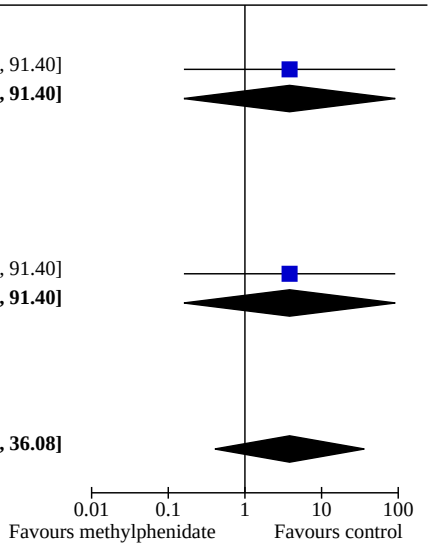


Footnotes
(1) Ritalin LA plus behaviour therapy versus behaviour therapy

Analysis 7.7. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 7: Urinary system

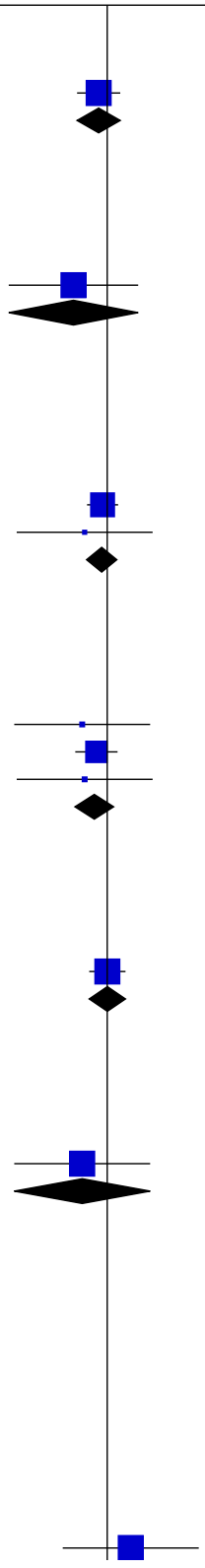
Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.7.1 Pollakiuria						
Childress 2020c	1	39	0	50	50.0%	3.83 [0.16 , 91.40]
Subtotal (95% CI)		**39**		**50**	**50.0%**	**3.83 [0.16 , 91.40]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
7.7.2 Urinary incontinence						
Childress 2020c	1	39	0	50	50.0%	3.83 [0.16 , 91.40]
Subtotal (95% CI)		**39**		**50**	**50.0%**	**3.83 [0.16 , 91.40]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
Total (95% CI)		**78**		**100**	**100.0%**	**3.83 [0.41 , 36.08]**
Total events:	2		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%



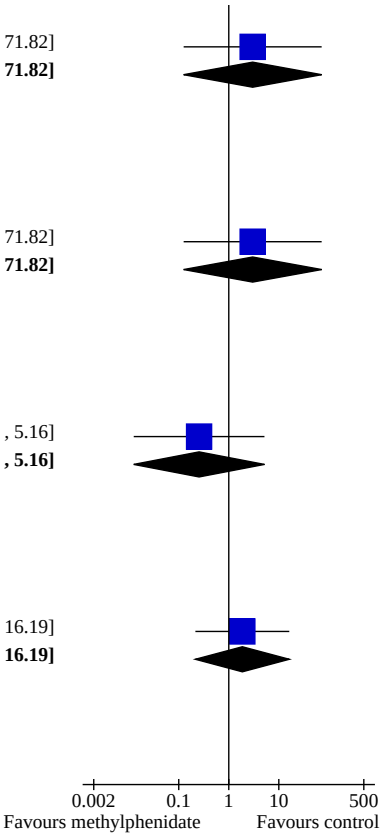
Analysis 7.8. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 8: Skeletal and muscular systems (including pain)

Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
7.8.1 Arthralgia						
Childress 2017	0	44	0	41		Not estimable
Riggs 2011	6	151	9	152	100.0%	0.67 [0.24 , 1.84]
Subtotal (95% CI)		**195**		**193**	**100.0%**	**0.67 [0.24 , 1.84]**
Total events:	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
7.8.2 Asthenia						
Wilens 2006b	0	87	2	90	100.0%	0.21 [0.01 , 4.25]
Subtotal (95% CI)		**87**		**90**	**100.0%**	**0.21 [0.01 , 4.25]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
7.8.3 Back pain						
Childress 2017	0	44	0	41		Not estimable
Riggs 2011	12	151	15	152	95.0%	0.81 [0.39 , 1.66]
Wigal 2017	0	42	1	44	5.0%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**237**		**237**	**100.0%**	**0.77 [0.38 , 1.57]**
Total events:	12		16			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 1 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 0.72 (P = 0.47)						
7.8.4 Myalgia						
Childress 2017	0	44	1	41	8.1%	0.31 [0.01 , 7.43]
Riggs 2011	6	151	10	152	83.8%	0.60 [0.23 , 1.62]
Wigal 2017	0	42	1	44	8.1%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**237**		**237**	**100.0%**	**0.55 [0.22 , 1.35]**
Total events:	6		12			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.24$, df = 2 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 1.31 (P = 0.19)						
7.8.5 Toothache						
Riggs 2011	10	151	10	152	100.0%	1.01 [0.43 , 2.35]
Subtotal (95% CI)		**151**		**152**	**100.0%**	**1.01 [0.43 , 2.35]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
7.8.6 Ligament strain						
Childress 2017	0	44	1	41	100.0%	0.31 [0.01 , 7.43]
Subtotal (95% CI)		**44**		**41**	**100.0%**	**0.31 [0.01 , 7.43]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
7.8.7 Muscle strain						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.8.8 Fractures						
Matthijssen 2019 (1)	1	47	0	47	100.0%	3.00 [0.13 , 71.82]



Analysis 7.8. (Continued)

7.8.8 Fractures						
Matthijssen 2019 (1)	1	47	0	47	100.0%	3.00 [0.13 , 71.82]
Subtotal (95% CI)		**47**		**47**	**100.0%**	**3.00 [0.13 , 71.82]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
7.8.9 Muscle cramps						
Matthijssen 2019 (1)	1	47	0	47	100.0%	3.00 [0.13 , 71.82]
Subtotal (95% CI)		**47**		**47**	**100.0%**	**3.00 [0.13 , 71.82]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
7.8.10 Pain in extremity						
Childress 2020c	0	39	2	50	100.0%	0.26 [0.01 , 5.16]
Subtotal (95% CI)		**39**		**50**	**100.0%**	**0.26 [0.01 , 5.16]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
7.8.11 Pain						
Wigal 2004	4	90	1	42	100.0%	1.87 [0.22 , 16.19]
Subtotal (95% CI)		**90**		**42**	**100.0%**	**1.87 [0.22 , 16.19]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						



Footnotes

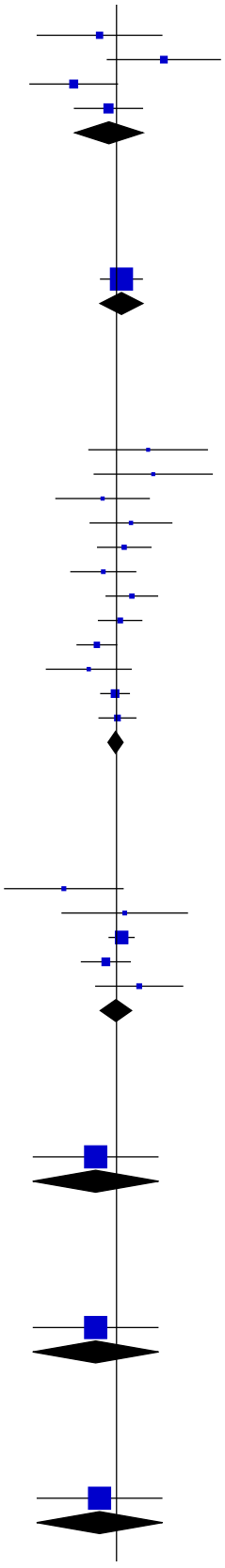
(1) Discontinuation study

Analysis 7.9. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 9: Immune system (including infections)

Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
7.9.1 Gastroenteritis						
Childress 2017	0	44	0	41		Not estimable
Coghill 2013	3	111	1	110	33.1%	2.97 [0.31 , 28.14]
Greenhill 2006	2	53	0	47	18.5%	4.44 [0.22 , 90.29]
Lin 2014	2	36	0	78	18.5%	10.68 [0.53 , 216.83]
Wigal 2017	1	42	2	44	30.0%	0.52 [0.05 , 5.56]
Subtotal (95% CI)		**286**		**320**	**100.0%**	**2.41 [0.66 , 8.78]**
Total events:	8		3			
Heterogeneity: Tau² = 0.00; Chi² = 2.73, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
7.9.2 Influenza						
Childress 2017	0	44	1	41	7.2%	0.31 [0.01 , 7.43]
Coghill 2013	3	111	0	110	8.3%	6.94 [0.36 , 132.75]
Greenhill 2006	2	53	4	47	25.3%	0.44 [0.09 , 2.31]
Riggs 2011	5	151	11	152	59.3%	0.46 [0.16 , 1.29]
Subtotal (95% CI)		**359**		**350**	**100.0%**	**0.55 [0.23 , 1.30]**
Total events:	10		16			
Heterogeneity: Tau² = 0.04; Chi² = 3.14, df = 3 (P = 0.37); I² = 5%						
Test for overall effect: Z = 1.36 (P = 0.18)						
7.9.3 Nasopharyngitis						
Childress 2017	0	44	1	41	1.6%	0.31 [0.01 , 7.43]
Coghill 2013	14	111	8	110	20.8%	1.73 [0.76 , 3.97]
Findling 2006	2	133	3	46	5.1%	0.23 [0.04 , 1.34]
Findling 2008	4	91	2	85	5.6%	1.87 [0.35 , 9.94]
Greenhill 2006	5	53	3	47	8.1%	1.48 [0.37 , 5.85]
Matthijssen 2019	0	47	1	47	1.6%	0.33 [0.01 , 7.98]
NCT00409708 (1)	4	52	4	52	8.6%	1.00 [0.26 , 3.79]
Newcorn 2017a (flexible dose)	13	184	1	91	3.9%	6.43 [0.85 , 48.39]
Riggs 2011	23	151	23	152	43.2%	1.01 [0.59 , 1.71]
Wigal 2017	0	42	1	44	1.6%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**908**		**715**	**100.0%**	**1.14 [0.76 , 1.70]**
Total events:	65		47			
Heterogeneity: Tau² = 0.02; Chi² = 9.46, df = 9 (P = 0.40); I² = 5%						
Test for overall effect: Z = 0.63 (P = 0.53)						
7.9.4 Otitis media						
Childress 2017	0	44	0	41		Not estimable
Greenhill 2006	2	53	1	47	64.2%	1.77 [0.17 , 18.94]
Wigal 2017	0	42	1	44	35.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**139**		**132**	**100.0%**	**0.99 [0.15 , 6.61]**
Total events:	2		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
7.9.5 Pharyngitis						
Childress 2017	0	44	0	41		Not estimable
Findling 2006	4	133	0	46	19.8%	3.16 [0.17 , 57.53]
Kollins 2021	2	74	0	76	18.3%	5.13 [0.25 , 105.15]
Lin 2014	2	36	2	78	45.3%	2.17 [0.32 , 14.78]
Wigal 2017	0	42	1	44	16.6%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**329**		**285**	**100.0%**	**2.02 [0.55 , 7.35]**
Total events:	8		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.29)						
7.9.6 Pyrexia						
Childress 2017	0	44	0	41		Not estimable
Childress 2020c	0	39	1	50	18.6%	0.42 [0.02 , 10.16]
Coghill 2013	5	111	0	110	20.9%	10.99 [0.61 , 194.82]

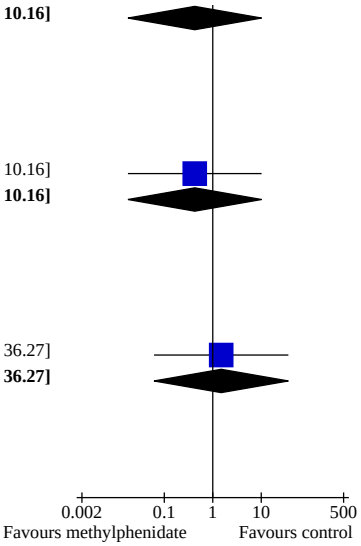
Analysis 7.9. (Continued)

Childress 2017	0	44	0	41		Not estimable
Childress 2020c	0	39	1	50	18.6%	0.42 [0.02 , 10.16]
Coghill 2013	5	111	0	110	20.9%	10.90 [0.61 , 194.82]
Findling 2006	1	133	3	46	27.3%	0.12 [0.01 , 1.08]
NCT00409708	2	52	3	52	33.2%	0.67 [0.12 , 3.83]
Subtotal (95% CI)		**379**		**299**	**100.0%**	**0.68 [0.12 , 3.81]**
Total events:	8		7			
Heterogeneity: Tau² = 1.53; Chi² = 6.03, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 0.44 (P = 0.66)						
7.9.7 Rhinitis						
Wigal 2004	11	90	4	42	100.0%	1.28 [0.43 , 3.79]
Subtotal (95% CI)		**90**		**42**	**100.0%**	**1.28 [0.43 , 3.79]**
Total events:	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
7.9.8 Upper respiratory tract infection - not otherwise specified (NOS)						
Childress 2020a	2	74	0	73	1.6%	4.93 [0.24 , 101.02]
Childress 2020c	2	39	0	50	1.6%	6.37 [0.31 , 129.08]
Coghill 2013	1	111	2	110	2.5%	0.50 [0.05 , 5.39]
Findling 2006	6	133	1	46	3.3%	2.08 [0.26 , 16.78]
Greenhill 2006	5	53	3	47	7.7%	1.48 [0.37 , 5.85]
Kollins 2021	2	74	4	76	5.2%	0.51 [0.10 , 2.72]
Lin 2014	4	36	4	78	8.2%	2.17 [0.57 , 8.18]
NCT00409708 (1)	6	52	5	52	11.5%	1.20 [0.39 , 3.69]
Newcorn 2017a (flexible dose)	6	184	8	91	13.7%	0.37 [0.13 , 1.04]
Pliszka 2017	1	81	4	80	3.1%	0.25 [0.03 , 2.16]
Riggs 2011	12	151	13	152	25.7%	0.93 [0.44 , 1.97]
Wigal 2017	7	42	7	44	15.8%	1.05 [0.40 , 2.73]
Subtotal (95% CI)		**1030**		**899**	**100.0%**	**0.95 [0.65 , 1.39]**
Total events:	54		51			
Heterogeneity: Tau² = 0.00; Chi² = 10.81, df = 11 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
7.9.9 Viral infection NOS						
Findling 2006	0	133	2	46	6.3%	0.07 [0.00 , 1.43]
Newcorn 2017b (forced dose)	1	219	0	110	5.7%	1.51 [0.06 , 36.85]
Riggs 2011	18	151	14	152	50.8%	1.29 [0.67 , 2.51]
Wigal 2004	5	90	4	42	26.2%	0.58 [0.17 , 2.06]
Wigal 2017	3	42	1	44	10.9%	3.14 [0.34 , 29.03]
Subtotal (95% CI)		**635**		**394**	**100.0%**	**0.97 [0.44 , 2.14]**
Total events:	27		21			
Heterogeneity: Tau² = 0.21; Chi² = 5.28, df = 4 (P = 0.26); I² = 24%						
Test for overall effect: Z = 0.07 (P = 0.94)						
7.9.10 Seasonal allergy						
Wigal 2017	0	42	1	44	100.0%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**100.0%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.9.11 Streptococcal impetigo						
Wigal 2017	0	42	1	44	100.0%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**100.0%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.9.12 Sinusitis						
Childress 2020c	0	39	1	50	100.0%	0.42 [0.02 , 10.16]
Subtotal (95% CI)		**39**		**50**	**100.0%**	**0.42 [0.02 , 10.16]**
Total events:	0		1			



Analysis 7.9. (Continued)

Subtotal (95% CI)		**39**		**50**	**100.0%**	**0.42 [0.02 , 10.16]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
7.9.13 Cellulitis						
Childress 2020c	0	39	1	50	100.0%	0.42 [0.02 , 10.16]
Subtotal (95% CI)		**39**		**50**	**100.0%**	**0.42 [0.02 , 10.16]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
7.9.14 Pleurisy						
Newcorn 2017a (flexible dose)	1	184	0	91	100.0%	1.49 [0.06 , 36.27]
Subtotal (95% CI)		**184**		**91**	**100.0%**	**1.49 [0.06 , 36.27]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.81)						

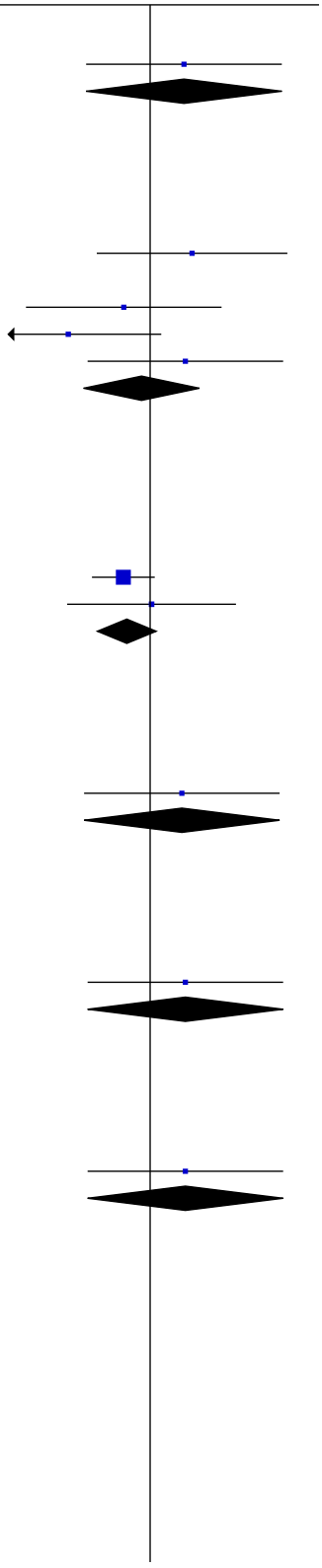


Footnotes

(1) Ritalin LA plus behaviour therapy versus behaviour therapy

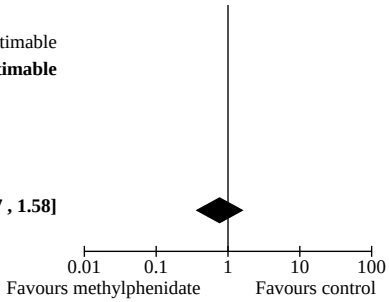
Analysis 7.10. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 10: Integumentary system

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo/No intervention Events	Placebo/No intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
7.10.1 Purple spots						
Matthijssen 2019	1	47	0	47	5.2%	3.00 [0.13 , 71.82]
Subtotal (95% CI)		**47**		**47**	**5.2%**	**3.00 [0.13 , 71.82]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
7.10.2 Skin disorder (rash)						
Carlson 2007	1	9	0	12	5.5%	3.90 [0.18 , 85.93]
Childress 2017	0	44	0	41		Not estimable
Childress 2020c	0	39	1	50	5.2%	0.42 [0.02 , 10.16]
Findling 2006	0	133	2	46	5.8%	0.07 [0.00 , 1.43]
Wigal 2017 (1)	1	42	0	44	5.2%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**267**		**193**	**21.7%**	**0.76 [0.12 , 4.96]**
Total events:	2		3			
Heterogeneity: Tau² = 1.16; Chi² = 4.38, df = 3 (P = 0.22); I² = 31%						
Test for overall effect: Z = 0.29 (P = 0.77)						
7.10.3 Skin laceration						
Childress 2017	0	44	0	41		Not estimable
Riggs 2011	5	151	12	152	50.5%	0.42 [0.15 , 1.16]
Wigal 2017	1	42	1	44	7.0%	1.05 [0.07 , 16.21]
Subtotal (95% CI)		**237**		**237**	**57.5%**	**0.47 [0.18 , 1.22]**
Total events:	6		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
7.10.4 Burns second degree						
Childress 2017	1	44	0	41	5.2%	2.80 [0.12 , 66.85]
Subtotal (95% CI)		**44**		**41**	**5.2%**	**2.80 [0.12 , 66.85]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
7.10.5 Burns first degree						
Wigal 2017	1	42	0	44	5.2%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**42**		**44**	**5.2%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.10.6 Subcutaneous haematoma						
Wigal 2017	1	42	0	44	5.2%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**42**		**44**	**5.2%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.10.7 Periorbital haematoma						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.10.8 Rash maculo-papular						
Childress 2017	0	44	0	41		Not estimable



Analysis 7.10. (Continued)

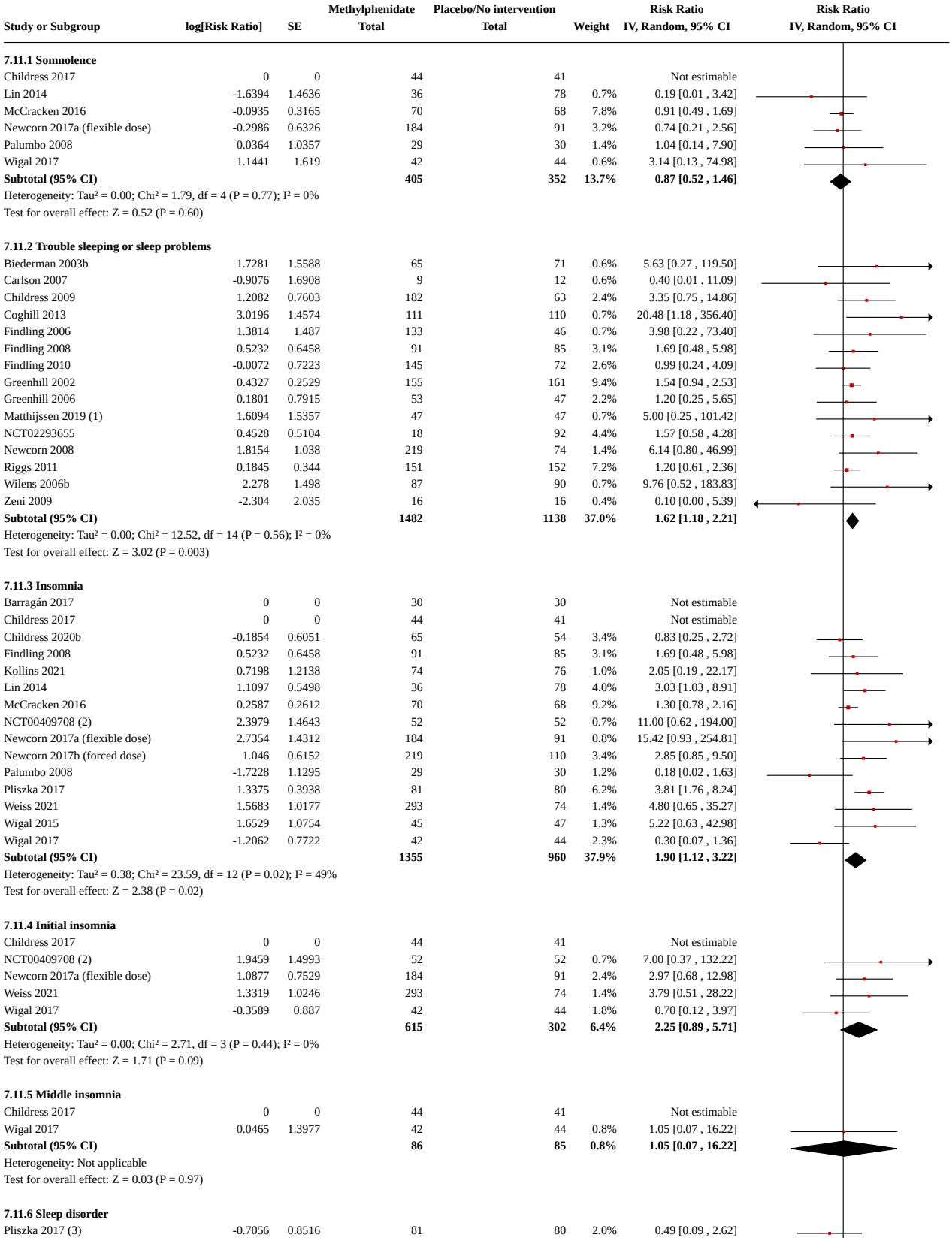
7.10.8 Rash maculo-papular						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**767**		**688**	**100.0%**	**0.76 [0.37 , 1.58]**
Total events:	12		16			
Heterogeneity: Tau² = 0.00; Chi² = 8.63, df = 9 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Chi² = 3.89, df = 5 (P = 0.57), I² = 0%						



Footnotes

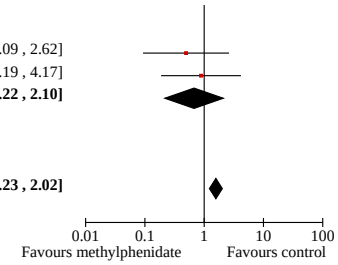
(1) Dermatitis contact

Analysis 7.11. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 11: Sleep variability



Analysis 7.11. (Continued)

7.11.6 Sleep disorder						
Pliszka 2017 (3)	-0.7056	0.8516	81	80	2.0%	0.49 [0.09 , 2.62]
Weiss 2021	-0.1233	0.7912	293	74	2.2%	0.88 [0.19 , 4.17]
Subtotal (95% CI)			**374**	**154**	**4.2%**	**0.67 [0.22 , 2.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)			**4317**	**2991**	**100.0%**	**1.57 [1.23 , 2.02]**
Heterogeneity: Tau² = 0.11; Chi² = 49.16, df = 39 (P = 0.13); I² = 21%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
Test for subgroup differences: Chi² = 7.85, df = 5 (P = 0.16), I² = 36.3%						



Footnotes

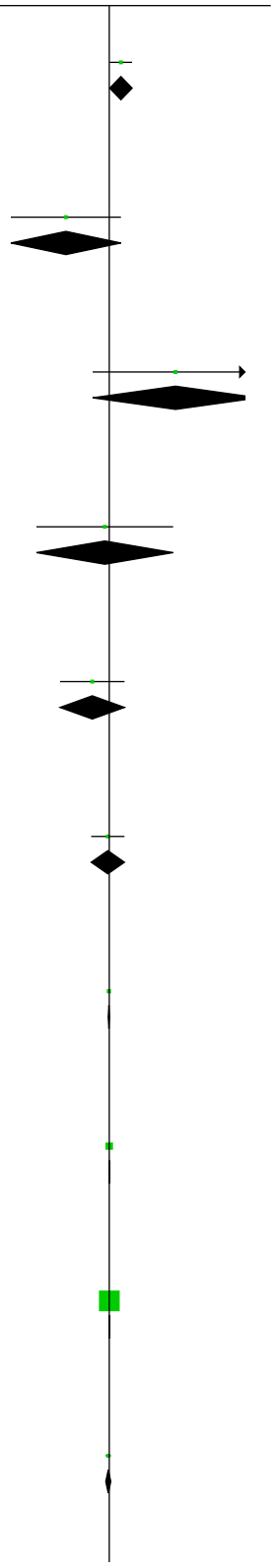
(1) Discontinuation study

(2) Ritalin LA plus behaviour therapy versus behaviour therapy

(3) Includes: Initial insomnia, Middle insomnia, Terminal insomnia and Insomnia, not specified.

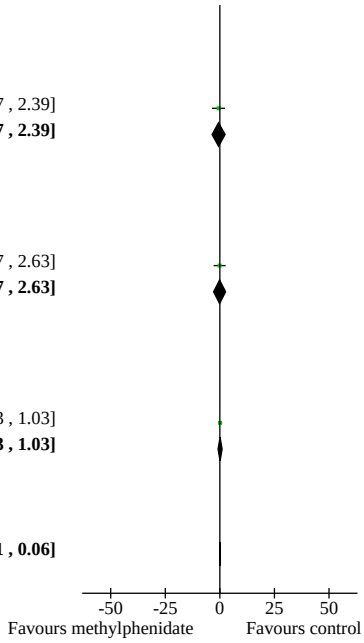
Analysis 7.12. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 12: Sleep variability continuous outcomes

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.12.1 Sleep efficiency after treatment discontinuation (percentage)								
Schrantee 2016	80.59	7.55	25	75.17	10.48	23	0.0%	5.42 [0.21 , 10.63]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**5.42 [0.21 , 10.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.04 (P = 0.04)								
7.12.2 Sleep onset latency (min)								
Schrantee 2016	31.98	34.79	25	52.14	52.95	23	0.0%	-20.16 [-45.74 , 5.42]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**-20.16 [-45.74 , 5.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.54 (P = 0.12)								
7.12.3 Total sleep time (min)								
Schrantee 2016	495.91	56.34	25	465.09	77.3	23	0.0%	30.82 [-7.73 , 69.37]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**30.82 [-7.73 , 69.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.57 (P = 0.12)								
7.12.4 Total in-bed time (min)								
Schrantee 2016	616.89	49.32	25	618.96	61.64	23	0.0%	-2.07 [-33.82 , 29.68]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**-2.07 [-33.82 , 29.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.13 (P = 0.90)								
7.12.5 Wake after sleep onset (min)								
Schrantee 2016	61.41	26.16	25	69.3	26.73	23	0.0%	-7.89 [-22.87 , 7.09]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**-7.89 [-22.87 , 7.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.03 (P = 0.30)								
7.12.6 Number of wake bouts								
Schrantee 2016	44.1	12.8	25	44.76	14.37	23	0.0%	-0.66 [-8.38 , 7.06]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**-0.66 [-8.38 , 7.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.87)								
7.12.7 Mean wake bout time (min)								
Schrantee 2016	1.39	0.5	25	1.56	0.55	23	1.5%	-0.17 [-0.47 , 0.13]
Subtotal (95% CI)			**25**			**23**	**1.5%**	**-0.17 [-0.47 , 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								
7.12.8 Interdaily stability								
Schrantee 2016	0.76	0.16	25	0.73	0.15	23	16.8%	0.03 [-0.06 , 0.12]
Subtotal (95% CI)			**25**			**23**	**16.8%**	**0.03 [-0.06 , 0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
7.12.9 Interdaily variability								
Schrantee 2016	0.38	0.08	25	0.35	0.06	23	81.5%	0.03 [-0.01 , 0.07]
Subtotal (95% CI)			**25**			**23**	**81.5%**	**0.03 [-0.01 , 0.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.48 (P = 0.14)								
7.12.10 Amount of activity during the 5 hours with the lowest activity								
Schrantee 2016	8.92	2.3	25	9.38	1.79	23	0.1%	-0.46 [-1.62 , 0.70]
Subtotal (95% CI)			**25**			**23**	**0.1%**	**-0.46 [-1.62 , 0.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.44)								



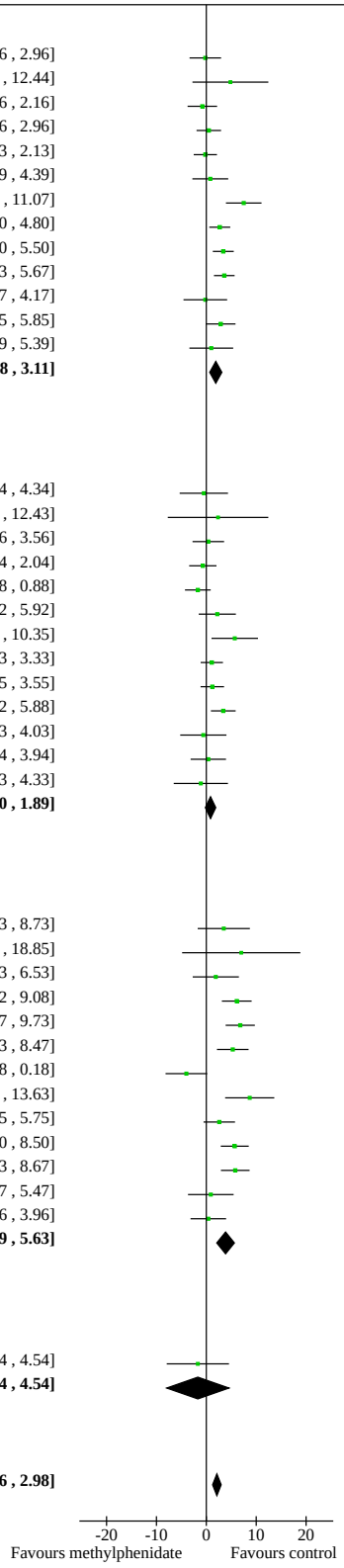
Analysis 7.12. (Continued)

Test for overall effect: Z = 0.78 (P = 0.44)								
7.12.11 Amount of activity during the 10 hours with the highest activity								
Schrantee 2016	53.37	5.65	25	53.96	4.89	23	0.0%	-0.59 [-3.57 , 2.39]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**-0.59 [-3.57 , 2.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.39 (P = 0.70)								
7.12.12 Amplitude of sleep-wake rhythm								
Schrantee 2016	44.46	5.09	25	44.58	4.64	23	0.0%	-0.12 [-2.87 , 2.63]
Subtotal (95% CI)			**25**			**23**	**0.0%**	**-0.12 [-2.87 , 2.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
7.12.13 Pittsburgh Sleep Quality Index (PSQI)								
Weiss 2021	5.5	3.4	293	5.4	3.7	74	0.1%	0.10 [-0.83 , 1.03]
Subtotal (95% CI)			**293**			**74**	**0.1%**	**0.10 [-0.83 , 1.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
Total (95% CI)			**593**			**350**	**100.0%**	**0.03 [-0.01 , 0.06]**
Heterogeneity: Chi² = 12.66, df = 12 (P = 0.39); I² = 5%								
Test for overall effect: Z = 1.46 (P = 0.14)								
Test for subgroup differences: Chi² = 12.66, df = 12 (P = 0.39), I² = 5.2%								



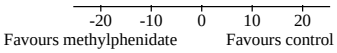
Analysis 7.13. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 13: Vital signs

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
7.13.1 Diastolic blood pressure (mmHg)								
Arnold 2004	0	7.1	35	0.2	6.8	40	2.8%	-0.20 [-3.36 , 2.96]
Carlson 2007	3	8.5	9	-1.83	7.5	8	1.0%	4.83 [-2.78 , 12.44]
Childress 2020b	5.1	8.1	65	5.9	8.27	54	2.9%	-0.80 [-3.76 , 2.16]
Coghill 2013	1.7	9.9	111	1.2	8.7	110	3.3%	0.50 [-1.96 , 2.96]
Jensen 1999 (MTA)	67.6	9.6	125	67.8	8.8	115	3.4%	-0.20 [-2.53 , 2.13]
Kollins 2006 (PATS)	61.8	8.4	61	61	10.8	53	2.5%	0.80 [-2.79 , 4.39]
McCracken 2016	3.7	9.9	70	-3.8	11.4	68	2.5%	7.50 [3.93 , 11.07]
Newcorn 2008	3.1	8.4	219	0.4	7.8	74	3.6%	2.70 [0.60 , 4.80]
Newcorn 2017a (flexible dose) (1)	2.2	8.64	184	-1.2	8.11	89	3.6%	3.40 [1.30 , 5.50]
Newcorn 2017b (forced dose) (1)	3.5	8.59	181	-0.1	8.1	93	3.6%	3.60 [1.53 , 5.67]
Palumbo 2008	0.1	10.3	29	0.3	6.3	30	2.1%	-0.20 [-4.57 , 4.17]
Pliszka 2017 (1)	2.5	9.06	81	-0.4	9.99	80	2.9%	2.90 [-0.05 , 5.85]
Van der Meere 1999a	69.5	5.3	24	68.5	9.6	24	2.1%	1.00 [-3.39 , 5.39]
Subtotal (95% CI)			**1194**			**838**	**36.3%**	**1.90 [0.68 , 3.11]**
Heterogeneity: Tau² = 2.50; Chi² = 26.24, df = 12 (P = 0.010); I² = 54%								
Test for overall effect: Z = 3.06 (P = 0.002)								
7.13.2 Systolic blood pressure (mmHg)								
Arnold 2004	2.6	11.6	35	3.1	9.5	40	1.9%	-0.50 [-5.34 , 4.34]
Carlson 2007	2.1	11.2	9	-0.25	10	8	0.6%	2.35 [-7.73 , 12.43]
Childress 2020b	6.3	9.32	65	5.9	8.27	54	2.8%	0.40 [-2.76 , 3.56]
Coghill 2013	0.3	11.1	111	1	9.6	110	3.1%	-0.70 [-3.44 , 2.04]
Jensen 1999 (MTA)	102.4	9.7	125	104.1	10.6	115	3.2%	-1.70 [-4.28 , 0.88]
Kollins 2006 (PATS)	101.6	9.4	61	99.4	10.7	53	2.4%	2.20 [-1.52 , 5.92]
McCracken 2016	3.5	14.1	70	-2.2	13.8	68	1.9%	5.70 [1.05 , 10.35]
Newcorn 2008	2.4	9.7	219	1.3	8	74	3.5%	1.10 [-1.13 , 3.33]
Newcorn 2017a (flexible dose) (1)	0.4	9.9	184	-0.8	8.97	89	3.4%	1.20 [-1.15 , 3.55]
Newcorn 2017b (forced dose) (1)	2.4	9.97	181	-1	9.88	93	3.3%	3.40 [0.92 , 5.88]
Palumbo 2008	-0.5	9.5	29	0.1	8.6	30	2.0%	-0.60 [-5.23 , 4.03]
Pliszka 2017 (1)	1.5	12.18	81	1.1	10.72	80	2.6%	0.40 [-3.14 , 3.94]
Van der Meere 1999a	103.9	9.5	24	105	9.7	24	1.6%	-1.10 [-6.53 , 4.33]
Subtotal (95% CI)			**1194**			**838**	**32.2%**	**0.85 [-0.20 , 1.89]**
Heterogeneity: Tau² = 0.75; Chi² = 15.26, df = 12 (P = 0.23); I² = 21%								
Test for overall effect: Z = 1.59 (P = 0.11)								
7.13.3 Pulse or heart rate (bpm)								
Arnold 2004	5.4	12.2	35	1.9	10.7	40	1.7%	3.50 [-1.73 , 8.73]
Carlson 2007	5	12.6	9	-2	12.3	8	0.5%	7.00 [-4.85 , 18.85]
Childress 2020b	1.7	11.12	65	-0.2	14.08	54	2.0%	1.90 [-2.73 , 6.53]
Coghill 2013	5	12.8	111	-1.1	9.6	110	2.9%	6.10 [3.12 , 9.08]
Findling 2010	5.1	12.53	143	-1.7	9.03	72	3.0%	6.80 [3.87 , 9.73]
Jensen 1999 (MTA)	84.2	12.4	128	78.9	12.9	118	2.8%	5.30 [2.13 , 8.47]
Kollins 2006 (PATS)	94.3	10.8	61	98.3	11.8	53	2.2%	-4.00 [-8.18 , 0.18]
McCracken 2016 (2)	4.6	16.7	70	-4.1	12.6	68	1.8%	8.70 [3.77 , 13.63]
Newcorn 2008	3	11.8	219	0.4	12	74	2.8%	2.60 [-0.55 , 5.75]
Newcorn 2017a (flexible dose) (1)	6	10.52	184	0.3	11.32	89	3.0%	5.70 [2.90 , 8.50]
Newcorn 2017b (forced dose) (1)	8.2	12.7	181	2.4	10.81	93	3.0%	5.80 [2.93 , 8.67]
Palumbo 2008	-0.3	10.3	29	-1.2	7.3	30	2.0%	0.90 [-3.67 , 5.47]
Pliszka 2017 (1)	3.5	11.49	81	3.1	11.58	80	2.5%	0.40 [-3.16 , 3.96]
Subtotal (95% CI)			**1316**			**889**	**30.2%**	**3.86 [2.09 , 5.63]**
Heterogeneity: Tau² = 6.36; Chi² = 33.96, df = 12 (P = 0.0007); I² = 65%								
Test for overall effect: Z = 4.29 (P < 0.0001)								
7.13.4 ECG: changes in QTcB								
McCracken 2016	-4.4	20.8	70	-2.7	16.4	68	1.3%	-1.70 [-7.94 , 4.54]
Subtotal (95% CI)			**70**			**68**	**1.3%**	**-1.70 [-7.94 , 4.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.59)								
Total (95% CI)			**3774**			**2633**	**100.0%**	**2.12 [1.26 , 2.98]**
Heterogeneity: Tau² = 4.28; Chi² = 101.23, df = 39 (P < 0.00001); I² = 61%								
Test for overall effect: Z = 4.82 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.57, df = 3 (P = 0.02), I² = 68.6%								



Analysis 7.13. (Continued)

Test for overall effect: Z = 4.82 (P < 0.00001)
Test for subgroup differences: Chi² = 9.57, df = 3 (P = 0.02), I² = 68.6%

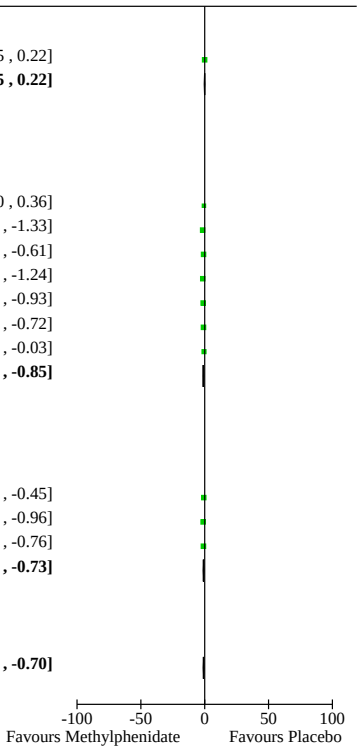


Footnotes
(1) Changes from baseline to EOT
(2) Changes in mean sitting pulse rate

Analysis 7.14. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 14: Physical parameters

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
7.14.1 Height								
Findling 2010	0.53	1.21	143	0.61	1.27	72	9.7%	-0.06 [-0.35 , 0.22]
Subtotal (95% CI)			**143**			**72**	**9.7%**	**-0.06 [-0.35 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.45 (P = 0.65)								
7.14.2 Weight								
Carlson 2007	-0.89	1.71	9	-0.05	0.47	8	4.5%	-0.62 [-1.60 , 0.36]
Coghill 2013	-1.3	1.4	111	0.7	1	110	9.6%	-1.64 [-1.94 , -1.33]
Findling 2010	-1.9	3.87	143	1.77	4.385	72	9.6%	-0.90 [-1.20 , -0.61]
Newcorn 2008	-0.9	1.3	219	1.1	1.3	74	9.7%	-1.53 [-1.83 , -1.24]
Newcorn 2017a (flexible dose) (1)	-1.34	2.133	184	1.14	1.884	89	9.8%	-1.20 [-1.48 , -0.93]
Newcorn 2017b (forced dose)	-1.07	2.259	216	0.95	1.728	106	10.0%	-0.96 [-1.20 , -0.72]
Palumbo 2008	0.3	2.3	29	1.4	1.6	30	7.7%	-0.55 [-1.07 , -0.03]
Subtotal (95% CI)			**911**			**489**	**60.8%**	**-1.13 [-1.40 , -0.85]**
Heterogeneity: Tau² = 0.10; Chi² = 27.68, df = 6 (P = 0.0001); I² = 78%								
Test for overall effect: Z = 7.97 (P < 0.00001)								
7.14.3 BMI								
Findling 2010	-0.29	0.763	143	0.31	0.883	72	9.7%	-0.74 [-1.03 , -0.45]
Newcorn 2017a (flexible dose) (1)	-0.47	0.747	184	0.44	0.715	89	9.8%	-1.23 [-1.51 , -0.96]
Newcorn 2017b (forced dose)	-0.4	0.785	216	0.34	0.629	106	10.0%	-1.00 [-1.25 , -0.76]
Subtotal (95% CI)			**543**			**267**	**29.4%**	**-1.00 [-1.26 , -0.73]**
Heterogeneity: Tau² = 0.04; Chi² = 5.74, df = 2 (P = 0.06); I² = 65%								
Test for overall effect: Z = 7.40 (P < 0.00001)								
Total (95% CI)			**1597**			**828**	**100.0%**	**-0.97 [-1.24 , -0.70]**
Heterogeneity: Tau² = 0.17; Chi² = 83.32, df = 10 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 7.09 (P < 0.00001)								
Test for subgroup differences: Chi² = 32.91, df = 2 (P < 0.00001), I² = 93.9%								

Std. Mean Difference
IV, Random, 95% CI



Footnotes
(1) Change from baseline to EOT

Analysis 7.15. Comparison 7: Non-serious adverse events: parallel-group trials and first-period cross-over trials, Outcome 15: Other (including drug toxicity)

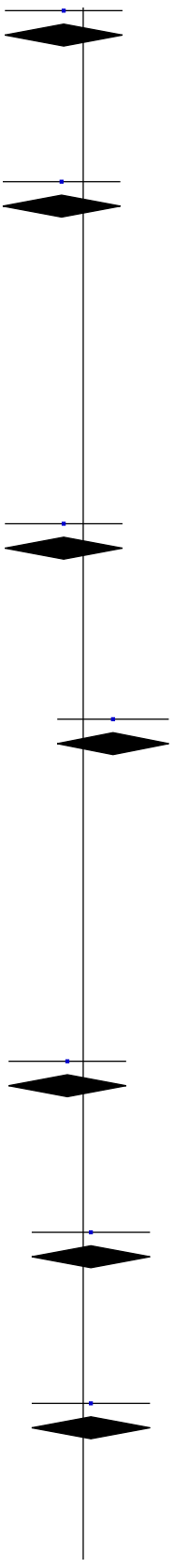
Study or Subgroup	Methylphenidate Events	Total	Placebo/No intervention Events	Total	Weight	Risk Ratio IV, Random, 95% CI
7.15.1 Accidental injury						
Coghill 2013	4	111	1	110	3.8%	3.96 [0.45 , 34.90]
Riggs 2011	7	151	9	152	19.6%	0.78 [0.30 , 2.05]
Wigal 2004	6	90	3	42	10.1%	0.93 [0.25 , 3.55]
Subtotal (95% CI)		**352**		**304**	**33.5%**	**0.99 [0.48 , 2.07]**
Total events:	17		13			
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.99)						
7.15.2 Excoriation						
Riggs 2011	14	151	4	152	15.3%	3.52 [1.19 , 10.46]
Wigal 2017	2	42	1	44	3.2%	2.10 [0.20 , 22.26]
Subtotal (95% CI)		**193**		**196**	**18.5%**	**3.22 [1.20 , 8.64]**
Total events:	16		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
7.15.3 Overdose						
Coghill 2013	1	111	0	110	1.8%	2.97 [0.12 , 72.20]
Subtotal (95% CI)		**111**		**110**	**1.8%**	**2.97 [0.12 , 72.20]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
7.15.4 Arthropod-bite						
Childress 2017	0	44	0	41		Not estimable
Wigal 2017	0	42	1	44	1.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**86**		**85**	**1.8%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.15.5 Contusion						
Wigal 2017	0	42	4	44	2.2%	0.12 [0.01 , 2.10]
Subtotal (95% CI)		**42**		**44**	**2.2%**	**0.12 [0.01 , 2.10]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
7.15.6 Wound						
Childress 2017	1	44	0	41	1.8%	2.80 [0.12 , 66.85]
Wigal 2017	0	42	2	44	2.0%	0.21 [0.01 , 4.24]
Subtotal (95% CI)		**86**		**85**	**3.8%**	**0.73 [0.06 , 9.22]**
Total events:	1		2			
Heterogeneity: Tau² = 0.88; Chi² = 1.35, df = 1 (P = 0.24); I² = 26%						
Test for overall effect: Z = 0.25 (P = 0.81)						
7.15.7 Tinnitus						
Wigal 2017	2	42	0	44	2.0%	5.23 [0.26 , 105.89]
Subtotal (95% CI)		**42**		**44**	**2.0%**	**5.23 [0.26 , 105.89]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
7.15.8 Dry eye						
Childress 2017	0	44	0	41		Not estimable
Wigal 2017	1	42	0	44	1.8%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**86**		**85**	**1.8%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						

Analysis 7.15. (Continued)

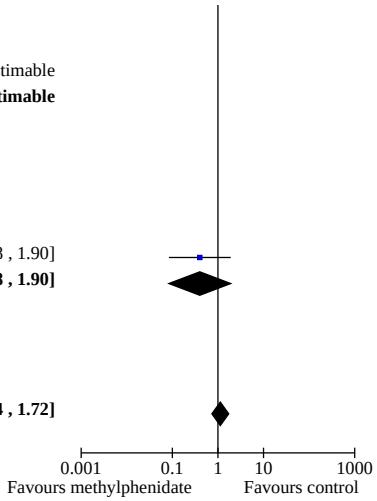
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.15.9 Excessive eye blinking						
Wigal 2017	0	42	1	44	1.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.15.10 Occular hyperaemia						
Wigal 2017	0	42	1	44	1.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.15.11 Visual impairment						
Wigal 2017	1	42	0	44	1.8%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.15.12 Red eyes						
Matthijssen 2019	0	47	1	47	1.8%	0.33 [0.01 , 7.98]
Subtotal (95% CI)		**47**		**47**	**1.8%**	**0.33 [0.01 , 7.98]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
7.15.13 Conjunctival abrasion						
Wigal 2017	1	42	0	44	1.8%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.15.14 Radius fracture						
Wigal 2017	1	42	0	44	1.8%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.15.15 Snake bite						
Wigal 2017	1	42	0	44	1.8%	3.14 [0.13 , 74.98]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**3.14 [0.13 , 74.98]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
7.15.16 Enuresis						
Wigal 2017	0	42	1	44	1.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.15.17 Night sweats						
Wigal 2017	0	42	1	44	1.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			

Analysis 7.15. (Continued)

Wigal 2017	0	42	1	44	1.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.15.18 Abnormal liver function test						
Childress 2017	0	44	1	41	1.8%	0.31 [0.01 , 7.43]
Subtotal (95% CI)		**44**		**41**	**1.8%**	**0.31 [0.01 , 7.43]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
7.15.19 Alopecia						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.15.20 Nail injury						
Wigal 2017	0	42	1	44	1.8%	0.35 [0.01 , 8.33]
Subtotal (95% CI)		**42**		**44**	**1.8%**	**0.35 [0.01 , 8.33]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.15.21 Itching						
Childress 2017	0	44	0	41		Not estimable
Matthijssen 2019	2	47	0	47	2.0%	5.00 [0.25 , 101.43]
Subtotal (95% CI)		**91**		**88**	**2.0%**	**5.00 [0.25 , 101.43]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
7.15.22 Ear pain						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.15.23 Corneal injury						
Childress 2020c	0	39	1	50	1.8%	0.42 [0.02 , 10.16]
Subtotal (95% CI)		**39**		**50**	**1.8%**	**0.42 [0.02 , 10.16]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
7.15.24 Wrist fracture						
Newcorn 2017b (forced dose)	1	219	0	110	1.8%	1.51 [0.06 , 36.85]
Subtotal (95% CI)		**219**		**110**	**1.8%**	**1.51 [0.06 , 36.85]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
7.15.25 Dysmennorhea						
Newcorn 2017b (forced dose)	1	219	0	110	1.8%	1.51 [0.06 , 36.85]
Subtotal (95% CI)		**219**		**110**	**1.8%**	**1.51 [0.06 , 36.85]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
7.15.26 Myopia						



Analysis 7.15. (Continued)



7.15.26 Myopia						
Childress 2017	0	44	0	41		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.15.27 Other AEs unspecified						
Barragán 2017	2	30	5	30	7.4%	0.40 [0.08 , 1.90]
Subtotal (95% CI)		**30**		**30**	**7.4%**	**0.40 [0.08 , 1.90]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**2197**		**1948**	**100.0%**	**1.13 [0.74 , 1.72]**
Total events:	48		38			
Heterogeneity: Tau² = 0.00; Chi² = 21.05, df = 27 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Chi² = 17.69, df = 23 (P = 0.77), I² = 0%						

Comparison 8. Non-serious adverse events: cross-over trials (endpoint data)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Proportion of participants with non-serious events	24	2696	Risk Ratio (IV, Random, 95% CI)	1.39 [1.13, 1.70]
8.2 Subgroup analysis: total number of non-serious adverse events according to dose	24	3483	Risk Ratio (IV, Random, 95% CI)	1.31 [1.12, 1.53]
8.2.1 Low dose	16	1539	Risk Ratio (IV, Random, 95% CI)	1.11 [0.94, 1.31]
8.2.2 High dose	12	1080	Risk Ratio (IV, Random, 95% CI)	1.57 [1.22, 2.01]
8.2.3 Unknown dose	5	864	Risk Ratio (IV, Random, 95% CI)	1.50 [0.88, 2.56]
8.3 Nervous system (including psychiatry)	52		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.3.1 Aggression	3	743	Risk Ratio (IV, Random, 95% CI)	0.52 [0.17, 1.60]
8.3.2 Agitation	2	273	Risk Ratio (IV, Random, 95% CI)	1.93 [0.37, 10.16]
8.3.3 Anger	3	264	Risk Ratio (IV, Random, 95% CI)	0.45 [0.26, 0.77]
8.3.4 Behavioural complaints	1	82	Risk Ratio (IV, Random, 95% CI)	0.55 [0.35, 0.86]
8.3.5 Buccal or lingual movements	5	569	Risk Ratio (IV, Random, 95% CI)	1.12 [0.81, 1.55]
8.3.6 Compulsive acts	1	90	Risk Ratio (IV, Random, 95% CI)	2.57 [1.45, 4.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3.7 Daydreaming	3	222	Risk Ratio (IV, Random, 95% CI)	0.66 [0.44, 0.98]
8.3.8 Dizziness	12	2163	Risk Ratio (IV, Random, 95% CI)	1.06 [0.91, 1.23]
8.3.9 Drowsiness: dull, tired, listless or sleepy	24	3011	Risk Ratio (IV, Random, 95% CI)	0.98 [0.80, 1.20]
8.3.10 Euphoria	7	1457	Risk Ratio (IV, Random, 95% CI)	0.97 [0.72, 1.31]
8.3.11 Headache	43	5981	Risk Ratio (IV, Random, 95% CI)	1.25 [1.06, 1.48]
8.3.12 Thirst	1	211	Risk Ratio (IV, Random, 95% CI)	2.78 [0.11, 69.04]
8.3.13 Irritability	27	4110	Risk Ratio (IV, Random, 95% CI)	0.97 [0.74, 1.27]
8.3.14 Nightmares	11	1738	Risk Ratio (IV, Random, 95% CI)	1.00 [0.73, 1.35]
8.3.15 Overly meticulous	1	96	Risk Ratio (IV, Random, 95% CI)	40.77 [2.35, 706.72]
8.3.16 Obsessive thinking	1	90	Risk Ratio (IV, Random, 95% CI)	2.35 [1.53, 3.62]
8.3.17 Picking at skin or fingers, nail biting, lip or cheek chewing	18	2549	Risk Ratio (IV, Random, 95% CI)	1.04 [0.86, 1.25]
8.3.18 Repetitive language	1	48	Risk Ratio (IV, Random, 95% CI)	1.00 [0.32, 3.10]
8.3.19 Sad, tearful or depressed	26	3510	Risk Ratio (IV, Random, 95% CI)	1.15 [0.96, 1.37]
8.3.20 Socially withdrawn - decreased interaction with others	15	2432	Risk Ratio (IV, Random, 95% CI)	1.36 [0.95, 1.95]
8.3.21 Stares a lot	11	2110	Risk Ratio (IV, Random, 95% CI)	1.04 [0.83, 1.31]
8.3.22 Tics or nervous movements	24	3429	Risk Ratio (IV, Random, 95% CI)	1.23 [1.02, 1.50]
8.3.23 Unusual blinking	1	48	Risk Ratio (IV, Random, 95% CI)	3.13 [0.12, 80.68]
8.3.24 Worried or anxious	23	3366	Risk Ratio (IV, Random, 95% CI)	0.85 [0.66, 1.11]
8.3.25 Fatique	1	211	Risk Ratio (IV, Random, 95% CI)	4.59 [0.22, 94.57]
8.3.26 Emotional lability	1	154	Risk Ratio (IV, Random, 95% CI)	9.25 [2.24, 38.22]
8.3.27 Dysphoria	1	154	Risk Ratio (IV, Random, 95% CI)	4.63 [0.23, 94.88]
8.3.28 Moody	1	211	Risk Ratio (IV, Random, 95% CI)	4.59 [0.22, 94.57]
8.3.29 Uninterested	1	1052	Risk Ratio (IV, Random, 95% CI)	1.20 [0.82, 1.75]
8.3.30 Prone to crying	1	1052	Risk Ratio (IV, Random, 95% CI)	1.72 [1.04, 2.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.4 Nervous system (including psychiatry) continuous outcomes	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-3.56, 1.96]
8.4.1 Anxiety	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-3.56, 1.96]
8.5 Digestive system	48		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.5.1 Decreased appetite or loss of appetite	41	6091	Risk Ratio (IV, Random, 95% CI)	3.89 [2.76, 5.48]
8.5.2 Diarrhoea	5	767	Risk Ratio (IV, Random, 95% CI)	0.95 [0.38, 2.34]
8.5.3 Dry mouth	6	496	Risk Ratio (IV, Random, 95% CI)	1.32 [0.59, 2.97]
8.5.4 Dyspepsia	1	62	Risk Ratio (IV, Random, 95% CI)	0.22 [0.02, 2.14]
8.5.5 Nausea	11	1182	Risk Ratio (IV, Random, 95% CI)	1.67 [1.13, 2.46]
8.5.6 Increased appetite	1	136	Risk Ratio (IV, Random, 95% CI)	0.20 [0.08, 0.50]
8.5.7 Stomach ache (abdominal pain)	38	5803	Risk Ratio (IV, Random, 95% CI)	1.70 [1.35, 2.15]
8.5.8 Vomiting	7	1278	Risk Ratio (IV, Random, 95% CI)	2.47 [0.82, 7.47]
8.5.9 Upper abdominal pain	1	107	Risk Ratio (IV, Random, 95% CI)	442413.39 [0.00, 29402595731294690000000000000
8.5.10 Decreased weight	2	365	Risk Ratio (IV, Random, 95% CI)	5.04 [0.59, 43.15]
8.5.11 Gastrointestinal distress	1	77	Risk Ratio (IV, Random, 95% CI)	8103.08 [0.00, 10110527023718684000000000000
8.5.12 Constipation	1	154	Risk Ratio (IV, Random, 95% CI)	4.63 [0.23, 94.88]
8.5.13 Oropharyngeal pain	1	211	Risk Ratio (IV, Random, 95% CI)	2.72 [0.00, 11653710777400273000000000000
8.5.14 Anorexia	1	203	Risk Ratio (IV, Random, 95% CI)	2.97 [0.61, 14.37]
8.6 Cardiovascular system	2	730	Risk Ratio (M-H, Random, 95% CI)	4.97 [1.09, 22.76]
8.6.1 Epistaxis	1	154	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.11, 67.14]
8.6.2 Heart palpitations	2	365	Risk Ratio (M-H, Random, 95% CI)	5.65 [0.67, 47.90]
8.6.3 Chest pain	1	211	Risk Ratio (M-H, Random, 95% CI)	6.43 [0.34, 123.02]
8.7 Respiratory system	2	673	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.36, 4.68]
8.7.1 Nasal congestion	1	154	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.06, 14.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.7.2 Strep throat/sore throat	1	154	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.30, 26.09]
8.7.3 Cough	1	154	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.04, 5.00]
8.7.4 Dyspnea	1	211	Risk Ratio (M-H, Random, 95% CI)	2.76 [0.11, 66.91]
8.8 Urinary system	1	136	Risk Ratio (IV, Random, 95% CI)	0.50 [0.05, 5.39]
8.8.1 Urinary incontinence	1	136	Risk Ratio (IV, Random, 95% CI)	0.50 [0.05, 5.39]
8.9 Skeletal and muscular system	2	673	Risk Ratio (M-H, Random, 95% CI)	4.86 [0.83, 28.54]
8.9.1 Ankle pain/strain	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.9.2 Muscle strain/pain	1	154	Risk Ratio (M-H, Random, 95% CI)	12.04 [0.69, 210.03]
8.9.3 Toe fracture	1	154	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.11, 67.14]
8.9.4 Asthenia	1	211	Risk Ratio (M-H, Random, 95% CI)	2.76 [0.11, 66.91]
8.10 Skeletal and muscular system continuous outcomes	1	82	Mean Difference (IV, Random, 95% CI)	0.85 [0.79, 0.91]
8.10.1 Somatic complaints	1	82	Mean Difference (IV, Random, 95% CI)	0.85 [0.79, 0.91]
8.11 Immune system (including infections)	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.11.1 Allergic rhinitis	4	475	Risk Ratio (IV, Random, 95% CI)	1.38 [0.35, 5.51]
8.11.2 Fever	2	91	Risk Ratio (IV, Random, 95% CI)	1.39 [0.09, 20.56]
8.11.3 Lymphadenitis	2	296	Risk Ratio (IV, Random, 95% CI)	3.93 [0.44, 35.11]
8.11.4 Pharyngolaryngeal pain	1	160	Risk Ratio (IV, Random, 95% CI)	2.00 [0.19, 21.62]
8.11.5 Pharyngitis	4	754	Risk Ratio (IV, Random, 95% CI)	0.71 [0.19, 2.62]
8.11.6 Upper respiratory tract infection	7	1245	Risk Ratio (IV, Random, 95% CI)	1.21 [0.51, 2.86]
8.11.7 Nasopharyngitis	1	203	Risk Ratio (IV, Random, 95% CI)	0.79 [0.22, 2.87]
8.11.8 Influenza	1	154	Risk Ratio (IV, Random, 95% CI)	4.63 [0.23, 94.87]
8.11.9 Mouth ulcers/bad breath	1	154	Risk Ratio (IV, Random, 95% CI)	4.63 [0.23, 94.87]
8.11.10 Urinary tract infection	1	154	Risk Ratio (IV, Random, 95% CI)	2.78 [0.11, 67.14]

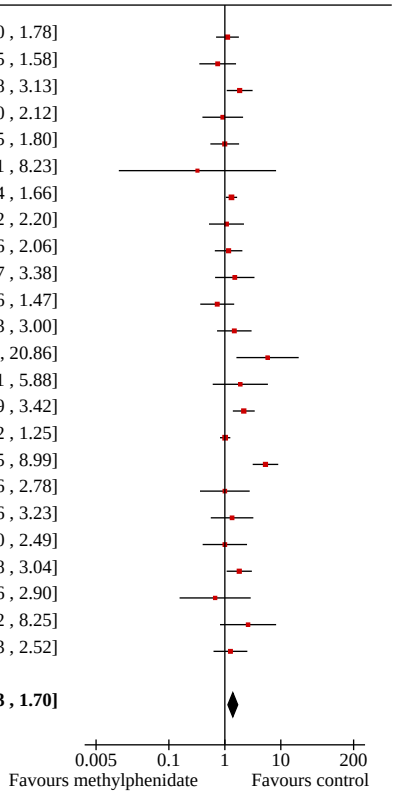
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.11.11 Otitis media (ear pain)	1	0	Risk Ratio (IV, Random, 95% CI)	Not estimable
8.12 Integumentary system	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.12.1 Rash	3	362	Risk Ratio (IV, Random, 95% CI)	1.49 [0.35, 6.37]
8.12.2 Skin laceration	1	167	Risk Ratio (IV, Random, 95% CI)	2.96 [0.12, 71.75]
8.12.3 Cellulitis	1	154	Risk Ratio (IV, Random, 95% CI)	2.78 [0.11, 67.14]
8.13 Sleep variability continuous outcomes	1	512	Mean Difference (IV, Fixed, 95% CI)	-2.21 [-5.23, 0.81]
8.13.1 Actigraphic total sleep time	1	52	Mean Difference (IV, Fixed, 95% CI)	-29.80 [-60.86, 1.26]
8.13.2 Actigraphic sleep onset latency	1	52	Mean Difference (IV, Fixed, 95% CI)	21.10 [1.33, 40.87]
8.13.3 Actigraphic sleep efficiency	1	52	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-8.16, 1.56]
8.13.4 Polysonmnographic total sleep time	1	252	Mean Difference (IV, Fixed, 95% CI)	-24.60 [-52.20, 3.00]
8.13.5 Polysomnographic sleep onset latency	1	52	Mean Difference (IV, Fixed, 95% CI)	8.40 [-7.11, 23.91]
8.13.6 Polysomnographic sleep efficiency	1	52	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-6.34, 1.94]
8.14 Sleep variability	39	5810	Risk Ratio (IV, Random, 95% CI)	1.81 [1.34, 2.44]
8.14.1 Insomnia or sleep problems	37	5499	Risk Ratio (IV, Random, 95% CI)	1.88 [1.39, 2.56]
8.14.2 Sleep efficiency (SEF)	2	108	Risk Ratio (IV, Random, 95% CI)	0.48 [0.02, 14.28]
8.14.3 Initial insomnia	1	203	Risk Ratio (IV, Random, 95% CI)	0.59 [0.15, 2.42]
8.15 Vital signs	14		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.15.1 Diastolic blood pressure (mmHg)	11	755	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.04, 0.34]
8.15.2 Systolic blood pressure (mmHg)	11	755	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.15, 0.26]
8.15.3 Pulse or heart rate (bpm)	14	939	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.23, 0.64]
8.16 Physical parameters	6	576	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.20, 0.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.16.1 Height (cm)	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.38, 0.78]
8.16.2 Weight	6	530	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.23, 0.11]
8.17 Other (including drug toxicity)	2	1443	Risk Ratio (M-H, Random, 95% CI)	3.25 [0.99, 10.62]
8.17.1 Growth hormone deficiency	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.17.2 Eye pain	1	154	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.11, 67.14]
8.17.3 Carious teeth	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.17.4 Foreign body swallowed	1	154	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.11, 67.14]
8.17.5 Bug bites/bee stings	1	154	Risk Ratio (M-H, Random, 95% CI)	4.63 [0.23, 94.87]
8.17.6 Sunburn	1	154	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.11, 67.14]
8.17.7 Finger laceration	1	154	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.11, 67.14]
8.17.8 Flat affect (lack of emotional expression)	1	154	Risk Ratio (M-H, Random, 95% CI)	4.63 [0.23, 94.87]
8.17.9 Peripheral oedema	1	211	Risk Ratio (M-H, Random, 95% CI)	2.76 [0.11, 66.91]

Analysis 8.1. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 1: Proportion of participants with non-serious events

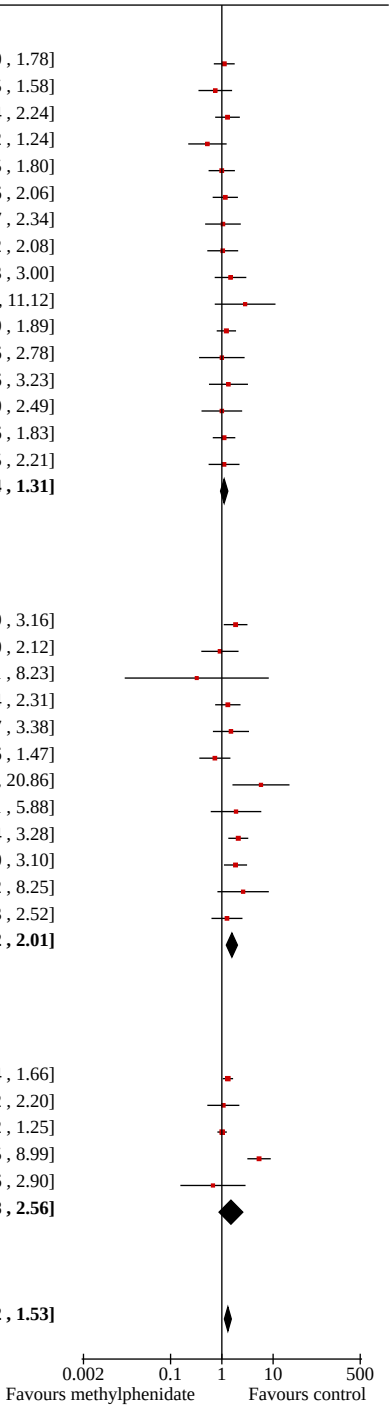
Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Barkley 2000	0.1084	0.2392	35	35	5.9%	1.11 [0.70 , 1.78]
Brams 2008	-0.2944	0.3851	86	86	3.9%	0.74 [0.35 , 1.58]
Brams 2012	0.6095	0.2714	162	159	5.4%	1.84 [1.08 , 3.13]
Brown 1988	-0.086	0.4266	11	11	3.5%	0.92 [0.40 , 2.12]
Brown 1991	-0.0044	0.3015	22	22	5.0%	1.00 [0.55 , 1.80]
Cox 2006	-1.1272	1.6504	35	35	0.4%	0.32 [0.01 , 8.23]
CRIT124US02	0.273	0.1184	102	101	7.9%	1.31 [1.04 , 1.66]
Döpfner 2004	0.0673	0.3669	82	82	4.1%	1.07 [0.52 , 2.20]
DuPaul 1996	0.1544	0.2891	24	24	5.2%	1.17 [0.66 , 2.06]
Fine 1993	0.4089	0.4133	12	12	3.6%	1.51 [0.67 , 3.38]
Kolko 1999	-0.3132	0.356	16	16	4.3%	0.73 [0.36 , 1.47]
McGough 2006	0.3895	0.3622	80	80	4.2%	1.48 [0.73 , 3.00]
Muniz 2008	1.7574	0.6534	84	83	1.9%	5.80 [1.61 , 20.86]
Murray 2011	0.6366	0.5792	67	67	2.3%	1.89 [0.61 , 5.88]
Musten 1997	0.779	0.2295	41	41	6.1%	2.18 [1.39 , 3.42]
NCT02039908	0.0126	0.1082	138	129	8.0%	1.01 [0.82 , 1.25]
NCT02536105	1.6712	0.268	80	74	5.5%	5.32 [3.15 , 8.99]
Quinn 2004	0	0.5215	31	31	2.7%	1.00 [0.36 , 2.78]
Silva 2006	0.2973	0.4466	54	54	3.3%	1.35 [0.56 , 3.23]
Silva 2008	0	0.4657	68	68	3.1%	1.00 [0.40 , 2.49]
Solanto 2009	0.5932	0.2642	30	30	5.5%	1.81 [1.08 , 3.04]
Taylor 1987	-0.3991	0.7464	38	38	1.6%	0.67 [0.16 , 2.90]
Wigal 2013	0.9555	0.5889	44	44	2.3%	2.60 [0.82 , 8.25]
Zeni 2009	0.2302	0.3549	16	16	4.3%	1.26 [0.63 , 2.52]
Total (95% CI)			**1358**	**1338**	**100.0%**	**1.39 [1.13 , 1.70]**

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 57.55$, df = 23 ($P < 0.0001$); $I^2 = 60\%$
Test for overall effect: Z = 3.19 (P = 0.001)
Test for subgroup differences: Not applicable



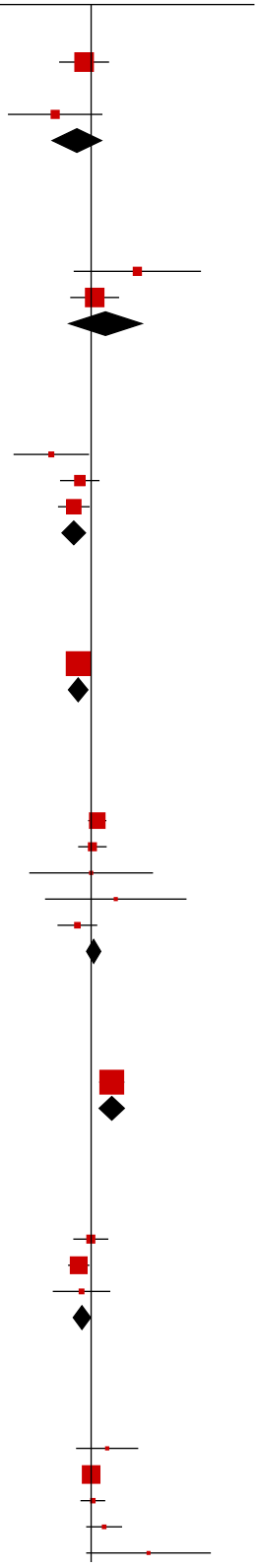
Analysis 8.2. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 2: Subgroup analysis: total number of non-serious adverse events according to dose

Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
8.2.1 Low dose						
Barkley 2000	0.1084	0.2392	35	35	4.4%	1.11 [0.70 , 1.78]
Brams 2008	-0.2944	0.3851	86	86	2.7%	0.74 [0.35 , 1.58]
Brams 2012	0.2542	0.2825	162	159	3.8%	1.29 [0.74 , 2.24]
Brown 1988	-0.6469	0.4398	11	11	2.2%	0.52 [0.22 , 1.24]
Brown 1991	-0.0044	0.3015	22	22	3.6%	1.00 [0.55 , 1.80]
DuPaul 1996	0.1544	0.2891	24	24	3.7%	1.17 [0.66 , 2.06]
Fine 1993	0.0501	0.4083	12	12	2.5%	1.05 [0.47 , 2.34]
Kolko 1999	0.0398	0.3536	16	16	3.0%	1.04 [0.52 , 2.08]
McGough 2006	0.3895	0.3622	80	80	2.9%	1.48 [0.73 , 3.00]
Muniz 2008	1.0454	0.6958	83	83	1.1%	2.84 [0.73 , 11.12]
Musten 1997	0.2035	0.2215	41	41	4.7%	1.23 [0.79 , 1.89]
Quinn 2004	0	0.5215	31	31	1.8%	1.00 [0.36 , 2.78]
Silva 2006	0.2973	0.4466	54	54	2.2%	1.35 [0.56 , 3.23]
Silva 2008	0	0.4657	68	68	2.1%	1.00 [0.40 , 2.49]
Solanto 2009	0.0982	0.2584	30	30	4.1%	1.10 [0.66 , 1.83]
Zeni 2009	0.0994	0.3538	16	16	3.0%	1.10 [0.55 , 2.21]
Subtotal (95% CI)			**771**	**768**	**47.8%**	**1.11 [0.94 , 1.31]**
Heterogeneity: Tau² = 0.00; Chi² = 7.41, df = 15 (P = 0.95); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
8.2.2 High dose						
Brams 2012	0.618	0.2715	162	159	4.0%	1.86 [1.09 , 3.16]
Brown 1988	-0.086	0.4266	11	11	2.3%	0.92 [0.40 , 2.12]
Cox 2006	-1.1272	1.6504	35	35	0.2%	0.32 [0.01 , 8.23]
DuPaul 1996	0.2691	0.2901	24	24	3.7%	1.31 [0.74 , 2.31]
Fine 1993	0.4089	0.4133	12	12	2.4%	1.51 [0.67 , 3.38]
Kolko 1999	-0.3132	0.356	16	16	3.0%	0.73 [0.36 , 1.47]
Muniz 2008	1.7574	0.6534	84	83	1.2%	5.80 [1.61 , 20.86]
Murray 2011	0.6366	0.5792	67	67	1.5%	1.89 [0.61 , 5.88]
Musten 1997	0.7384	0.2286	41	41	4.6%	2.09 [1.34 , 3.28]
Solanto 2009	0.6142	0.2646	30	30	4.1%	1.85 [1.10 , 3.10]
Wigal 2013	0.9555	0.5889	44	44	1.4%	2.60 [0.82 , 8.25]
Zeni 2009	0.2302	0.3549	16	16	3.0%	1.26 [0.63 , 2.52]
Subtotal (95% CI)			**542**	**538**	**31.4%**	**1.57 [1.22 , 2.01]**
Heterogeneity: Tau² = 0.05; Chi² = 15.05, df = 11 (P = 0.18); I² = 27%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
8.2.3 Unknown dose						
CRIT124US02	0.273	0.1184	102	101	6.4%	1.31 [1.04 , 1.66]
Döpfner 2004	0.0673	0.3669	82	82	2.9%	1.07 [0.52 , 2.20]
NCT02039908	0.0126	0.1082	138	129	6.5%	1.01 [0.82 , 1.25]
NCT02536105	1.6712	0.268	80	74	4.0%	5.32 [3.15 , 8.99]
Taylor 1987	-0.3991	0.7464	38	38	1.0%	0.67 [0.16 , 2.90]
Subtotal (95% CI)			**440**	**424**	**20.8%**	**1.50 [0.88 , 2.56]**
Heterogeneity: Tau² = 0.27; Chi² = 33.97, df = 4 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 1.50 (P = 0.13)						
Total (95% CI)			**1753**	**1730**	**100.0%**	**1.31 [1.12 , 1.53]**
Heterogeneity: Tau² = 0.08; Chi² = 63.92, df = 32 (P = 0.0007); I² = 50%						
Test for overall effect: Z = 3.43 (P = 0.0006)						
Test for subgroup differences: Chi² = 5.72, df = 2 (P = 0.06), I² = 65.0%						



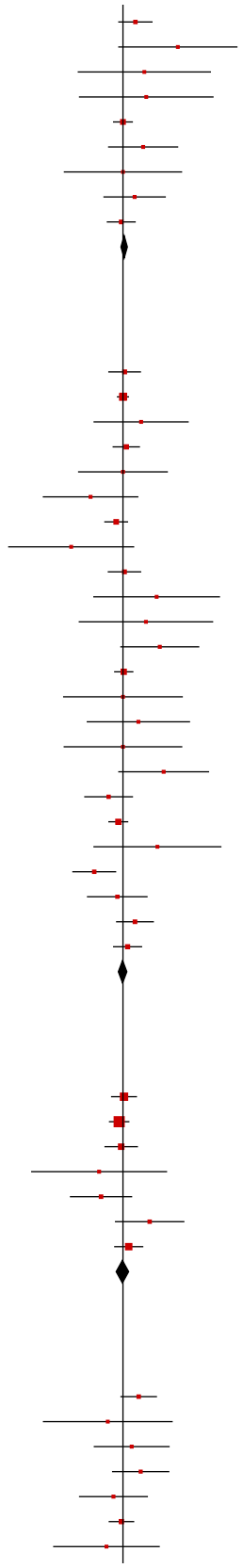
Analysis 8.3. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 3: Nervous system (including psychiatry)

Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
8.3.1 Aggression						
Kollins 2006 (PATS)	-0.3213	0.5824	136	160	75.0%	0.73 [0.23 , 2.27]
NCT02536105 (1)	0	0	80	74		Not estimable
Schulz 2010	-1.6443	1.1018	147	146	25.0%	0.19 [0.02 , 1.67]
Subtotal (95% CI)			**363**	**380**	**100.0%**	**0.52 [0.17 , 1.60]**
Heterogeneity: Tau² = 0.10; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%						
Test for overall effect: Z = 1.14 (P = 0.25)						
8.3.2 Agitation						
Huang 2021	2.1127	1.4844	110	101	25.3%	8.27 [0.45 , 151.73]
Quinn 2004	0.1622	0.5701	31	31	74.7%	1.18 [0.38 , 3.60]
Subtotal (95% CI)			**141**	**132**	**100.0%**	**1.93 [0.37 , 10.16]**
Heterogeneity: Tau² = 0.64; Chi² = 1.50, df = 1 (P = 0.22); I² = 34%						
Test for overall effect: Z = 0.77 (P = 0.44)						
8.3.3 Anger						
Fitzpatrick 1992a	-1.8216	0.8802	19	19	9.7%	0.16 [0.03 , 0.91]
Klorman 1990	-0.5199	0.4601	48	48	35.3%	0.59 [0.24 , 1.47]
Rapport 2008	-0.7918	0.3688	65	65	55.0%	0.45 [0.22 , 0.93]
Subtotal (95% CI)			**132**	**132**	**100.0%**	**0.45 [0.26 , 0.77]**
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.91 (P = 0.004)						
8.3.4 Behavioural complaints						
Gorman 2006	-0.5936	0.2259	41	41	100.0%	0.55 [0.35 , 0.86]
Subtotal (95% CI)			**41**	**41**	**100.0%**	**0.55 [0.35 , 0.86]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
8.3.5 Buccal or lingual movements						
Borcherding 1990	0.2804	0.2119	45	45	60.5%	1.32 [0.87 , 2.01]
NCT02039908	0.0577	0.3324	138	129	24.6%	1.06 [0.55 , 2.03]
Pelham 1999	0	1.4434	25	25	1.3%	1.00 [0.06 , 16.93]
Pelham 2005	1.1264	1.6499	36	36	1.0%	3.08 [0.12 , 78.27]
Smith 1998	-0.6295	0.4635	45	45	12.6%	0.53 [0.21 , 1.32]
Subtotal (95% CI)			**289**	**280**	**100.0%**	**1.12 [0.81 , 1.55]**
Heterogeneity: Tau² = 0.00; Chi² = 3.60, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
8.3.6 Compulsive acts						
Borcherding 1990	0.943	0.293	45	45	100.0%	2.57 [1.45 , 4.56]
Subtotal (95% CI)			**45**	**45**	**100.0%**	**2.57 [1.45 , 4.56]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.22 (P = 0.001)						
8.3.7 Daydreaming						
Fine 1993	-0.0145	0.4083	12	12	24.5%	0.99 [0.44 , 2.19]
Ramtvedt 2013	-0.5681	0.2477	34	34	66.5%	0.57 [0.35 , 0.92]
Rapport 2008	-0.4388	0.6708	65	65	9.1%	0.64 [0.17 , 2.40]
Subtotal (95% CI)			**111**	**111**	**100.0%**	**0.66 [0.44 , 0.98]**
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
8.3.8 Dizziness						
Barkley 1989b	0.7319	0.7251	82	82	1.1%	2.08 [0.50 , 8.61]
Bhat 2020	0	0.0926	526	526	70.3%	1.00 [0.83 , 1.20]
DuPaul 1996	0.0787	0.2888	24	24	7.2%	1.08 [0.61 , 1.91]
Fine 1993	0.5948	0.4189	12	12	3.4%	1.81 [0.80 , 4.12]
Huang 2021	2.6235	1.4541	110	101	0.3%	13.78 [0.80 , 238.29]



Analysis 8.3. (Continued)

Fine 1993	0.5948	0.4189	12	12	3.4%	1.81 [0.80 , 4.12]
Huang 2021	2.6235	1.4541	110	101	0.3%	13.78 [0.80 , 238.29]
NCT02536105	1.0217	1.6251	80	74	0.2%	2.78 [0.11 , 67.14]
Pelham 2001a	1.1133	1.642	68	68	0.2%	3.04 [0.12 , 76.06]
Ramtvedt 2013	0	0.2425	34	34	10.2%	1.00 [0.62 , 1.61]
Rapport 2008	0.9651	0.8559	65	65	0.8%	2.63 [0.49 , 14.05]
Stein 1996	0	1.4434	25	25	0.3%	1.00 [0.06 , 16.93]
Stein 2003	0.5573	0.7615	47	47	1.0%	1.75 [0.39 , 7.77]
Zeni 2009	-0.082	0.3537	16	16	4.8%	0.92 [0.46 , 1.84]
Subtotal (95% CI)			**1089**	**1074**	**100.0%**	**1.06 [0.91 , 1.23]**
Heterogeneity: Tau² = 0.00; Chi² = 8.55, df = 11 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
8.3.9 Drowsiness: dull, tired, listless or sleepy						
Barkley 1989b	0.0796	0.3991	82	82	5.6%	1.08 [0.50 , 2.37]
Bhat 2020	0	0.1481	526	526	20.5%	1.00 [0.75 , 1.34]
Buitelaar 1995	0.8675	1.1609	26	11	0.8%	2.38 [0.24 , 23.17]
Bukstein 1998	0.1588	0.3339	18	18	7.6%	1.17 [0.61 , 2.26]
Carlson 1995	0	1.0954	12	12	0.9%	1.00 [0.12 , 8.56]
Chronis 2003	-1.5488	1.1657	21	21	0.8%	0.21 [0.02 , 2.09]
DuPaul 1996	-0.324	0.2907	24	24	9.3%	0.72 [0.41 , 1.28]
Findling 2007	-2.4749	1.5371	13	13	0.4%	0.08 [0.00 , 1.71]
Fine 1993	0.0719	0.4084	12	12	5.4%	1.07 [0.48 , 2.39]
Froehlich 2018	1.6094	1.5454	171	171	0.4%	5.00 [0.24 , 103.37]
Muniz 2008	1.0986	1.6403	84	83	0.4%	3.00 [0.12 , 74.70]
Musten 1997	1.76	0.9632	41	41	1.1%	5.81 [0.88 , 38.39]
NCT02039908	0.0379	0.2353	138	129	12.5%	1.04 [0.65 , 1.65]
Overtoom 2003	0	1.4606	16	16	0.5%	1.00 [0.06 , 17.51]
Pearson 2013	0.7376	1.2605	24	24	0.7%	2.09 [0.18 , 24.73]
Pelham 1990a	0	1.4475	22	22	0.5%	1.00 [0.06 , 17.07]
Pelham 2005	1.9459	1.1084	36	36	0.9%	7.00 [0.80 , 61.46]
Quinn 2004	-0.6852	0.5952	31	31	2.8%	0.50 [0.16 , 1.62]
Ramtvedt 2013	-0.2237	0.2433	34	34	12.0%	0.80 [0.50 , 1.29]
Silva 2006	1.6468	1.5612	54	54	0.4%	5.19 [0.24 , 110.69]
Smith 1998	-1.3728	0.5356	45	45	3.4%	0.25 [0.09 , 0.72]
Stein 1996	-0.2719	0.74	25	25	1.9%	0.76 [0.18 , 3.25]
Stein 2003	0.5736	0.4612	47	47	4.4%	1.77 [0.72 , 4.38]
Zeni 2009	0.222	0.3548	16	16	6.9%	1.25 [0.62 , 2.50]
Subtotal (95% CI)			**1518**	**1493**	**100.0%**	**0.98 [0.80 , 1.20]**
Heterogeneity: Tau² = 0.03; Chi² = 26.63, df = 23 (P = 0.27); I² = 14%						
Test for overall effect: Z = 0.18 (P = 0.86)						
8.3.10 Euphoria						
Barkley 1989b	0.05	0.3164	82	82	23.0%	1.05 [0.57 , 1.95]
Bhat 2020	-0.1814	0.2499	526	526	36.9%	0.83 [0.51 , 1.36]
Fine 1993	-0.0847	0.4085	12	12	13.8%	0.92 [0.41 , 2.05]
Pearson 2013	-1.1403	1.6583	24	24	0.8%	0.32 [0.01 , 8.25]
Stein 1996	-1.048	0.7597	25	25	4.0%	0.35 [0.08 , 1.55]
Stein 2011	1.2763	0.8472	42	45	3.2%	3.58 [0.68 , 18.86]
Zeni 2009	0.2756	0.3555	16	16	18.2%	1.32 [0.66 , 2.64]
Subtotal (95% CI)			**727**	**730**	**100.0%**	**0.97 [0.72 , 1.31]**
Heterogeneity: Tau² = 0.00; Chi² = 5.81, df = 6 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
8.3.11 Headache						
Barkley 1989b	0.7521	0.4461	82	82	3.6%	2.12 [0.88 , 5.09]
Bhat 2020	-0.7256	1.5827	526	526	0.3%	0.48 [0.02 , 10.77]
Brams 2008	0.4174	0.9259	86	86	0.8%	1.52 [0.25 , 9.32]
Brams 2012	0.8473	0.6993	163	159	1.5%	2.33 [0.59 , 9.19]
Buitelaar 1995	-0.4543	0.8402	26	11	1.0%	0.63 [0.12 , 3.30]
Bukstein 1998	-0.0726	0.312	18	18	7.4%	0.93 [0.50 , 1.71]
Carlson 1995	-0.7885	1.3003	12	12	0.4%	0.45 [0.04 , 5.81]

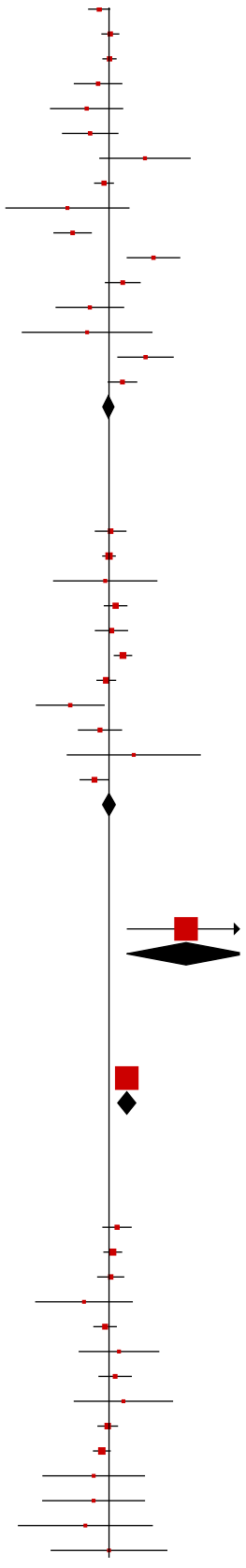


Analysis 8.3. (Continued)

Bukstein 1998	-0.0726	0.312	18	18	7.4%	0.93 [0.50 , 1.71]
Carlson 1995	-0.7885	1.3003	12	12	0.4%	0.45 [0.04 , 5.81]
Chronis 2003	-2.4031	1.5251	21	21	0.3%	0.09 [0.00 , 1.80]
CRIT124US02	0.335	0.2842	102	101	8.9%	1.40 [0.80 , 2.44]
DuPaul 1996	-0.10884	0.6628	24	24	1.6%	0.90 [0.24 , 3.29]
Fine 1993	0.2612	0.4103	12	12	4.3%	1.30 [0.58 , 2.90]
Fitzpatrick 1992a	0	1.0572	19	19	0.6%	1.00 [0.13 , 7.94]
Froehlich 2018	2.1972	1.4868	171	171	0.3%	9.00 [0.49 , 165.88]
Huang 2021	2.1119	1.045	110	101	0.7%	8.26 [1.07 , 64.08]
Klorman 1990	0.7621	0.7389	48	48	1.3%	2.14 [0.50 , 9.12]
McBride 1988a	0.4274	0.9366	48	48	0.8%	1.53 [0.24 , 9.61]
McGough 2006	0	0.8323	80	80	1.0%	1.00 [0.20 , 5.11]
Muniz 2008	2.6267	1.476	84	83	0.3%	13.83 [0.77 , 249.54]
Murray 2011	0.7244	0.8839	67	67	0.9%	2.06 [0.36 , 11.67]
Musten 1997	0.4374	0.2236	41	41	14.4%	1.55 [1.00 , 2.40]
NCT02039908	0.0438	0.3106	138	129	7.5%	1.04 [0.57 , 1.92]
NCT02536105	2.6946	1.0181	80	74	0.7%	14.80 [2.01 , 108.86]
Pearson 2013	0.7885	0.9195	24	24	0.9%	2.20 [0.36 , 13.34]
Pelham 1990a	-1.7025	1.579	22	22	0.3%	0.18 [0.01 , 4.02]
Pelham 1999	1.5198	1.1573	25	25	0.5%	4.57 [0.47 , 44.17]
Pelham 2001a	-0.4665	0.4361	68	68	3.8%	0.63 [0.27 , 1.47]
Pelham 2005	0.5733	0.7719	36	36	1.2%	1.77 [0.39 , 8.05]
Quinn 2004	-1.675	1.5702	31	31	0.3%	0.19 [0.01 , 4.07]
Ramtvedt 2013	0.1156	0.2428	34	34	12.2%	1.12 [0.70 , 1.81]
Rapport 2008	0.1712	0.5863	65	65	2.1%	1.19 [0.38 , 3.74]
Schachar 2008	0	1.4552	18	18	0.3%	1.00 [0.06 , 17.32]
Schulz 2010	0.3436	0.5976	147	146	2.0%	1.41 [0.44 , 4.55]
Silva 2005a	0.6931	1.2403	54	53	0.5%	2.00 [0.18 , 22.74]
Silva 2006	-1.1371	1.1712	54	54	0.5%	0.32 [0.03 , 3.18]
Silva 2008	0	1.4247	68	68	0.4%	1.00 [0.06 , 16.32]
Smith 1998	-0.2076	0.646	45	45	1.7%	0.81 [0.23 , 2.88]
Stein 1996	0.9045	0.6939	25	25	1.5%	2.47 [0.63 , 9.63]
Stein 2003	0.0934	0.4323	47	47	3.9%	1.10 [0.47 , 2.56]
Stein 2011	1.1906	1.647	42	45	0.3%	3.29 [0.13 , 82.99]
Swanson 2004b	0.1712	0.5665	181	183	2.2%	1.19 [0.39 , 3.60]
Wigal 2014	1.9904	1.4822	21	22	0.3%	7.32 [0.40 , 133.68]
Wilens 2010	1.7579	1.1289	30	30	0.6%	5.80 [0.63 , 53.01]
Zeni 2009	-0.393	0.3574	16	16	5.6%	0.68 [0.34 , 1.36]
Subtotal (95% CI)			**3011**	**2970**	**100.0%**	**1.25 [1.06 , 1.48]**
Heterogeneity: Tau² = 0.00; Chi² = 41.15, df = 42 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
8.3.12 Thirst						
Huang 2021	1.0227	1.6388	110	101	100.0%	2.78 [0.11 , 69.04]
Subtotal (95% CI)			**110**	**101**	**100.0%**	**2.78 [0.11 , 69.04]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
8.3.13 Irritability						
Barkley 1989b	-0.2853	0.3386	82	82	5.8%	0.75 [0.39 , 1.46]
Bhat 2020	0	0.3147	526	526	6.1%	1.00 [0.54 , 1.85]
Buitelaar 1995	0.1699	0.7993	26	11	2.2%	1.19 [0.25 , 5.68]
Bukstein 1998	0.1478	0.3338	18	18	5.8%	1.16 [0.60 , 2.23]
Chronis 2003	-1.0986	0.7766	21	21	2.3%	0.33 [0.07 , 1.53]
DuPaul 1996	0.1088	1.4634	24	24	0.8%	1.11 [0.06 , 19.63]
Findling 2007	-0.9555	0.8228	16	16	2.1%	0.38 [0.08 , 1.93]
Fine 1993	0.1065	0.4086	12	12	5.0%	1.11 [0.50 , 2.48]
Froehlich 2018	0.5878	0.5472	171	171	3.7%	1.80 [0.62 , 5.26]
Huang 2021	1.8614	1.5056	110	101	0.8%	6.43 [0.34 , 123.02]
Kollins 2006 (PATS)	-0.0409	0.4654	136	160	4.4%	0.96 [0.39 , 2.39]
Manos 1999	-0.4727	0.2723	177	177	6.6%	0.62 [0.37 , 1.06]
Musten 1997	0.0646	0.2209	41	41	7.2%	1.07 [0.69 , 1.64]
NCT02039908	0.0235	0.1748	138	129	7.8%	1.02 [0.73 , 1.44]

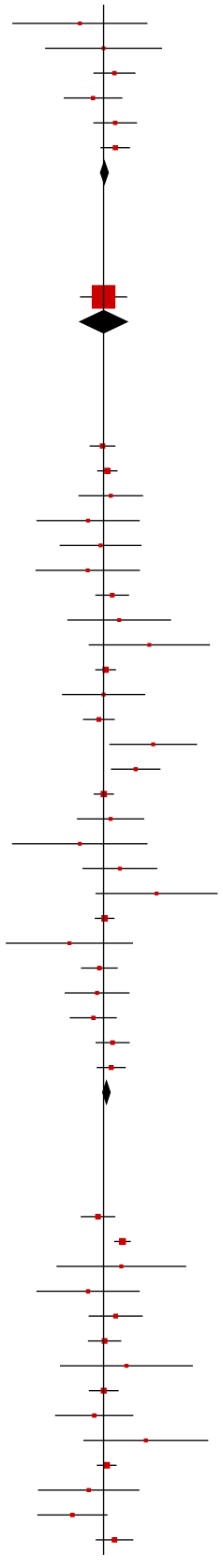
Analysis 8.3. (Continued)

Musten 1997	0.0646	0.2209	41	41	7.2%	1.07 [0.69 , 1.64]
NCT02039908	0.0235	0.1748	138	129	7.8%	1.02 [0.73 , 1.44]
Pearson 2013	-0.5261	0.5961	24	24	3.3%	0.59 [0.18 , 1.90]
Pelham 1990a	-1.0788	0.8993	22	22	1.8%	0.34 [0.06 , 1.98]
Pelham 1999	-0.9045	0.6939	25	25	2.7%	0.40 [0.10 , 1.58]
Pelham 2005	1.7308	1.1229	36	36	1.3%	5.65 [0.62 , 50.99]
Ramtvedt 2013	-0.2417	0.2435	34	34	7.0%	0.79 [0.49 , 1.27]
Silva 2006	-2.0025	1.5243	54	54	0.7%	0.13 [0.01 , 2.68]
Smith 1998	-1.7518	0.4723	45	45	4.3%	0.17 [0.07 , 0.44]
Stein 1996	2.1401	0.6587	25	25	2.9%	8.50 [2.34 , 30.91]
Stein 2003	0.6613	0.4397	47	47	4.6%	1.94 [0.82 , 4.59]
Swanson 2004b	-0.9219	0.8433	181	183	2.0%	0.40 [0.08 , 2.08]
Wigal 2014	-1.0542	1.6055	21	22	0.7%	0.35 [0.01 , 8.11]
Wilens 2010	1.7579	0.6928	30	30	2.7%	5.80 [1.49 , 22.55]
Zeni 2009	0.6467	0.3639	16	16	5.5%	1.91 [0.94 , 3.90]
Subtotal (95% CI)			**2058**	**2052**	**100.0%**	**0.97 [0.74 , 1.27]**
Heterogeneity: Tau² = 0.21; Chi² = 56.76, df = 26 (P = 0.0005); I² = 54%						
Test for overall effect: Z = 0.23 (P = 0.82)						
8.3.14 Nightmares						
Barkley 1989b	0.0759	0.3897	82	82	9.4%	1.08 [0.50 , 2.32]
Bhat 2020	0	0.1666	526	526	18.0%	1.00 [0.72 , 1.39]
Buitelaar 1995	-0.1823	1.2813	26	11	1.4%	0.83 [0.07 , 10.27]
DuPaul 1996	0.3165	0.2906	24	24	12.7%	1.37 [0.78 , 2.43]
Fine 1993	0.1168	0.4087	12	12	8.9%	1.12 [0.50 , 2.50]
Musten 1997	0.6716	0.2273	41	41	15.3%	1.96 [1.25 , 3.06]
Ramtvedt 2013	-0.1315	0.2428	34	34	14.6%	0.88 [0.54 , 1.41]
Stein 1996	-1.867	0.8468	25	25	2.9%	0.15 [0.03 , 0.81]
Stein 2003	-0.4346	0.543	47	47	6.0%	0.65 [0.22 , 1.88]
Stein 2011	1.1906	1.647	42	45	0.9%	3.29 [0.13 , 82.99]
Zeni 2009	-0.7008	0.3657	16	16	10.1%	0.50 [0.24 , 1.02]
Subtotal (95% CI)			**875**	**863**	**100.0%**	**1.00 [0.73 , 1.35]**
Heterogeneity: Tau² = 0.11; Chi² = 19.63, df = 10 (P = 0.03); I² = 49%						
Test for overall effect: Z = 0.02 (P = 0.98)						
8.3.15 Overly meticulous						
Sharp 1999	3.7079	1.4555	48	48	100.0%	40.77 [2.35 , 706.72]
Subtotal (95% CI)			**48**	**48**	**100.0%**	**40.77 [2.35 , 706.72]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						
8.3.16 Obsessive thinking						
Borcherding 1990	0.8547	0.2207	45	45	100.0%	2.35 [1.53 , 3.62]
Subtotal (95% CI)			**45**	**45**	**100.0%**	**2.35 [1.53 , 3.62]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.87 (P = 0.0001)						
8.3.17 Picking at skin or fingers, nail biting, lip or cheek chewing						
Barkley 1989b	0.3861	0.3607	82	82	6.9%	1.47 [0.73 , 2.98]
Bhat 2020	0.1814	0.2314	526	526	16.8%	1.20 [0.76 , 1.89]
Bukstein 1998	0.0814	0.3335	18	18	8.1%	1.08 [0.56 , 2.09]
Chronis 2003	-1.204	1.1995	21	21	0.6%	0.30 [0.03 , 3.15]
DuPaul 1996	-0.1887	0.2894	24	24	10.8%	0.83 [0.47 , 1.46]
Findling 2007	0.4796	0.9908	16	16	0.9%	1.62 [0.23 , 11.26]
Fine 1993	0.2948	0.4109	12	12	5.3%	1.34 [0.60 , 3.00]
Froehlich 2018	0.6931	1.22	171	171	0.6%	2.00 [0.18 , 21.85]
Musten 1997	-0.0621	0.2541	31	31	14.0%	0.94 [0.57 , 1.55]
NCT02039908	-0.3462	0.2185	138	129	18.9%	0.71 [0.46 , 1.09]
Pearson 2013	-0.7376	1.2605	24	24	0.6%	0.48 [0.04 , 5.66]
Pelham 1990a	-0.7419	1.264	22	22	0.6%	0.48 [0.04 , 5.67]
Pelham 1999	-1.1386	1.6573	25	25	0.3%	0.32 [0.01 , 8.25]
Pelham 2005	0	1.4343	36	36	0.4%	1.00 [0.06 , 16.63]



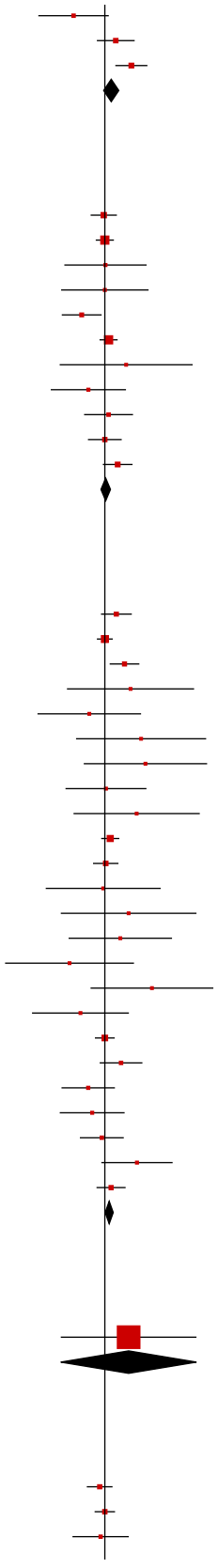
Analysis 8.3. (Continued)

Pelham 1999	-1.1386	1.6573	25	25	0.3%	0.32 [0.01 , 8.25]
Pelham 2005	0	1.4343	36	36	0.4%	1.00 [0.06 , 16.63]
Smith 1998	0.5199	0.5154	45	45	3.4%	1.68 [0.61 , 4.62]
Stein 1996	-0.5055	0.719	25	25	1.7%	0.60 [0.15 , 2.47]
Stein 2003	0.5573	0.5353	47	47	3.1%	1.75 [0.61 , 4.99]
Zeni 2009	0.5609	0.3614	16	16	6.9%	1.75 [0.86 , 3.56]
Subtotal (95% CI)			**1279**	**1270**	**100.0%**	**1.04 [0.86 , 1.25]**
Heterogeneity: Tau² = 0.00; Chi² = 12.89, df = 17 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
8.3.18 Repetitive language						
Pearson 2013	0	0.5774	24	24	100.0%	1.00 [0.32 , 3.10]
Subtotal (95% CI)			**24**	**24**	**100.0%**	**1.00 [0.32 , 3.10]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
8.3.19 Sad, tearful or depressed						
Barkley 1989b	-0.05	0.3164	82	82	8.1%	0.95 [0.51 , 1.77]
Bhat 2020	0.1814	0.2499	526	526	13.0%	1.20 [0.73 , 1.96]
Buitelaar 1995	0.3448	0.7926	26	11	1.3%	1.41 [0.30 , 6.67]
Chronis 2003	-0.7444	1.266	21	21	0.5%	0.48 [0.04 , 5.68]
DuPaul 1996	-0.145	1.0039	24	24	0.8%	0.87 [0.12 , 6.19]
Findling 2007	-0.7621	1.2799	16	16	0.5%	0.47 [0.04 , 5.73]
Fine 1993	0.4139	0.4134	12	12	4.7%	1.51 [0.67 , 3.40]
Fitzpatrick 1992a	0.7503	1.2706	19	19	0.5%	2.12 [0.18 , 25.55]
Froehlich 2018	2.1972	1.4868	171	171	0.4%	9.00 [0.49 , 165.88]
Gadow 2007	0.0987	0.2542	31	31	12.5%	1.10 [0.67 , 1.82]
Klorman 1990	0	1.0215	48	48	0.8%	1.00 [0.14 , 7.40]
Manos 1999	-0.2261	0.3895	177	177	5.3%	0.80 [0.37 , 1.71]
McBride 1988a	2.3838	1.0761	48	48	0.7%	10.85 [1.32 , 89.38]
Musten 1997	1.543	0.6075	41	41	2.2%	4.68 [1.42 , 15.39]
NCT02039908	0.0095	0.2491	138	129	13.1%	1.01 [0.62 , 1.64]
Pearson 2013	0.3365	0.8252	24	24	1.2%	1.40 [0.28 , 7.06]
Pelham 1990a	-1.1441	1.6606	22	22	0.3%	0.32 [0.01 , 8.25]
Pelham 1999	0.7841	0.9171	25	25	1.0%	2.19 [0.36 , 13.22]
Pelham 2005	2.5452	1.497	36	36	0.4%	12.75 [0.68 , 239.67]
Ramtvedt 2013	0.0489	0.2426	34	34	13.8%	1.05 [0.65 , 1.69]
Rapport 2008	-1.6404	1.5592	65	65	0.3%	0.19 [0.01 , 4.12]
Sharp 1999	-0.2019	0.45	48	48	4.0%	0.82 [0.34 , 1.97]
Smith 1998	-0.3118	0.7947	45	45	1.3%	0.73 [0.15 , 3.48]
Stein 1996	-0.4953	0.5778	25	25	2.4%	0.61 [0.20 , 1.89]
Stein 2003	0.4344	0.4185	47	47	4.6%	1.54 [0.68 , 3.51]
Zeni 2009	0.3662	0.3569	16	16	6.4%	1.44 [0.72 , 2.90]
Subtotal (95% CI)			**1767**	**1743**	**100.0%**	**1.15 [0.96 , 1.37]**
Heterogeneity: Tau² = 0.00; Chi² = 23.17, df = 25 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.52 (P = 0.13)						
8.3.20 Socially withdrawn - decreased interaction with others						
Barkley 1989b	-0.2669	0.4233	82	82	9.6%	0.77 [0.33 , 1.76]
Bhat 2020	0.907	0.2036	526	526	15.7%	2.48 [1.66 , 3.69]
Buitelaar 1995	0.8531	1.5899	26	11	1.3%	2.35 [0.10 , 52.94]
Chronis 2003	-0.7444	1.266	21	21	1.9%	0.48 [0.04 , 5.68]
DuPaul 1996	0.5805	0.6628	24	24	5.5%	1.79 [0.49 , 6.55]
Fine 1993	0.0483	0.4083	12	12	10.0%	1.05 [0.47 , 2.34]
Froehlich 2018	1.0986	1.6294	171	171	1.2%	3.00 [0.12 , 73.12]
NCT02039908	0.0067	0.3652	138	129	11.0%	1.01 [0.49 , 2.06]
Pelham 1999	-0.4499	0.9603	25	25	3.1%	0.64 [0.10 , 4.19]
Pelham 2005	2.0317	1.5307	36	36	1.4%	7.63 [0.38 , 153.21]
Ramtvedt 2013	0.1482	0.2429	34	34	14.5%	1.16 [0.72 , 1.87]
Smith 1998	-0.7161	1.2434	45	45	2.0%	0.49 [0.04 , 5.59]
Stein 1996	-1.4979	0.8613	25	25	3.7%	0.22 [0.04 , 1.21]
Stein 2003	0.5242	0.462	47	47	8.8%	1.69 [0.68 , 4.18]



Analysis 8.3. (Continued)

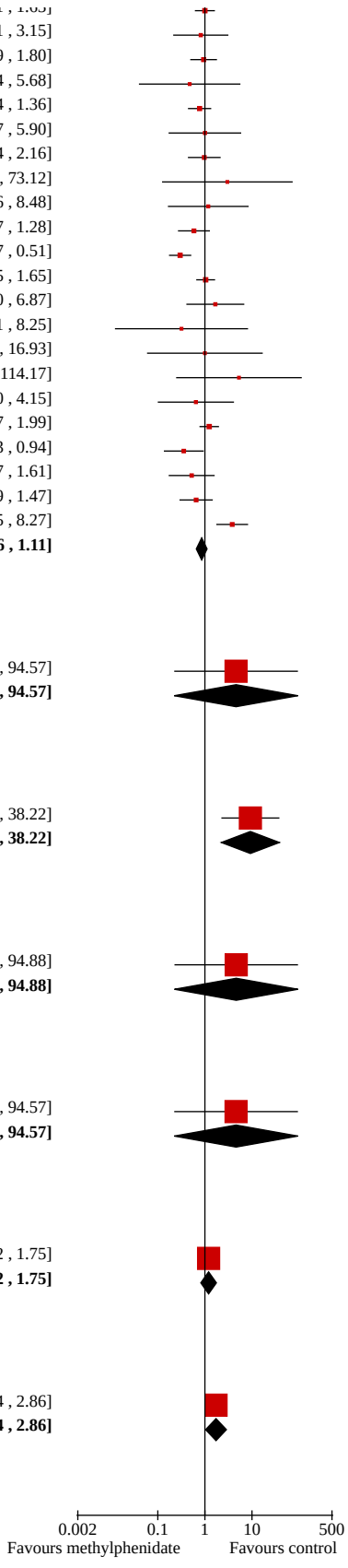
Stein 1996	-1.4979	0.8613	25	25	3.7%	0.22 [0.04 , 1.21]
Stein 2003	0.5242	0.462	47	47	8.8%	1.69 [0.68 , 4.18]
Zeni 2009	1.2716	0.3922	16	16	10.3%	3.57 [1.65 , 7.69]
Subtotal (95% CI)			**1228**	**1204**	**100.0%**	**1.36 [0.95 , 1.95]**
Heterogeneity: Tau² = 0.17; Chi² = 25.35, df = 14 (P = 0.03); I² = 45%						
Test for overall effect: Z = 1.67 (P = 0.10)						
8.3.21 Stares a lot						
Barkley 1989b	-0.0516	0.3211	82	82	13.1%	0.95 [0.51 , 1.78]
Bhat 2020	0	0.2221	526	526	27.3%	1.00 [0.65 , 1.55]
DuPaul 1996	0.031	1.0056	24	24	1.3%	1.03 [0.14 , 7.40]
Findling 2007	0.0013	1.069	16	16	1.2%	1.00 [0.12 , 8.14]
Manos 1999	-1.1079	0.4874	177	177	5.7%	0.33 [0.13 , 0.86]
Musten 1997	0.1802	0.2213	41	41	27.5%	1.20 [0.78 , 1.85]
NCT02536105	1.0217	1.6251	80	74	0.5%	2.78 [0.11 , 67.14]
Pearson 2013	-0.7885	0.9195	24	24	1.6%	0.45 [0.07 , 2.76]
Stein 1996	0.1784	0.5979	25	25	3.8%	1.20 [0.37 , 3.86]
Stein 2003	0	0.4127	47	47	7.9%	1.00 [0.45 , 2.25]
Zeni 2009	0.6164	0.363	16	16	10.2%	1.85 [0.91 , 3.77]
Subtotal (95% CI)			**1058**	**1052**	**100.0%**	**1.04 [0.83 , 1.31]**
Heterogeneity: Tau² = 0.00; Chi² = 9.82, df = 10 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
8.3.22 Tics or nervous movements						
Barkley 1989b	0.5546	0.3769	82	82	6.4%	1.74 [0.83 , 3.64]
Bhat 2020	0	0.1944	526	526	21.1%	1.00 [0.68 , 1.46]
Borcherding 1990	0.9433	0.363	45	45	6.9%	2.57 [1.26 , 5.23]
Buitelaar 1995	1.2313	1.5541	26	11	0.4%	3.43 [0.16 , 72.04]
Chronis 2003	-0.7444	1.266	21	21	0.6%	0.48 [0.04 , 5.68]
Findling 2007	1.7386	1.5905	16	16	0.4%	5.69 [0.25 , 128.50]
Froehlich 2018	1.9459	1.508	171	171	0.4%	7.00 [0.36 , 134.49]
Gadow 2007	0.05492	0.9894	71	71	1.0%	1.06 [0.15 , 7.35]
Huang 2021	1.5249	1.5431	110	101	0.4%	4.59 [0.22 , 94.57]
Musten 1997	0.2598	0.2218	41	41	16.9%	1.30 [0.84 , 2.00]
NCT02039908	0.0438	0.3106	138	129	9.2%	1.04 [0.57 , 1.92]
NCT02536105	-0.078	1.405	80	74	0.5%	0.92 [0.06 , 14.52]
Pearson 2013	1.1403	1.6583	24	24	0.4%	3.13 [0.12 , 80.68]
Pelham 1990a	0.7419	1.264	22	22	0.6%	2.10 [0.18 , 25.01]
Pelham 1999	-1.6911	1.5754	25	25	0.4%	0.18 [0.01 , 4.04]
Pelham 2001a	2.2574	1.5008	68	68	0.4%	9.56 [0.50 , 181.08]
Quinn 2004	-1.1676	1.1842	31	31	0.7%	0.31 [0.03 , 3.17]
Ramtvedt 2013	0	0.2425	34	34	14.5%	1.00 [0.62 , 1.61]
Sharp 1999	0.7773	0.5222	48	48	3.4%	2.18 [0.78 , 6.05]
Smith 1998	-0.7958	0.653	45	45	2.2%	0.45 [0.13 , 1.62]
Stein 1996	-0.6061	0.793	25	25	1.5%	0.55 [0.12 , 2.58]
Stein 2003	-0.1438	0.5367	47	47	3.3%	0.87 [0.30 , 2.48]
Tannock 1993	1.5404	0.8715	22	22	1.3%	4.67 [0.85 , 25.75]
Zeni 2009	0.2995	0.3558	16	16	7.2%	1.35 [0.67 , 2.71]
Subtotal (95% CI)			**1734**	**1695**	**100.0%**	**1.23 [1.02 , 1.50]**
Heterogeneity: Tau² = 0.01; Chi² = 23.81, df = 23 (P = 0.41); I² = 3%						
Test for overall effect: Z = 2.14 (P = 0.03)						
8.3.23 Unusual blinking						
Pearson 2013	1.1403	1.6583	24	24	100.0%	3.13 [0.12 , 80.68]
Subtotal (95% CI)			**24**	**24**	**100.0%**	**3.13 [0.12 , 80.68]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
8.3.24 Worried or anxious						
Barkley 1989b	-0.2472	0.3149	82	82	7.1%	0.78 [0.42 , 1.45]
Bhat 2020	0	0.2499	526	526	8.3%	1.00 [0.61 , 1.63]
Buitelaar 1995	-0.2007	0.6885	26	11	2.9%	0.82 [0.21 , 3.15]
Bukstein 1998	-0.0629	0.3334	18	18	6.8%	0.94 [0.49 , 1.80]



Analysis 8.3. (Continued)

Bhat 2020	0	0.2499	526	526	0.5%	1.00 [0.61 , 1.63]
Buitelaar 1995	-0.2007	0.6885	26	11	2.9%	0.82 [0.21 , 3.15]
Bukstein 1998	-0.0629	0.3334	18	18	6.8%	0.94 [0.49 , 1.80]
Chronis 2003	-0.7444	1.266	21	21	1.0%	0.48 [0.04 , 5.68]
DuPaul 1996	-0.2589	0.29	24	24	7.6%	0.77 [0.44 , 1.36]
Findling 2007	0	0.9058	16	16	1.8%	1.00 [0.17 , 5.90]
Fine 1993	-0.0299	0.4083	12	12	5.6%	0.97 [0.44 , 2.16]
Froehlich 2018	1.0986	1.6294	171	171	0.6%	3.00 [0.12 , 73.12]
Kollins 2006 (PATS)	0.1648	1.0069	136	160	1.5%	1.18 [0.16 , 8.48]
Manos 1999	-0.5356	0.3985	177	177	5.8%	0.59 [0.27 , 1.28]
Musten 1997	-1.2106	0.2777	31	31	7.8%	0.30 [0.17 , 0.51]
NCT02039908	0.0379	0.2353	138	129	8.6%	1.04 [0.65 , 1.65]
Pearson 2013	0.5108	0.7226	24	24	2.7%	1.67 [0.40 , 6.87]
Pelham 1990a	-1.1441	1.6606	22	22	0.6%	0.32 [0.01 , 8.25]
Pelham 1999	0	1.4434	25	25	0.8%	1.00 [0.06 , 16.93]
Pelham 2005	1.6658	1.5673	36	36	0.7%	5.29 [0.25 , 114.17]
Quinn 2004	-0.4406	0.9505	31	31	1.7%	0.64 [0.10 , 4.15]
Ramtvedt 2013	0.2118	0.2433	34	34	8.5%	1.24 [0.77 , 1.99]
Smith 1998	-1.0325	0.4966	45	45	4.5%	0.36 [0.13 , 0.94]
Stein 1996	-0.6466	0.5736	25	25	3.7%	0.52 [0.17 , 1.61]
Stein 2003	-0.4279	0.4153	47	47	5.5%	0.65 [0.29 , 1.47]
Zeni 2009	1.3363	0.396	16	16	5.8%	3.80 [1.75 , 8.27]
Subtotal (95% CI)			**1683**	**1683**	**100.0%**	**0.85 [0.66 , 1.11]**
Heterogeneity: Tau² = 0.15; Chi² = 41.14, df = 22 (P = 0.008); I² = 47%						
Test for overall effect: Z = 1.17 (P = 0.24)						
8.3.25 Fatique						
Huang 2021	1.5249	1.5431	110	101	100.0%	4.59 [0.22 , 94.57]
Subtotal (95% CI)			**110**	**101**	**100.0%**	**4.59 [0.22 , 94.57]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.3.26 Emotional lability						
NCT02536105	2.2246	0.7239	80	74	100.0%	9.25 [2.24 , 38.22]
Subtotal (95% CI)			**80**	**74**	**100.0%**	**9.25 [2.24 , 38.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.07 (P = 0.002)						
8.3.27 Dysphoria						
NCT02536105	1.5325	1.5409	80	74	100.0%	4.63 [0.23 , 94.88]
Subtotal (95% CI)			**80**	**74**	**100.0%**	**4.63 [0.23 , 94.88]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.3.28 Moody						
Huang 2021	1.5249	1.5431	110	101	100.0%	4.59 [0.22 , 94.57]
Subtotal (95% CI)			**110**	**101**	**100.0%**	**4.59 [0.22 , 94.57]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.3.29 Uninterested						
Bhat 2020	0.1814	0.1944	526	526	100.0%	1.20 [0.82 , 1.75]
Subtotal (95% CI)			**526**	**526**	**100.0%**	**1.20 [0.82 , 1.75]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
8.3.30 Prone to crying						
Bhat 2020	0.5442	0.2591	526	526	100.0%	1.72 [1.04 , 2.86]
Subtotal (95% CI)			**526**	**526**	**100.0%**	**1.72 [1.04 , 2.86]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						

Test for subgroup differences: Chi² = 0.00, df = 29 (P < 0.00001), I² = 0%

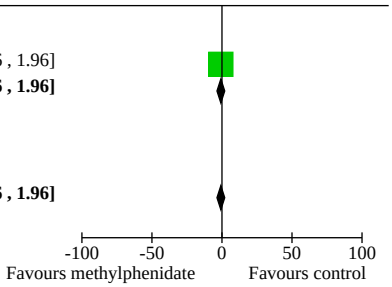


Footnotes

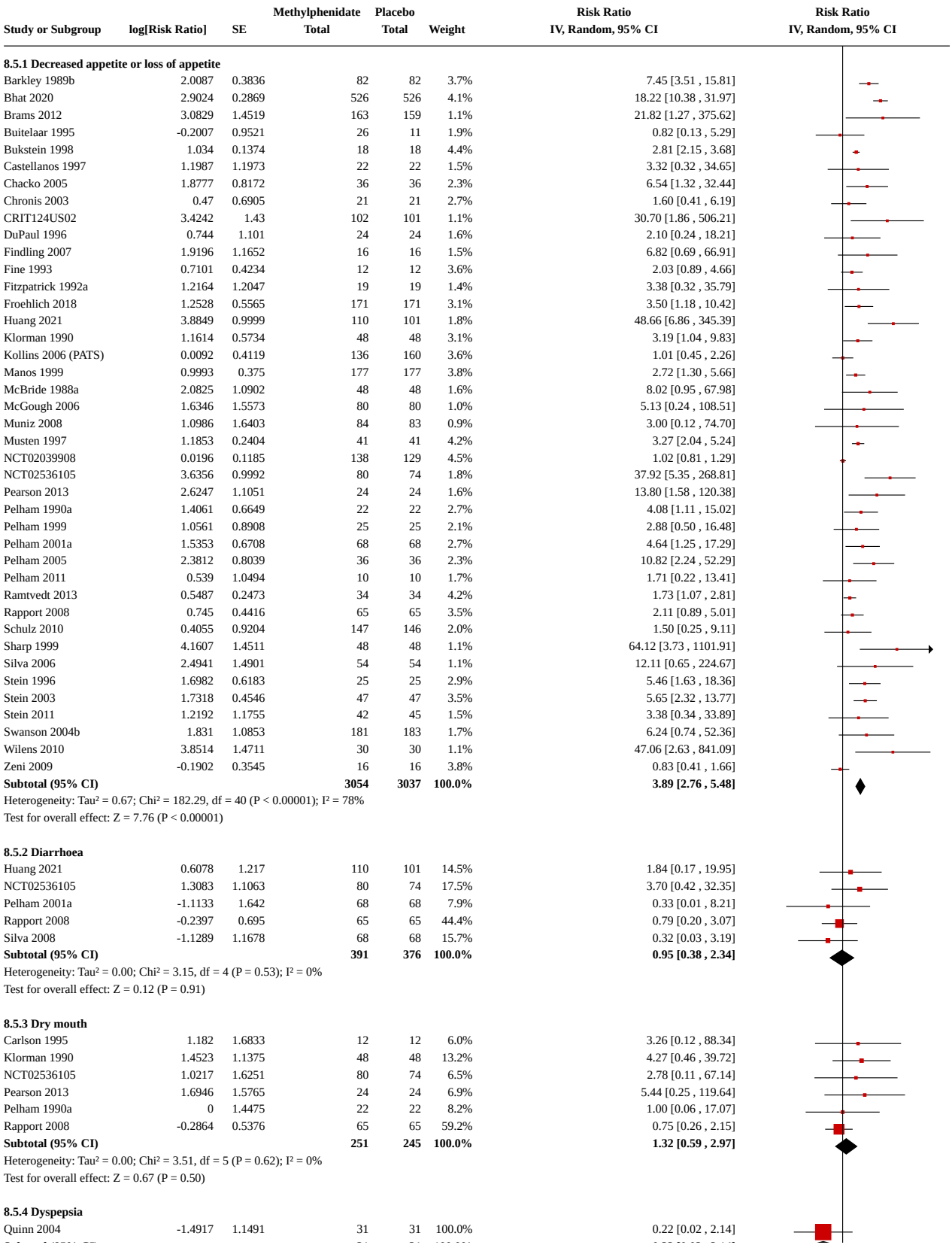
(1) Anger/aggression/oppositional behaviour

Analysis 8.4. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 4: Nervous system (including psychiatry) continuous outcomes

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
8.4.1 Anxiety								
Kritchman 2019	45.15	4.77	20	45.95	4.12	20	100.0%	-0.80 [-3.56 , 1.96]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-0.80 [-3.56 , 1.96]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								
Total (95% CI)			**20**			**20**	**100.0%**	**-0.80 [-3.56 , 1.96]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								
Test for subgroup differences: Not applicable								

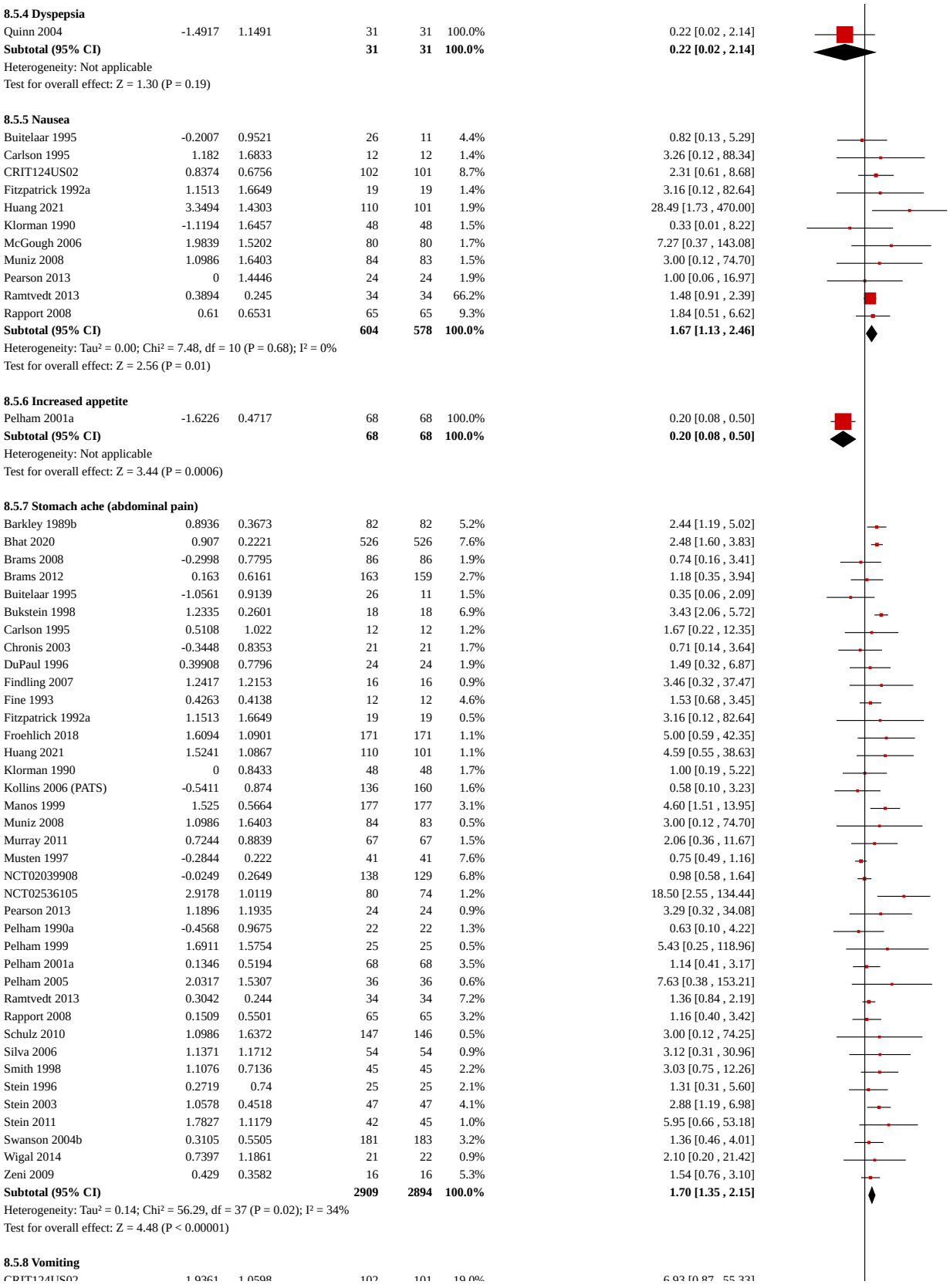


Analysis 8.5. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 5: Digestive system



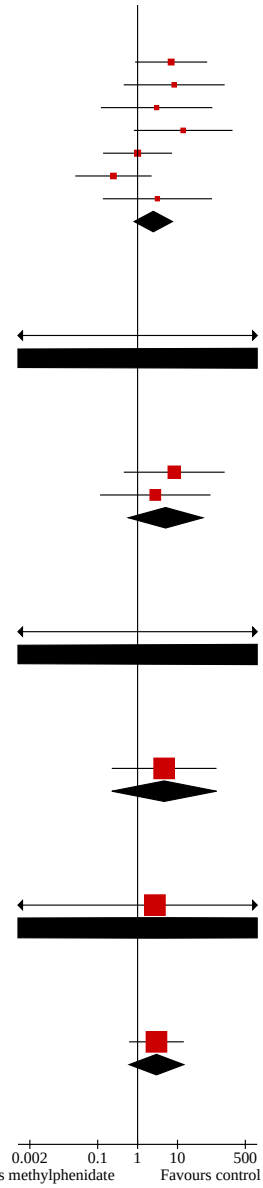
Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
8.5.1 Decreased appetite or loss of appetite						
Barkley 1989b	2.0087	0.3836	82	82	3.7%	7.45 [3.51 , 15.81]
Bhat 2020	2.9024	0.2869	526	526	4.1%	18.22 [10.38 , 31.97]
Brams 2012	3.0829	1.4519	163	159	1.1%	21.82 [1.27 , 375.62]
Buitelaar 1995	-0.2007	0.9521	26	11	1.9%	0.82 [0.13 , 5.29]
Bukstein 1998	1.034	0.1374	18	18	4.4%	2.81 [2.15 , 3.68]
Castellanos 1997	1.1987	1.1973	22	22	1.5%	3.32 [0.32 , 34.65]
Chacko 2005	1.8777	0.8172	36	36	2.3%	6.54 [1.32 , 32.44]
Chronis 2003	0.47	0.6905	21	21	2.7%	1.60 [0.41 , 6.19]
CRIT124US02	3.4242	1.43	102	101	1.1%	30.70 [1.86 , 506.21]
DuPaul 1996	0.744	1.101	24	24	1.6%	2.10 [0.24 , 18.21]
Findling 2007	1.9196	1.1652	16	16	1.5%	6.82 [0.69 , 66.91]
Fine 1993	0.7101	0.4234	12	12	3.6%	2.03 [0.89 , 4.66]
Fitzpatrick 1992a	1.2164	1.2047	19	19	1.4%	3.38 [0.32 , 35.79]
Froehlich 2018	1.2528	0.5565	171	171	3.1%	3.50 [1.18 , 10.42]
Huang 2021	3.8849	0.9999	110	101	1.8%	48.66 [6.86 , 345.39]
Klorman 1990	1.1614	0.5734	48	48	3.1%	3.19 [1.04 , 9.83]
Kollins 2006 (PATS)	0.0092	0.4119	136	160	3.6%	1.01 [0.45 , 2.26]
Manos 1999	0.9993	0.375	177	177	3.8%	2.72 [1.30 , 5.66]
McBride 1988a	2.0825	1.0902	48	48	1.6%	8.02 [0.95 , 67.98]
McGough 2006	1.6346	1.5573	80	80	1.0%	5.13 [0.24 , 108.51]
Muniz 2008	1.0986	1.6403	84	83	0.9%	3.00 [0.12 , 74.70]
Musten 1997	1.1853	0.2404	41	41	4.2%	3.27 [2.04 , 5.24]
NCT02039908	0.0196	0.1185	138	129	4.5%	1.02 [0.81 , 1.29]
NCT02536105	3.6356	0.9992	80	74	1.8%	37.92 [5.35 , 268.81]
Pearson 2013	2.6247	1.1051	24	24	1.6%	13.80 [1.58 , 120.38]
Pelham 1990a	1.4061	0.6649	22	22	2.7%	4.08 [1.11 , 15.02]
Pelham 1999	1.0561	0.8908	25	25	2.1%	2.88 [0.50 , 16.48]
Pelham 2001a	1.5353	0.6708	68	68	2.7%	4.64 [1.25 , 17.29]
Pelham 2005	2.3812	0.8039	36	36	2.3%	10.82 [2.24 , 52.29]
Pelham 2011	0.539	1.0494	10	10	1.7%	1.71 [0.22 , 13.41]
Ramtvedt 2013	0.5487	0.2473	34	34	4.2%	1.73 [1.07 , 2.81]
Rapport 2008	0.745	0.4416	65	65	3.5%	2.11 [0.89 , 5.01]
Schulz 2010	0.4055	0.9204	147	146	2.0%	1.50 [0.25 , 9.11]
Sharp 1999	4.1607	1.4511	48	48	1.1%	64.12 [3.73 , 1101.91]
Silva 2006	2.4941	1.4901	54	54	1.1%	12.11 [0.65 , 224.67]
Stein 1996	1.6982	0.6183	25	25	2.9%	5.46 [1.63 , 18.36]
Stein 2003	1.7318	0.4546	47	47	3.5%	5.65 [2.32 , 13.77]
Stein 2011	1.2192	1.1755	42	45	1.5%	3.38 [0.34 , 33.89]
Swanson 2004b	1.831	1.0853	181	183	1.7%	6.24 [0.74 , 52.36]
Wilens 2010	3.8514	1.4711	30	30	1.1%	47.06 [2.63 , 841.09]
Zeni 2009	-0.1902	0.3545	16	16	3.8%	0.83 [0.41 , 1.66]
Subtotal (95% CI)			**3054**	**3037**	**100.0%**	**3.89 [2.76 , 5.48]**
Heterogeneity: Tau² = 0.67; Chi² = 182.29, df = 40 (P < 0.00001); I² = 78%						
Test for overall effect: Z = 7.76 (P < 0.00001)						
8.5.2 Diarrhoea						
Huang 2021	0.6078	1.217	110	101	14.5%	1.84 [0.17 , 19.95]
NCT02536105	1.3083	1.1063	80	74	17.5%	3.70 [0.42 , 32.35]
Pelham 2001a	-1.1133	1.642	68	68	7.9%	0.33 [0.01 , 8.21]
Rapport 2008	-0.2397	0.695	65	65	44.4%	0.79 [0.20 , 3.07]
Silva 2008	-1.1289	1.1678	68	68	15.7%	0.32 [0.03 , 3.19]
Subtotal (95% CI)			**391**	**376**	**100.0%**	**0.95 [0.38 , 2.34]**
Heterogeneity: Tau² = 0.00; Chi² = 3.15, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
8.5.3 Dry mouth						
Carlson 1995	1.182	1.6833	12	12	6.0%	3.26 [0.12 , 88.34]
Klorman 1990	1.4523	1.1375	48	48	13.2%	4.27 [0.46 , 39.72]
NCT02536105	1.0217	1.6251	80	74	6.5%	2.78 [0.11 , 67.14]
Pearson 2013	1.6946	1.5765	24	24	6.9%	5.44 [0.25 , 119.64]
Pelham 1990a	0	1.4475	22	22	8.2%	1.00 [0.06 , 17.07]
Rapport 2008	-0.2864	0.5376	65	65	59.2%	0.75 [0.26 , 2.15]
Subtotal (95% CI)			**251**	**245**	**100.0%**	**1.32 [0.59 , 2.97]**
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
8.5.4 Dyspepsia						
Quinn 2004	-1.4917	1.1491	31	31	100.0%	0.22 [0.02 , 2.14]

Analysis 8.5. (Continued)



8.5.4 Dyspepsia							
Quinn 2004	-1.4917	1.1491	31	31	100.0%	0.22 [0.02 , 2.14]	
Subtotal (95% CI)			**31**	**31**	**100.0%**	**0.22 [0.02 , 2.14]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.30 (P = 0.19)							
8.5.5 Nausea							
Buitelaar 1995	-0.2007	0.9521	26	11	4.4%	0.82 [0.13 , 5.29]	
Carlson 1995	1.182	1.6833	12	12	1.4%	3.26 [0.12 , 88.34]	
CRIT124US02	0.8374	0.6756	102	101	8.7%	2.31 [0.61 , 8.68]	
Fitzpatrick 1992a	1.1513	1.6649	19	19	1.4%	3.16 [0.12 , 82.64]	
Huang 2021	3.3494	1.4303	110	101	1.9%	28.49 [1.73 , 470.00]	
Klorman 1990	-1.1194	1.6457	48	48	1.5%	0.33 [0.01 , 8.22]	
McGough 2006	1.9839	1.5202	80	80	1.7%	7.27 [0.37 , 143.08]	
Muniz 2008	1.0986	1.6403	84	83	1.5%	3.00 [0.12 , 74.70]	
Pearson 2013	0	1.4446	24	24	1.9%	1.00 [0.06 , 16.97]	
Ramtvedt 2013	0.3894	0.245	34	34	66.2%	1.48 [0.91 , 2.39]	
Rapport 2008	0.61	0.6531	65	65	9.3%	1.84 [0.51 , 6.62]	
Subtotal (95% CI)			**604**	**578**	**100.0%**	**1.67 [1.13 , 2.46]**	
Heterogeneity: Tau² = 0.00; Chi² = 7.48, df = 10 (P = 0.68); I² = 0%							
Test for overall effect: Z = 2.56 (P = 0.01)							
8.5.6 Increased appetite							
Pelham 2001a	-1.6226	0.4717	68	68	100.0%	0.20 [0.08 , 0.50]	
Subtotal (95% CI)			**68**	**68**	**100.0%**	**0.20 [0.08 , 0.50]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.44 (P = 0.0006)							
8.5.7 Stomach ache (abdominal pain)							
Barkley 1989b	0.8936	0.3673	82	82	5.2%	2.44 [1.19 , 5.02]	
Bhat 2020	0.907	0.2221	526	526	7.6%	2.48 [1.60 , 3.83]	
Brams 2008	-0.2998	0.7795	86	86	1.9%	0.74 [0.16 , 3.41]	
Brams 2012	0.163	0.6161	163	159	2.7%	1.18 [0.35 , 3.94]	
Buitelaar 1995	-1.0561	0.9139	26	11	1.5%	0.35 [0.06 , 2.09]	
Bukstein 1998	1.2335	0.2601	18	18	6.9%	3.43 [2.06 , 5.72]	
Carlson 1995	0.5108	1.022	12	12	1.2%	1.67 [0.22 , 12.35]	
Chronis 2003	-0.3448	0.8353	21	21	1.7%	0.71 [0.14 , 3.64]	
DuPaul 1996	0.39908	0.7796	24	24	1.9%	1.49 [0.32 , 6.87]	
Findling 2007	1.2417	1.2153	16	16	0.9%	3.46 [0.32 , 37.47]	
Fine 1993	0.4263	0.4138	12	12	4.6%	1.53 [0.68 , 3.45]	
Fitzpatrick 1992a	1.1513	1.6649	19	19	0.5%	3.16 [0.12 , 82.64]	
Froehlich 2018	1.6094	1.0901	171	171	1.1%	5.00 [0.59 , 42.35]	
Huang 2021	1.5241	1.0867	110	101	1.1%	4.59 [0.55 , 38.63]	
Klorman 1990	0	0.8433	48	48	1.7%	1.00 [0.19 , 5.22]	
Kollins 2006 (PATS)	-0.5411	0.874	136	160	1.6%	0.58 [0.10 , 3.23]	
Manos 1999	1.525	0.5664	177	177	3.1%	4.60 [1.51 , 13.95]	
Muniz 2008	1.0986	1.6403	84	83	0.5%	3.00 [0.12 , 74.70]	
Murray 2011	0.7244	0.8839	67	67	1.5%	2.06 [0.36 , 11.67]	
Musten 1997	-0.2844	0.222	41	41	7.6%	0.75 [0.49 , 1.16]	
NCT02039908	-0.0249	0.2649	138	129	6.8%	0.98 [0.58 , 1.64]	
NCT02536105	2.9178	1.0119	80	74	1.2%	18.50 [2.55 , 134.44]	
Pearson 2013	1.1896	1.1935	24	24	0.9%	3.29 [0.32 , 34.08]	
Pelham 1990a	-0.4568	0.9675	22	22	1.3%	0.63 [0.10 , 4.22]	
Pelham 1999	1.6911	1.5754	25	25	0.5%	5.43 [0.25 , 118.96]	
Pelham 2001a	0.1346	0.5194	68	68	3.5%	1.14 [0.41 , 3.17]	
Pelham 2005	2.0317	1.5307	36	36	0.6%	7.63 [0.38 , 153.21]	
Ramtvedt 2013	0.3042	0.244	34	34	7.2%	1.36 [0.84 , 2.19]	
Rapport 2008	0.1509	0.5501	65	65	3.2%	1.16 [0.40 , 3.42]	
Schulz 2010	1.0986	1.6372	147	146	0.5%	3.00 [0.12 , 74.25]	
Silva 2006	1.1371	1.1712	54	54	0.9%	3.12 [0.31 , 30.96]	
Smith 1998	1.1076	0.7136	45	45	2.2%	3.03 [0.75 , 12.26]	
Stein 1996	0.2719	0.74	25	25	2.1%	1.31 [0.31 , 5.60]	
Stein 2003	1.0578	0.4518	47	47	4.1%	2.88 [1.19 , 6.98]	
Stein 2011	1.7827	1.1179	42	45	1.0%	5.95 [0.66 , 53.18]	
Swanson 2004b	0.3105	0.5505	181	183	3.2%	1.36 [0.46 , 4.01]	
Wigal 2014	0.7397	1.1861	21	22	0.9%	2.10 [0.20 , 21.42]	
Zeni 2009	0.429	0.3582	16	16	5.3%	1.54 [0.76 , 3.10]	
Subtotal (95% CI)			**2909**	**2894**	**100.0%**	**1.70 [1.35 , 2.15]**	
Heterogeneity: Tau² = 0.14; Chi² = 56.29, df = 37 (P = 0.02); I² = 34%							
Test for overall effect: Z = 4.48 (P < 0.00001)							
8.5.8 Vomiting							
CRIT124US02	1.9361	1.0598	102	101	19.0%	6.93 [0.87 , 55.33]	

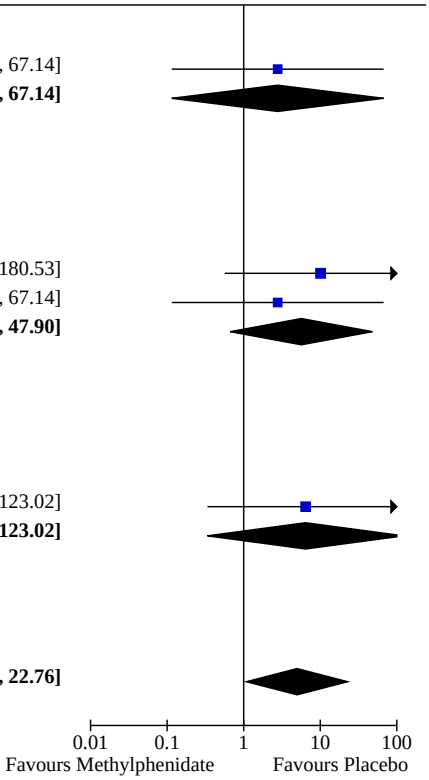
Analysis 8.5. (Continued)



8.5.8 Vomiting							
CRIT124US02	1.9361	1.0598	102	101	19.0%	6.93 [0.87 , 55.33]	
Huang 2021	2.1127	1.4844	110	101	11.5%	8.27 [0.45 , 151.73]	
Muniz 2008	1.0986	1.6403	84	83	9.8%	3.00 [0.12 , 74.70]	
NCT02536105	2.6311	1.4518	80	74	12.0%	13.89 [0.81 , 239.03]	
Pelham 2001a	0	1.015	68	68	20.1%	1.00 [0.14 , 7.31]	
Swanson 2004b	-1.3919	1.123	181	183	17.5%	0.25 [0.03 , 2.25]	
Wigal 2014	1.1431	1.6055	21	22	10.2%	3.14 [0.13 , 72.95]	
Subtotal (95% CI)			**646**	**632**	**100.0%**	**2.47 [0.82 , 7.47]**	
Heterogeneity: Tau² = 0.56; Chi² = 8.02, df = 6 (P = 0.24); I² = 25%							
Test for overall effect: Z = 1.60 (P = 0.11)							
8.5.9 Upper abdominal pain							
CRIT124US02	13	102	6	101	100.0%	442413.39 [0.00 , 2.940259573129469e+92]	
Subtotal (95% CI)			**6**	**101**	**100.0%**	**442413.39 [0.00 , 2.940259573129469e+92]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.13 (P = 0.90)							
8.5.10 Decreased weight							
Huang 2021	2.1127	1.4844	110	101	54.5%	8.27 [0.45 , 151.73]	
NCT02536105	1.0217	1.6251	80	74	45.5%	2.78 [0.11 , 67.14]	
Subtotal (95% CI)			**190**	**175**	**100.0%**	**5.04 [0.59 , 43.15]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%							
Test for overall effect: Z = 1.47 (P = 0.14)							
8.5.11 Gastrointestinal distress							
NCT02536105	9	80	3	74	100.0%	8103.08 [0.00 , 1.0110527023718684e+72]	
Subtotal (95% CI)			**3**	**74**	**100.0%**	**8103.08 [0.00 , 1.0110527023718684e+72]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.11 (P = 0.91)							
8.5.12 Constipation							
NCT02536105	1.5325	1.5409	80	74	100.0%	4.63 [0.23 , 94.88]	
Subtotal (95% CI)			**80**	**74**	**100.0%**	**4.63 [0.23 , 94.88]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
8.5.13 Oropharyngeal pain							
Huang 2021	1	110	110	101	100.0%	2.72 [0.00 , 1.1653710777400273e+94]	
Subtotal (95% CI)			**110**	**101**	**100.0%**	**2.72 [0.00 , 1.1653710777400273e+94]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.01 (P = 0.99)							
8.5.14 Anorexia							
CRIT124US02	1.0888	0.8043	102	101	100.0%	2.97 [0.61 , 14.37]	
Subtotal (95% CI)			**102**	**101**	**100.0%**	**2.97 [0.61 , 14.37]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							
Test for subgroup differences: Chi² = 0.00, df = 13 (P < 0.00001), I² = 0%							

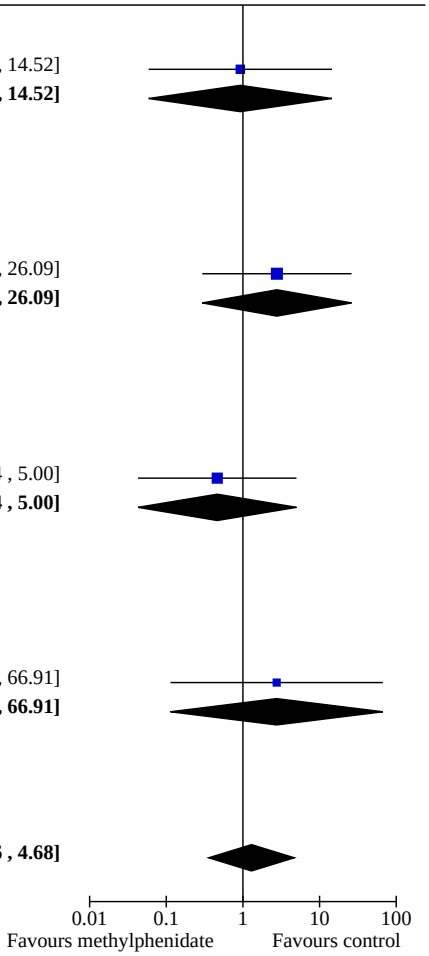
Analysis 8.6. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 6: Cardiovascular system

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.6.1 Epistaxis						
NCT02536105	1	80	0	74	22.8%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**22.8%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.6.2 Heart palpitations						
Huang 2021	5	110	0	101	27.8%	10.11 [0.57 , 180.53]
NCT02536105	1	80	0	74	22.8%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**190**		**175**	**50.6%**	**5.65 [0.67 , 47.90]**
Total events:	6		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0\%$						
Test for overall effect: Z = 1.59 (P = 0.11)						
8.6.3 Chest pain						
Huang 2021	3	110	0	101	26.6%	6.43 [0.34 , 123.02]
Subtotal (95% CI)		**110**		**101**	**26.6%**	**6.43 [0.34 , 123.02]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
Total (95% CI)		**380**		**350**	**100.0%**	**4.97 [1.09 , 22.76]**
Total events:	10		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.54$, df = 3 (P = 0.91); $I^2 = 0\%$						
Test for overall effect: Z = 2.07 (P = 0.04)						
Test for subgroup differences: $Chi^2 = 0.17$, df = 2 (P = 0.92), $I^2 = 0\%$						



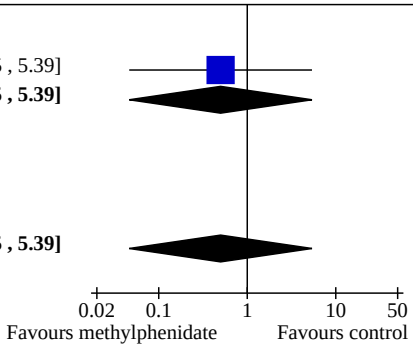
Analysis 8.7. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 7: Respiratory system

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.7.1 Nasal congestion						
NCT02536105	1	80	1	74	21.8%	0.93 [0.06 , 14.52]
Subtotal (95% CI)		**80**		**74**	**21.8%**	**0.93 [0.06 , 14.52]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.96)						
8.7.2 Strep throat/sore throat						
NCT02536105	3	80	1	74	32.9%	2.77 [0.30 , 26.09]
Subtotal (95% CI)		**80**		**74**	**32.9%**	**2.77 [0.30 , 26.09]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
8.7.3 Cough						
NCT02536105	1	80	2	74	29.1%	0.46 [0.04 , 5.00]
Subtotal (95% CI)		**80**		**74**	**29.1%**	**0.46 [0.04 , 5.00]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.53)						
8.7.4 Dyspnea						
Huang 2021	1	110	0	101	16.2%	2.76 [0.11 , 66.91]
Subtotal (95% CI)		**110**		**101**	**16.2%**	**2.76 [0.11 , 66.91]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
Total (95% CI)		**350**		**323**	**100.0%**	**1.29 [0.36 , 4.68]**
Total events:	6		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.44$, df = 3 (P = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 0.39 (P = 0.69)						
Test for subgroup differences: $Chi^2 = 1.44$, df = 3 (P = 0.70), $I^2 = 0\%$						



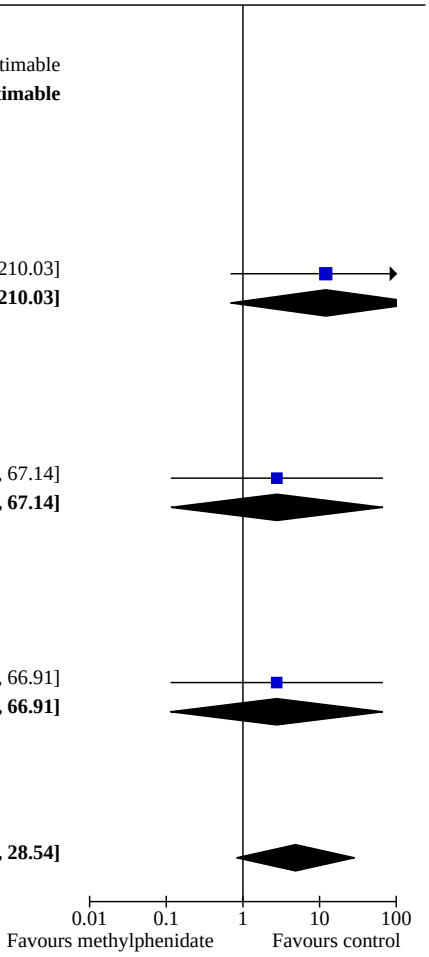
Analysis 8.8. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 8: Urinary system

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
8.8.1 Urinary incontinence						
Pelham 2001a	1	68	2	68	100.0%	0.50 [0.05 , 5.39]
Subtotal (95% CI)		**68**		**68**	**100.0%**	**0.50 [0.05 , 5.39]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**68**		**68**	**100.0%**	**0.50 [0.05 , 5.39]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Not applicable						



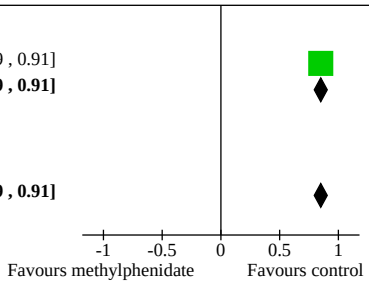
Analysis 8.9. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 9: Skeletal and muscular system

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.9.1 Ankle pain/strain						
NCT02536105	0	80	0	74		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.9.2 Muscle strain/pain						
NCT02536105	6	80	0	74	38.3%	12.04 [0.69 , 210.03]
Subtotal (95% CI)		**80**		**74**	**38.3%**	**12.04 [0.69 , 210.03]**
Total events:	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
8.9.3 Toe fracture						
NCT02536105	1	80	0	74	30.9%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**30.9%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.9.4 Asthenia						
Huang 2021	1	110	0	101	30.8%	2.76 [0.11 , 66.91]
Subtotal (95% CI)		**110**		**101**	**30.8%**	**2.76 [0.11 , 66.91]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
Total (95% CI)		**350**		**323**	**100.0%**	**4.86 [0.83 , 28.54]**
Total events:	8		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 0.63, df = 2 (P = 0.73), I² = 0%						



Analysis 8.10. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 10: Skeletal and muscular system continuous outcomes

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
8.10.1 Somatic complaints								
Gorman 2006	1.14	0.15	41	0.29	0.1	41	100.0%	0.85 [0.79 , 0.91]
Subtotal (95% CI)			**41**			**41**	**100.0%**	**0.85 [0.79 , 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 30.19 (P < 0.00001)								
Total (95% CI)			**41**			**41**	**100.0%**	**0.85 [0.79 , 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 30.19 (P < 0.00001)								
Test for subgroup differences: Not applicable								

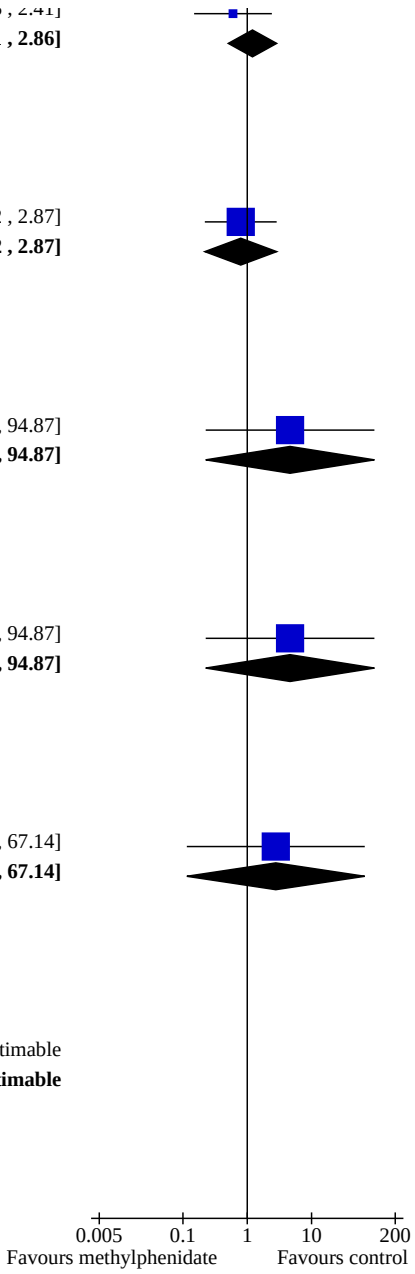


Analysis 8.11. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 11: Immune system (including infections)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
8.11.1 Allergic rhinitis						
McGough 2006	2	80	0	80	21.0%	5.00 [0.24 , 102.53]
Pelham 2001a	1	68	0	68	18.9%	3.00 [0.12 , 72.37]
Silva 2008	1	68	2	68	33.9%	0.50 [0.05 , 5.39]
Wigal 2014	1	21	1	22	26.2%	1.05 [0.07 , 15.69]
Subtotal (95% CI)		**237**		**238**	**100.0%**	**1.38 [0.35 , 5.51]**
Total events:	5		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.67, df = 3 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
8.11.2 Fever						
Pearson 2013	0	24	1	24	48.2%	0.33 [0.01 , 7.80]
Wigal 2014	2	21	0	22	51.8%	5.23 [0.27 , 102.87]
Subtotal (95% CI)		**45**		**46**	**100.0%**	**1.39 [0.09 , 20.56]**
Total events:	2		1			
Heterogeneity: Tau² = 1.34; Chi² = 1.55, df = 1 (P = 0.21); I² = 35%						
Test for overall effect: Z = 0.24 (P = 0.81)						
8.11.3 Lymphadenitis						
McGough 2006	2	80	0	80	52.6%	5.00 [0.24 , 102.53]
Silva 2008	1	68	0	68	47.4%	3.00 [0.12 , 72.37]
Subtotal (95% CI)		**148**		**148**	**100.0%**	**3.93 [0.44 , 35.11]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
8.11.4 Pharyngolaryngeal pain						
McGough 2006	2	80	1	80	100.0%	2.00 [0.19 , 21.62]
Subtotal (95% CI)		**80**		**80**	**100.0%**	**2.00 [0.19 , 21.62]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
8.11.5 Pharyngitis						
Brams 2012	1	163	4	159	36.0%	0.24 [0.03 , 2.16]
McGough 2006	1	80	2	80	30.2%	0.50 [0.05 , 5.40]
Pelham 2001a	1	68	0	68	16.9%	3.00 [0.12 , 72.37]
Silva 2008	1	68	0	68	16.9%	3.00 [0.12 , 72.37]
Subtotal (95% CI)		**379**		**375**	**100.0%**	**0.71 [0.19 , 2.62]**
Total events:	4		6			
Heterogeneity: Tau² = 0.00; Chi² = 2.58, df = 3 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.60)						
8.11.6 Upper respiratory tract infection						
Brams 2012	3	163	4	159	17.1%	0.73 [0.17 , 3.22]
CRIT124US02	15	102	5	101	24.0%	2.97 [1.12 , 7.87]
McGough 2006	0	80	3	80	6.9%	0.14 [0.01 , 2.72]
Murray 2011	1	67	1	67	7.7%	1.00 [0.06 , 15.66]
NCT02536105	10	80	1	74	11.9%	9.25 [1.21 , 70.51]
Pelham 2001a	2	68	3	68	14.2%	0.67 [0.12 , 3.86]
Silva 2008	3	68	5	68	18.2%	0.60 [0.15 , 2.41]
Subtotal (95% CI)		**628**		**617**	**100.0%**	**1.21 [0.51 , 2.86]**

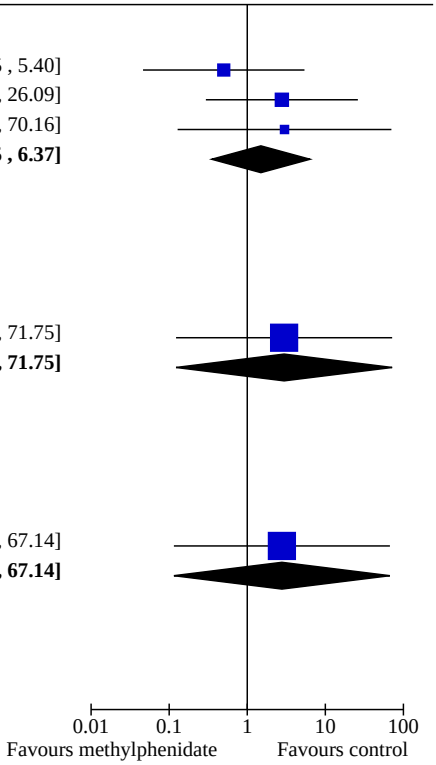
Analysis 8.11. (Continued)

Silva 2006	3	68	3	68	18.2%	0.60 [0.13 , 2.41]
Subtotal (95% CI)		**628**		**617**	**100.0%**	**1.21 [0.51 , 2.86]**
Total events:	34		22			
Heterogeneity: Tau² = 0.57; Chi² = 10.82, df = 6 (P = 0.09); I² = 45%						
Test for overall effect: Z = 0.42 (P = 0.67)						
8.11.7 Nasopharyngitis						
CRIT124US02	4	102	5	101	100.0%	0.79 [0.22 , 2.87]
Subtotal (95% CI)		**102**		**101**	**100.0%**	**0.79 [0.22 , 2.87]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
8.11.8 Influenza						
NCT02536105	2	80	0	74	100.0%	4.63 [0.23 , 94.87]
Subtotal (95% CI)		**80**		**74**	**100.0%**	**4.63 [0.23 , 94.87]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.11.9 Mouth ulcers/bad breath						
NCT02536105	2	80	0	74	100.0%	4.63 [0.23 , 94.87]
Subtotal (95% CI)		**80**		**74**	**100.0%**	**4.63 [0.23 , 94.87]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.11.10 Urinary tract infection						
NCT02536105	1	80	0	74	100.0%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**100.0%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.11.11 Otitis media (ear pain)						
NCT02536105	0	80	0	74		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

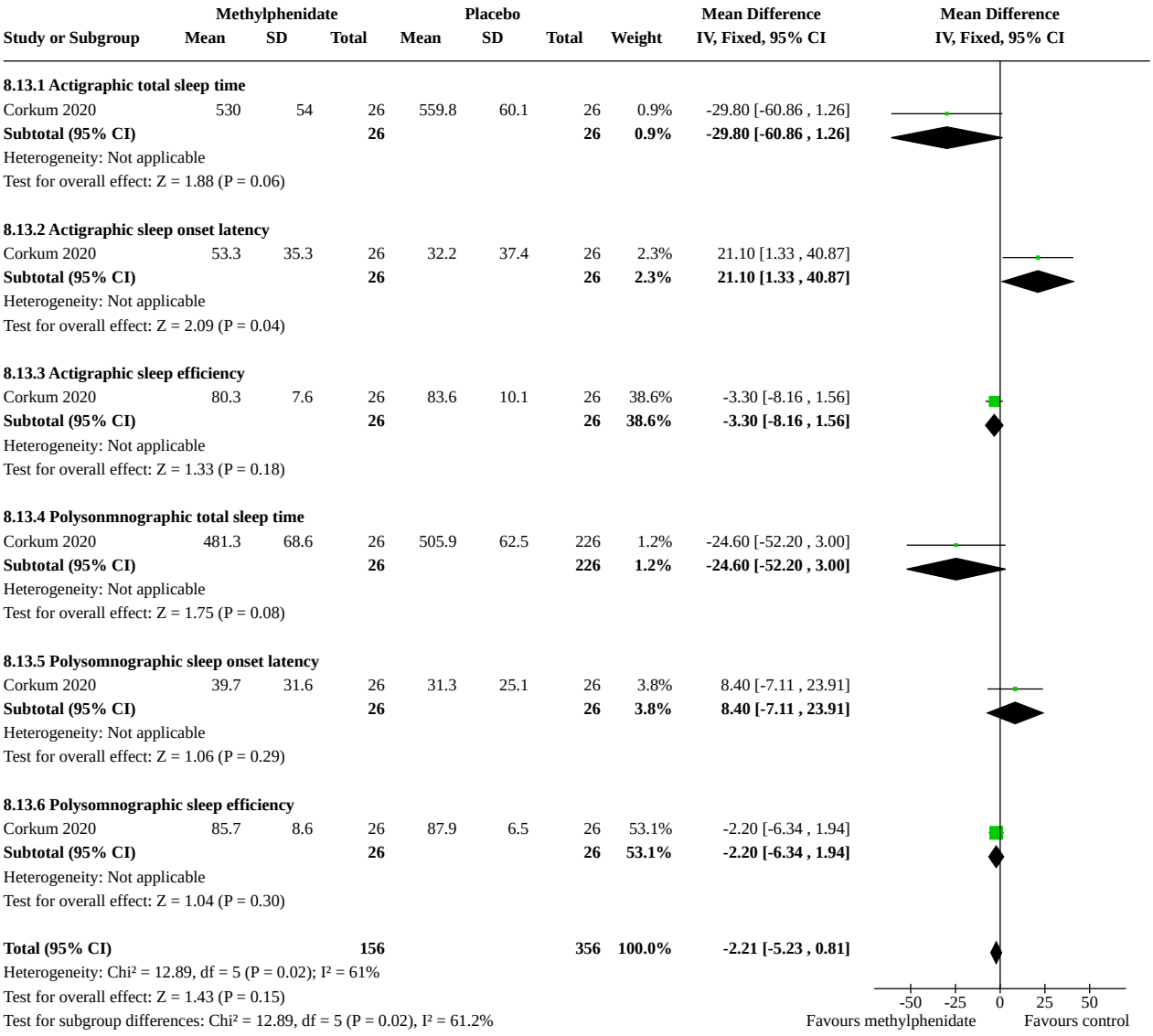


Analysis 8.12. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 12: Integumentary system

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
8.12.1 Rash						
McGough 2006	1	80	2	80	37.1%	0.50 [0.05 , 5.40]
NCT02536105	3	80	1	74	41.8%	2.77 [0.30 , 26.09]
Pearson 2013	1	24	0	24	21.1%	3.00 [0.13 , 70.16]
Subtotal (95% CI)		**184**		**178**	**100.0%**	**1.49 [0.35 , 6.37]**
Total events:	5		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
8.12.2 Skin laceration						
Muniz 2008	1	84	0	83	100.0%	2.96 [0.12 , 71.75]
Subtotal (95% CI)		**84**		**83**	**100.0%**	**2.96 [0.12 , 71.75]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
8.12.3 Cellulitis						
NCT02536105	1	80	0	74	100.0%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**100.0%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						

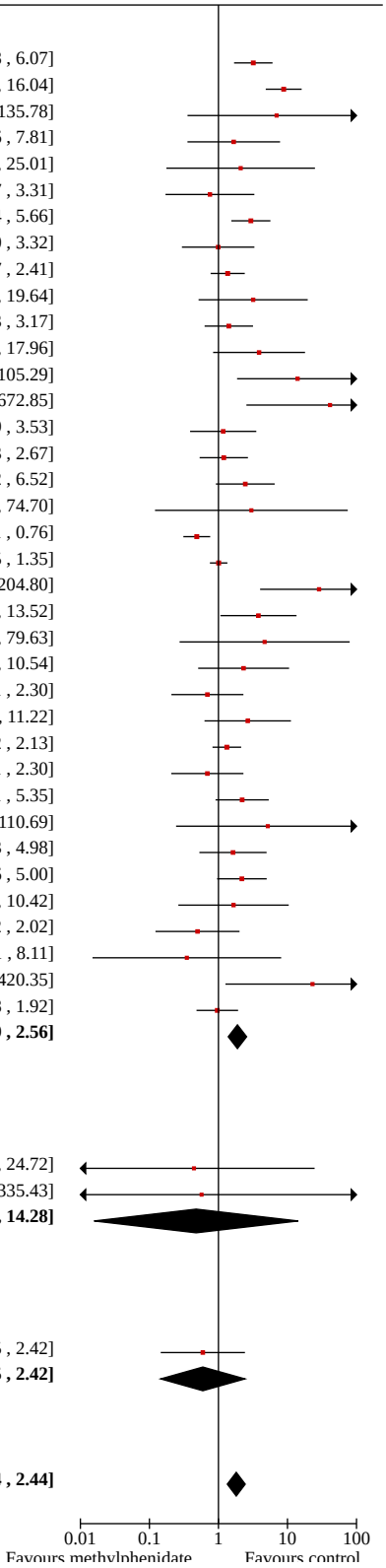


Analysis 8.13. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 13: Sleep variability continuous outcomes



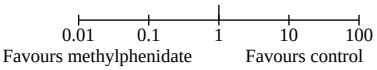
Analysis 8.14. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 14: Sleep variability

Study or Subgroup	log[Risk Ratio]	SE	Methylphenidate Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
8.14.1 Insomnia or sleep problems						
Barkley 1989b	1.1626	0.3272	82	82	4.1%	3.20 [1.68 , 6.07]
Bhat 2020	2.1768	0.3054	526	526	4.2%	8.82 [4.85 , 16.04]
Brams 2012	1.9397	1.516	163	159	0.8%	6.96 [0.36 , 135.78]
Buitelaar 1995	0.5108	0.7879	26	11	2.2%	1.67 [0.36 , 7.81]
Castellanos 1997	0.7419	1.264	22	22	1.1%	2.10 [0.18 , 25.01]
Chronis 2003	-0.2838	0.7559	21	21	2.3%	0.75 [0.17 , 3.31]
Corkum 2008	1.0814	0.3326	21	21	4.1%	2.95 [1.54 , 5.66]
CRIT124US02	-0.0099	0.6167	102	101	2.8%	0.99 [0.30 , 3.32]
DuPaul 1996	0.3083	0.2905	24	24	4.3%	1.36 [0.77 , 2.41]
Findling 2007	1.1575	0.9286	16	16	1.8%	3.18 [0.52 , 19.64]
Fine 1993	0.346	0.4119	12	12	3.7%	1.41 [0.63 , 3.17]
Fitzpatrick 1992a	1.3555	0.7821	19	19	2.2%	3.88 [0.84 , 17.96]
Froehlich 2018	2.6391	1.0294	171	171	1.5%	14.00 [1.86 , 105.29]
Huang 2021	3.7221	1.4232	110	101	0.9%	41.35 [2.54 , 672.85]
Klorman 1990	0.1582	0.5632	48	48	3.0%	1.17 [0.39 , 3.53]
Kollins 2006 (PATS)	0.1782	0.4108	136	160	3.7%	1.20 [0.53 , 2.67]
Manos 1999	0.8952	0.5001	177	177	3.3%	2.45 [0.92 , 6.52]
Muniz 2008	1.0986	1.6403	84	83	0.7%	3.00 [0.12 , 74.70]
Musten 1997	-0.7228	0.2283	41	41	4.6%	0.49 [0.31 , 0.76]
NCT02039908	0.0067	0.1486	138	129	4.9%	1.01 [0.75 , 1.35]
NCT02536105	3.356	1.0031	80	74	1.6%	28.67 [4.01 , 204.80]
Pearson 2013	1.335	0.6475	24	24	2.7%	3.80 [1.07 , 13.52]
Pelham 1990a	1.5404	1.4475	22	22	0.9%	4.67 [0.27 , 79.63]
Pelham 1999	0.8398	0.7734	25	25	2.2%	2.32 [0.51 , 10.54]
Pelham 2001a	-0.3687	0.6125	68	68	2.8%	0.69 [0.21 , 2.30]
Pelham 2005	0.9765	0.7355	36	36	2.3%	2.66 [0.63 , 11.22]
Ramtvedt 2013	0.2796	0.2438	34	34	4.5%	1.32 [0.82 , 2.13]
Rapport 2008	-0.3704	0.6138	65	65	2.8%	0.69 [0.21 , 2.30]
Sharp 1999	0.7902	0.4528	48	48	3.5%	2.20 [0.91 , 5.35]
Silva 2006	1.6468	1.5612	54	54	0.8%	5.19 [0.24 , 110.69]
Stein 1996	0.4855	0.5718	25	25	3.0%	1.62 [0.53 , 4.98]
Stein 2003	0.7816	0.4222	47	47	3.7%	2.18 [0.96 , 5.00]
Stein 2011	0.5031	0.9393	42	45	1.7%	1.65 [0.26 , 10.42]
Swanson 2004b	-0.6988	0.715	181	183	2.4%	0.50 [0.12 , 2.02]
Wigal 2014	-1.0542	1.6055	21	22	0.8%	0.35 [0.01 , 8.11]
Wilens 2010	3.1374	1.4815	30	30	0.9%	23.04 [1.26 , 420.35]
Zeni 2009	-0.0382	0.3536	16	16	4.0%	0.96 [0.48 , 1.92]
Subtotal (95% CI)			**2757**	**2742**	**96.9%**	**1.88 [1.39 , 2.56]**
Heterogeneity: Tau² = 0.47; Chi² = 117.21, df = 36 (P < 0.00001); I² = 69%						
Test for overall effect: Z = 4.05 (P < 0.0001)						
8.14.2 Sleep efficiency (SEF)						
Schwartz 2004	-0.8163	2.053	44	44	0.5%	0.44 [0.01 , 24.72]
Tirosh 1993b	-0.5623	3.254	10	10	0.2%	0.57 [0.00 , 335.43]
Subtotal (95% CI)			**54**	**54**	**0.7%**	**0.48 [0.02 , 14.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
8.14.3 Initial insomnia						
CRIT124US02	-0.5207	0.7167	102	101	2.4%	0.59 [0.15 , 2.42]
Subtotal (95% CI)			**102**	**101**	**2.4%**	**0.59 [0.15 , 2.42]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)			**2913**	**2897**	**100.0%**	**1.81 [1.34 , 2.44]**
Heterogeneity: Tau² = 0.46; Chi² = 119.24, df = 39 (P < 0.00001); I² = 67%						
Test for overall effect: Z = 3.90 (P < 0.0001)						
Test for subgroup differences: Chi² = 3.05, df = 2 (P = 0.22), I² = 34.5%						



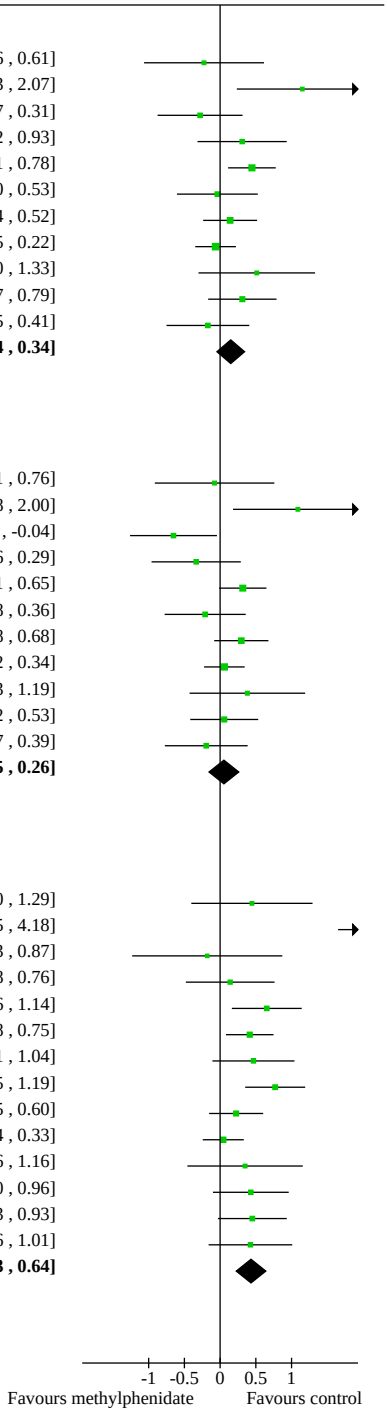
Analysis 8.14. (Continued)

Test for overall effect: Z = 3.90 (P < 0.0001)
Test for subgroup differences: Chi² = 3.05, df = 2 (P = 0.22), I² = 34.5%



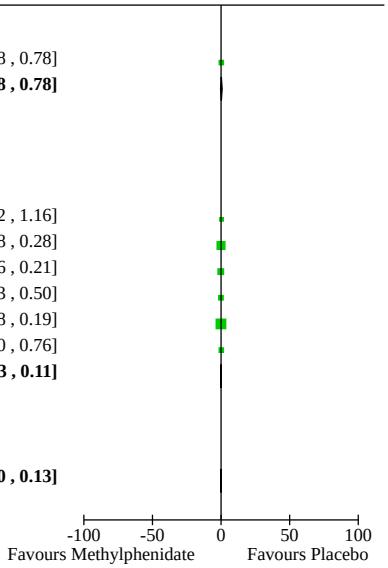
Analysis 8.15. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 15: Vital signs

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
8.15.1 Diastolic blood pressure (mmHg)								
Brown 1984a	61.27	2.87	11	62	3.35	11	4.4%	-0.23 [-1.06 , 0.61]
Brown 1988	83	4.51	11	69	15.93	11	3.8%	1.15 [0.23 , 2.07]
Brown 1991	72	12.65	22	76	15.23	22	7.6%	-0.28 [-0.87 , 0.31]
Findling 2007	64.7	8.6	20	61.7	10.4	20	7.1%	0.31 [-0.32 , 0.93]
Gadow 2007	64.5	11	71	60	9	71	15.2%	0.45 [0.11 , 0.78]
Pearson 2013	70.17	7.5	24	70.48	8.3	24	8.2%	-0.04 [-0.60 , 0.53]
Silva 2005a	66.8	9.6	54	65.5	8.8	54	13.4%	0.14 [-0.24 , 0.52]
Stein 2011	63.96	9.386	90	64.53	8.57	101	17.3%	-0.06 [-0.35 , 0.22]
Tannock 1989	66.6	5.7	12	63.8	4.8	12	4.7%	0.51 [-0.30 , 1.33]
Urman 1995	75.8	5.3	34	74.1	5.5	34	10.3%	0.31 [-0.17 , 0.79]
Zeiner 1999	66.9	12.2	23	68.7	8.1	23	7.9%	-0.17 [-0.75 , 0.41]
Subtotal (95% CI)			**372**			**383**	**100.0%**	**0.15 [-0.04 , 0.34]**
Heterogeneity: Tau² = 0.04; Chi² = 15.58, df = 10 (P = 0.11); I² = 36%								
Test for overall effect: Z = 1.51 (P = 0.13)								
8.15.2 Systolic blood pressure (mmHg)								
Brown 1984a	92.36	5.57	11	92.73	3.38	11	4.9%	-0.08 [-0.91 , 0.76]
Brown 1988	98	1.54	11	94.66	3.88	11	4.3%	1.09 [0.18 , 2.00]
Brown 1991	119.5	8.23	22	124	4.9	22	7.7%	-0.65 [-1.26 , -0.04]
Findling 2007	114.9	11.7	20	118.1	6.2	20	7.5%	-0.33 [-0.96 , 0.29]
Gadow 2007	104.3	15.2	71	99	17.9	71	14.5%	0.32 [-0.01 , 0.65]
Pearson 2013	103.6	9.4	24	105.7	10.3	24	8.5%	-0.21 [-0.78 , 0.36]
Silva 2005a	104.7	9.4	54	101.8	10	54	13.0%	0.30 [-0.08 , 0.68]
Stein 2011	103.96	12.017	90	103.25	11.725	101	16.0%	0.06 [-0.22 , 0.34]
Tannock 1989	104.4	9.8	12	100.7	8.9	12	5.1%	0.38 [-0.43 , 1.19]
Urman 1995	105	9.2	34	104.5	7.8	34	10.4%	0.06 [-0.42 , 0.53]
Zeiner 1999	111.8	14.3	23	114.3	10.8	23	8.2%	-0.19 [-0.77 , 0.39]
Subtotal (95% CI)			**372**			**383**	**100.0%**	**0.05 [-0.15 , 0.26]**
Heterogeneity: Tau² = 0.05; Chi² = 17.80, df = 10 (P = 0.06); I² = 44%								
Test for overall effect: Z = 0.50 (P = 0.62)								
8.15.3 Pulse or heart rate (bpm)								
Brown 1984a	86.82	8.59	11	82.91	8.3	11	4.3%	0.45 [-0.40 , 1.29]
Brown 1988	82.5	3.2	11	71.83	3.81	11	2.3%	2.92 [1.65 , 4.18]
Brown 1991	87.25	8.54	7	89	9.63	7	3.1%	-0.18 [-1.23 , 0.87]
Findling 2007	91.4	14.3	20	89.5	12	20	6.4%	0.14 [-0.48 , 0.76]
Gadow 1995	93.5	13.9	34	85.5	10	34	8.2%	0.65 [0.16 , 1.14]
Gadow 2007	91.6	14.8	71	86	11.9	71	10.8%	0.41 [0.08 , 0.75]
Pearson 2013	97.43	15.8	24	89.57	17.3	24	7.0%	0.47 [-0.11 , 1.04]
Rapport 1987	94.2	11.2	47	86.2	9.3	47	9.3%	0.77 [0.35 , 1.19]
Silva 2005a	90.6	12.4	54	88.2	8.5	54	10.0%	0.22 [-0.15 , 0.60]
Stein 2011	73.2	9.853	89	72.72	11.801	98	11.7%	0.04 [-0.24 , 0.33]
Tannock 1989	96.3	12.3	12	91.9	12	12	4.6%	0.35 [-0.46 , 1.16]
Tannock 1995a	95.9	8.9	28	91.7	10.3	28	7.5%	0.43 [-0.10 , 0.96]
Urman 1995	91.2	12.4	34	86.1	9.8	34	8.3%	0.45 [-0.03 , 0.93]
Zeiner 1999	75.8	15.5	23	69.6	13.1	23	6.8%	0.42 [-0.16 , 1.01]
Subtotal (95% CI)			**465**			**474**	**100.0%**	**0.43 [0.23 , 0.64]**
Heterogeneity: Tau² = 0.07; Chi² = 27.84, df = 13 (P = 0.010); I² = 53%								
Test for overall effect: Z = 4.11 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%								



Analysis 8.16. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 16: Physical parameters

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
8.16.1 Height (cm)								
Zeiner 1999	150.4	11.2	23	148.3	9.4	23	8.0%	0.20 [-0.38 , 0.78]
Subtotal (95% CI)			**23**			**23**	**8.0%**	**0.20 [-0.38 , 0.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
8.16.2 Weight								
Brown 1988	103.66	4.63	11	102.16	4.4	11	3.8%	0.32 [-0.52 , 1.16]
Gadow 2007	77.8	31.6	71	79.3	32.3	71	24.8%	-0.05 [-0.38 , 0.28]
Gorman 2006	36.09	1.99	41	36.54	2.01	41	14.2%	-0.22 [-0.66 , 0.21]
Pearson 2013	32.47	8.8	24	33.03	8.6	24	8.4%	-0.06 [-0.63 , 0.50]
Stein 2011	49.716	18.9817	88	51.624	22.2636	102	32.9%	-0.09 [-0.38 , 0.19]
Zeiner 1999	42	10.2	23	40.3	8	23	8.0%	0.18 [-0.40 , 0.76]
Subtotal (95% CI)			**258**			**272**	**92.0%**	**-0.06 [-0.23 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 2.04, df = 5 (P = 0.84); I² = 0%								
Test for overall effect: Z = 0.65 (P = 0.52)								
Total (95% CI)			**281**			**295**	**100.0%**	**-0.04 [-0.20 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 2.73, df = 6 (P = 0.84); I² = 0%								
Test for overall effect: Z = 0.43 (P = 0.67)								
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%								

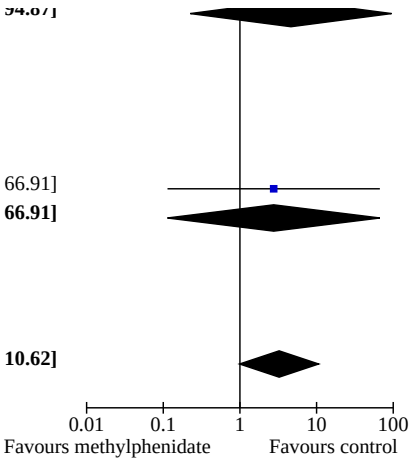


Analysis 8.17. Comparison 8: Non-serious adverse events: cross-over trials (endpoint data), Outcome 17: Other (including drug toxicity)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.17.1 Growth hormone deficiency						
NCT02536105	0	80	0	74		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.17.2 Eye pain						
NCT02536105	1	80	0	74	13.8%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**13.8%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.17.3 Carious teeth						
NCT02536105	0	80	0	74		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.17.4 Foreign body swallowed						
NCT02536105	1	80	0	74	13.8%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**13.8%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.17.5 Bug bites/bee stings						
NCT02536105	2	80	0	74	15.4%	4.63 [0.23 , 94.87]
Subtotal (95% CI)		**80**		**74**	**15.4%**	**4.63 [0.23 , 94.87]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.17.6 Sunburn						
NCT02536105	1	80	0	74	13.8%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**13.8%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.17.7 Finger laceration						
NCT02536105	1	80	0	74	13.8%	2.78 [0.11 , 67.14]
Subtotal (95% CI)		**80**		**74**	**13.8%**	**2.78 [0.11 , 67.14]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
8.17.8 Flat affect (lack of emotional expression)						
NCT02536105	2	80	0	74	15.4%	4.63 [0.23 , 94.87]
Subtotal (95% CI)		**80**		**74**	**15.4%**	**4.63 [0.23 , 94.87]**
Total events:	2		0			

Analysis 8.17. (Continued)

Subtotal (95% CI)		**80**		**74**	**13.4%**	**4.63 [0.23 , 94.87]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
8.17.9 Peripheral oedema						
Huang 2021	1	110	0	101	13.8%	2.76 [0.11 , 66.91]
Subtotal (95% CI)		**110**		**101**	**13.8%**	**2.76 [0.11 , 66.91]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
Total (95% CI)		**750**		**693**	**100.0%**	**3.25 [0.99 , 10.62]**
Total events:	9		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 6 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.95 (P = 0.05)						
Test for subgroup differences: Chi² = 0.15, df = 6 (P = 1.00), I² = 0%						



Comparison 9. Teacher-rated general behaviour

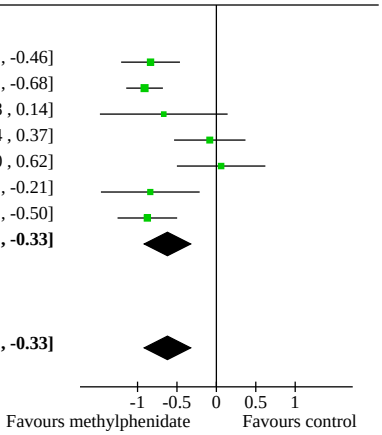
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 All parallel-group trials and first-period cross-over trials	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.1.1 High risk of bias	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.2 Subgroup analysis: types of scales	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.2.1 Conners' Global Index - Teacher (CGI-T)	1	314	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.14, -0.68]
9.2.2 Groninger Behaviour Observation Scale (GBOS)	1	43	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.46, -0.21]
9.2.3 Conners' Teacher Rating Scale (CTRS-RS)	1	75	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.54, 0.37]
9.2.4 Conners' Teacher Rating Scale - Oppositional behaviour (CRS-R)	1	49	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.50, 0.62]
9.2.5 Conners' Teacher Rating Scale - Conduct problems	1	25	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.48, 0.14]
9.2.6 IOWA Conners' Rating Scale - Oppositional/Defiant (IOWA-O/D)	2	286	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.12, -0.59]
9.3 Subgroup analysis: dose	7	820	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-0.88, -0.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3.1 Low dose	2	71	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.16, -0.19]
9.3.2 High dose	4	541	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-1.05, -0.27]
9.3.3 Unknown dose	2	208	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-1.29, 0.46]
9.4 Subgroup analysis: duration of treatment	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.4.1 Short term (up to 6 months)	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.5 Subgroup analysis: parallel-group trials versus first-period cross-over trials	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.5.1 Parallel-group trials	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.6 Cross-over trials (endpoint data)	16	1302	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.87, -0.63]
9.6.1 High risk of bias	16	1302	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.87, -0.63]
9.7 Subgroup analysis: cross-over trials (endpoint data): dose	16	2008	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-0.78, -0.60]
9.7.1 Low dose	13	1104	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.72, -0.48]
9.7.2 High dose	12	904	Std. Mean Difference (IV, Random, 95% CI)	-0.82 [-0.95, -0.68]
9.8 Subgroup analysis: all parallel-group trials and first-period cross-over trials (teacher-rated) versus cross-over trials (endpoint data)	23	2094	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-0.84, -0.60]
9.8.1 All parallel-group trials and first-period cross-over trials	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
9.8.2 Cross-over trials (endpoint data)	16	1302	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.87, -0.63]
9.9 Subgroup analysis: all parallel-group trials and cross-over trials: vested interest	23	2094	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-0.84, -0.60]
9.9.1 Low risk of vested interest	6	509	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-0.90, -0.43]

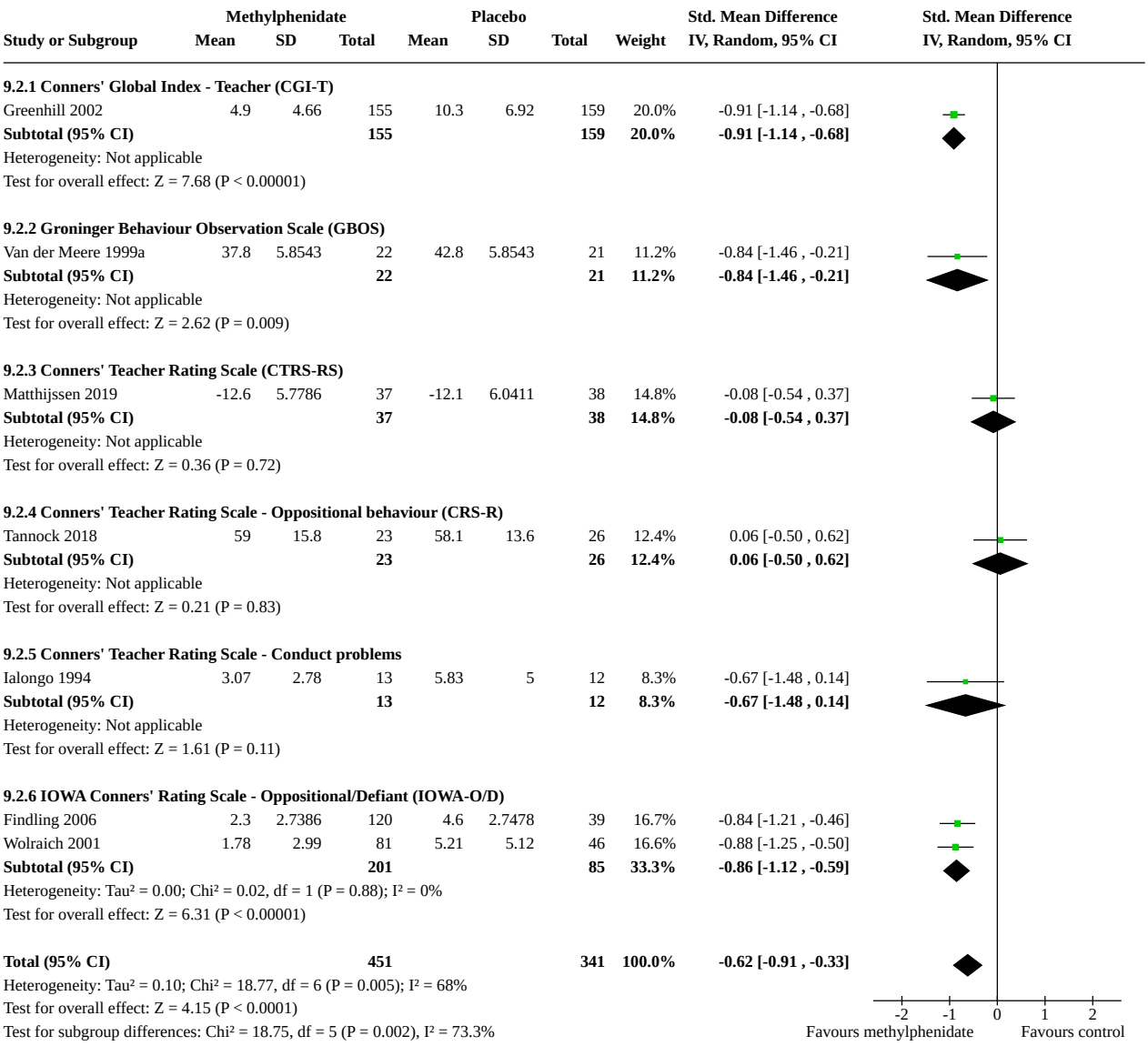
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.9.2 High risk of vested interest	17	1585	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-0.89, -0.60]

Analysis 9.1. Comparison 9: Teacher-rated general behaviour, Outcome 1: All parallel-group trials and first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.1.1 High risk of bias								
Findling 2006	2.3	2.7386	120	4.6	2.7478	39	16.7%	-0.84 [-1.21 , -0.46]
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	20.0%	-0.91 [-1.14 , -0.68]
Ialongo 1994	3.07	2.78	13	5.83	5	12	8.3%	-0.67 [-1.48 , 0.14]
Matthijssen 2019	-12.6	5.7786	37	-12.1	6.0411	38	14.8%	-0.08 [-0.54 , 0.37]
Tannock 2018	59	15.8	23	58.1	13.6	26	12.4%	0.06 [-0.50 , 0.62]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	11.2%	-0.84 [-1.46 , -0.21]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	16.6%	-0.88 [-1.25 , -0.50]
Subtotal (95% CI)			**451**			**341**	**100.0%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Total (95% CI)			**451**			**341**	**100.0%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Test for subgroup differences: Not applicable								

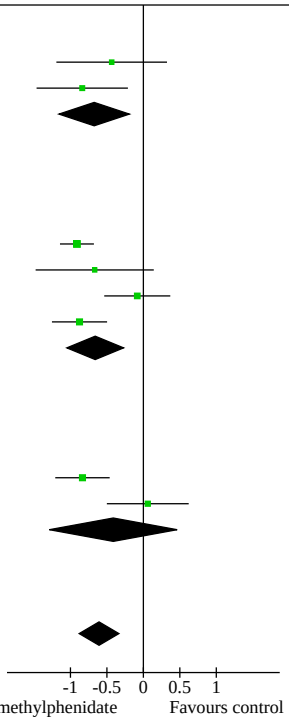


Analysis 9.2. Comparison 9: Teacher-rated general behaviour, Outcome 2: Subgroup analysis: types of scales



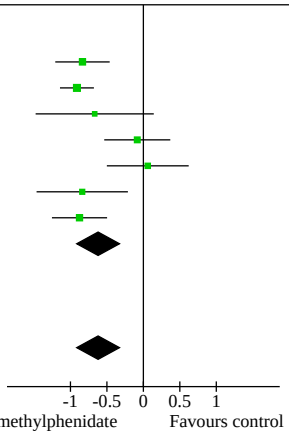
Analysis 9.3. Comparison 9: Teacher-rated general behaviour, Outcome 3: Subgroup analysis: dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.3.1 Low dose								
Ialongo 1994	3.85	3.95	16	5.83	5	12	8.1%	-0.43 [-1.19 , 0.32]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	10.1%	-0.84 [-1.46 , -0.21]
Subtotal (95% CI)			**38**			**33**	**18.2%**	**-0.67 [-1.16 , -0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%								
Test for overall effect: Z = 2.74 (P = 0.006)								
9.3.2 High dose								
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	18.8%	-0.91 [-1.14 , -0.68]
Ialongo 1994	3.07	2.78	13	5.83	5	12	7.4%	-0.67 [-1.48 , 0.14]
Matthijssen 2019	-12.6	5.7786	37	-12.1	6.0411	38	13.6%	-0.08 [-0.54 , 0.37]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	15.3%	-0.88 [-1.25 , -0.50]
Subtotal (95% CI)			**286**			**255**	**55.1%**	**-0.66 [-1.05 , -0.27]**
Heterogeneity: Tau² = 0.11; Chi² = 10.59, df = 3 (P = 0.01); I² = 72%								
Test for overall effect: Z = 3.33 (P = 0.0009)								
9.3.3 Unknown dose								
Findling 2006	2.3	2.7386	120	4.6	2.7478	39	15.4%	-0.84 [-1.21 , -0.46]
Tannock 2018	59	15.8	23	58.1	13.6	26	11.3%	0.06 [-0.50 , 0.62]
Subtotal (95% CI)			**143**			**65**	**26.7%**	**-0.41 [-1.29 , 0.46]**
Heterogeneity: Tau² = 0.34; Chi² = 6.78, df = 1 (P = 0.009); I² = 85%								
Test for overall effect: Z = 0.92 (P = 0.36)								
Total (95% CI)			**467**			**353**	**100.0%**	**-0.61 [-0.88 , -0.34]**
Heterogeneity: Tau² = 0.09; Chi² = 19.30, df = 7 (P = 0.007); I² = 64%								
Test for overall effect: Z = 4.38 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.29, df = 2 (P = 0.87), I² = 0%								



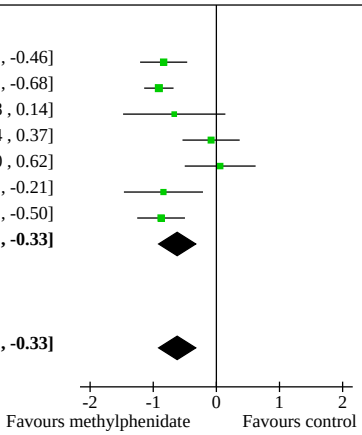
Analysis 9.4. Comparison 9: Teacher-rated general behaviour, Outcome 4: Subgroup analysis: duration of treatment

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.4.1 Short term (up to 6 months)								
Findling 2006	2.3	2.7386	120	4.6	2.7478	39	16.7%	-0.84 [-1.21 , -0.46]
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	20.0%	-0.91 [-1.14 , -0.68]
Ialongo 1994	3.07	2.78	13	5.83	5	12	8.3%	-0.67 [-1.48 , 0.14]
Matthijssen 2019	-12.6	5.7786	37	-12.1	6.0411	38	14.8%	-0.08 [-0.54 , 0.37]
Tannock 2018	59	15.8	23	58.1	13.6	26	12.4%	0.06 [-0.50 , 0.62]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	11.2%	-0.84 [-1.46 , -0.21]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	16.6%	-0.88 [-1.25 , -0.50]
Subtotal (95% CI)			**451**			**341**	**100.0%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Total (95% CI)			**451**			**341**	**100.0%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Test for subgroup differences: Not applicable								



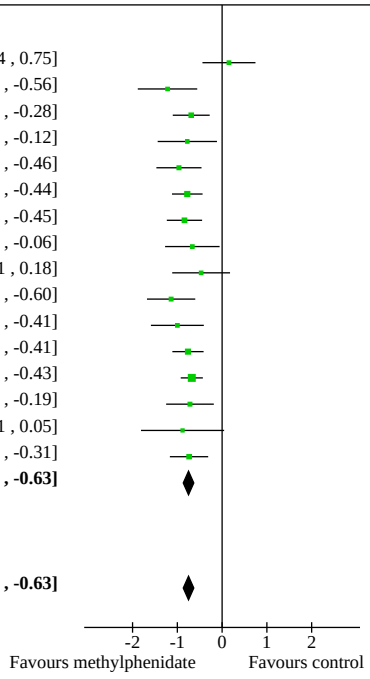
Analysis 9.5. Comparison 9: Teacher-rated general behaviour, Outcome 5: Subgroup analysis: parallel-group trials versus first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.5.1 Parallel-group trials								
Findling 2006	2.3	2.7386	120	4.6	2.7478	39	16.7%	-0.84 [-1.21 , -0.46]
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	20.0%	-0.91 [-1.14 , -0.68]
Ialongo 1994	3.07	2.78	13	5.83	5	12	8.3%	-0.67 [-1.48 , 0.14]
Matthijssen 2019	-12.6	5.7786	37	-12.1	6.0411	38	14.8%	-0.08 [-0.54 , 0.37]
Tannock 2018	59	15.8	23	58.1	13.6	26	12.4%	0.06 [-0.50 , 0.62]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	11.2%	-0.84 [-1.46 , -0.21]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	16.6%	-0.88 [-1.25 , -0.50]
Subtotal (95% CI)			**451**			**341**	**100.0%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Total (95% CI)			**451**			**341**	**100.0%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Test for subgroup differences: Not applicable								



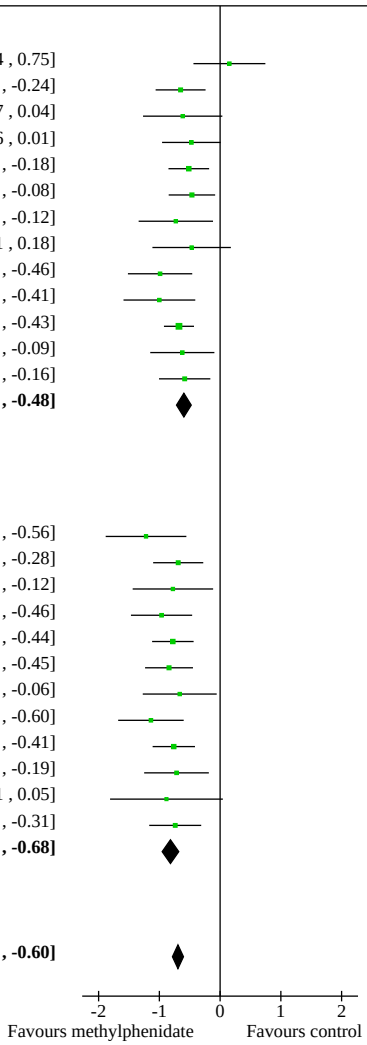
Analysis 9.6. Comparison 9: Teacher-rated general behaviour, Outcome 6: Cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.6.1 High risk of bias								
Brown 1991	0.44	0.7	22	0.35	0.42	22	3.8%	0.15 [-0.44 , 0.75]
Chronis 2003	0.4	0.5	21	2.9	2.8	21	3.1%	-1.22 [-1.88 , -0.56]
Fabiano 2007	0.4	1.22	48	1.68	2.3	48	7.6%	-0.69 [-1.10 , -0.28]
Fitzpatrick 1992a	0.26	0.31	19	0.7	0.72	19	3.1%	-0.78 [-1.44 , -0.12]
Gadow 1995	1.4	2	34	4.3	3.7	34	5.2%	-0.96 [-1.47 , -0.46]
Gadow 2007	1.1	1.9	71	3.4	3.7	71	10.8%	-0.78 [-1.12 , -0.44]
Gadow 2011	1.6	2.1	54	4.2	3.8	54	8.3%	-0.84 [-1.24 , -0.45]
Kolko 1999	2.7	3.5	22	5.7	5.2	22	3.6%	-0.66 [-1.27 , -0.06]
Lufi 2007	8.59	9.73	19	14	12.68	19	3.2%	-0.47 [-1.11 , 0.18]
Pelham 1993a	0.4	1	31	4	4.3	31	4.6%	-1.14 [-1.68 , -0.60]
Pelham 1999	0.6	1	25	2.6	2.6	25	3.8%	-1.00 [-1.59 , -0.41]
Pelham 2001a	1.99	3.03	68	5.09	4.85	68	10.4%	-0.76 [-1.11 , -0.41]
Pelham 2002	0.5	1.1	133	1.9	2.7	133	19.1%	-0.68 [-0.92 , -0.43]
Pelham 2005	0.4	1.1	29	1.9	2.7	29	4.7%	-0.72 [-1.25 , -0.19]
Pelham 2011	4.7	4.3	10	9	5	10	1.6%	-0.88 [-1.81 , 0.05]
Smith 1998	0.6	1.2	45	2.5	3.4	45	7.1%	-0.74 [-1.17 , -0.31]
Subtotal (95% CI)			**651**			**651**	**100.0%**	**-0.75 [-0.87 , -0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 15.80, df = 15 (P = 0.40); I² = 5%								
Test for overall effect: Z = 12.51 (P < 0.00001)								
Total (95% CI)			**651**			**651**	**100.0%**	**-0.75 [-0.87 , -0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 15.80, df = 15 (P = 0.40); I² = 5%								
Test for overall effect: Z = 12.51 (P < 0.00001)								
Test for subgroup differences: Not applicable								



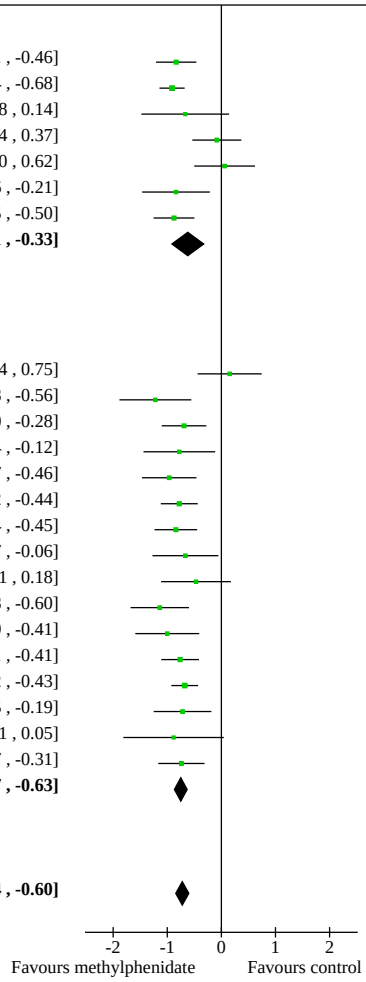
Analysis 9.7. Comparison 9: Teacher-rated general behaviour, Outcome 7: Subgroup analysis: cross-over trials (endpoint data): dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.7.1 Low dose								
Brown 1991	0.44	0.7	22	0.35	0.42	22	2.3%	0.15 [-0.44 , 0.75]
Fabiano 2007	0.5	1.09	48	1.68	2.3	48	4.8%	-0.65 [-1.06 , -0.24]
Fitzpatrick 1992a	0.31	0.5	19	0.7	0.72	19	1.9%	-0.62 [-1.27 , 0.04]
Gadow 1995	2.6	3.4	34	4.3	3.7	34	3.5%	-0.47 [-0.96 , 0.01]
Gadow 2007	1.7	2.8	71	3.4	3.7	71	7.3%	-0.52 [-0.85 , -0.18]
Gadow 2011	2.6	3	54	4.2	3.8	54	5.6%	-0.46 [-0.85 , -0.08]
Kolko 1999	2.6	2.8	22	5.7	5.2	22	2.2%	-0.73 [-1.34 , -0.12]
Lufi 2007	8.59	9.73	19	14	12.68	19	2.0%	-0.47 [-1.11 , 0.18]
Pelham 1993a	0.8	1.4	31	4	4.3	31	2.9%	-0.99 [-1.52 , -0.46]
Pelham 1999	0.6	1	25	2.6	2.6	25	2.3%	-1.00 [-1.59 , -0.41]
Pelham 2002	0.5	1.1	133	1.9	2.7	133	13.4%	-0.68 [-0.92 , -0.43]
Pelham 2005	0.6	1.1	29	1.9	2.7	29	2.9%	-0.62 [-1.15 , -0.09]
Smith 1998	0.9	1.8	45	2.5	3.4	45	4.6%	-0.58 [-1.01 , -0.16]
Subtotal (95% CI)			**552**			**552**	**55.9%**	**-0.60 [-0.72 , -0.48]**
Heterogeneity: Tau² = 0.00; Chi² = 11.81, df = 12 (P = 0.46); I² = 0%								
Test for overall effect: Z = 9.66 (P < 0.00001)								
9.7.2 High dose								
Chronis 2003	0.4	0.5	21	2.9	2.8	21	1.9%	-1.22 [-1.88 , -0.56]
Fabiano 2007	0.4	1.22	48	1.68	2.3	48	4.8%	-0.69 [-1.10 , -0.28]
Fitzpatrick 1992a	0.26	0.31	19	0.7	0.72	19	1.9%	-0.78 [-1.44 , -0.12]
Gadow 1995	1.4	2	34	4.3	3.7	34	3.2%	-0.96 [-1.47 , -0.46]
Gadow 2007	1.1	1.9	71	3.4	3.7	71	7.0%	-0.78 [-1.12 , -0.44]
Gadow 2011	1.6	2.1	54	4.2	3.8	54	5.3%	-0.84 [-1.24 , -0.45]
Kolko 1999	2.7	3.5	22	5.7	5.2	22	2.2%	-0.66 [-1.27 , -0.06]
Pelham 1993a	0.4	1	31	4	4.3	31	2.8%	-1.14 [-1.68 , -0.60]
Pelham 2001a	1.99	3.03	68	5.09	4.85	68	6.7%	-0.76 [-1.11 , -0.41]
Pelham 2005	0.4	1.1	29	1.9	2.7	29	2.9%	-0.72 [-1.25 , -0.19]
Pelham 2011	4.7	4.3	10	9	5	10	1.0%	-0.88 [-1.81 , 0.05]
Smith 1998	0.6	1.2	45	2.5	3.4	45	4.5%	-0.74 [-1.17 , -0.31]
Subtotal (95% CI)			**452**			**452**	**44.1%**	**-0.82 [-0.95 , -0.68]**
Heterogeneity: Tau² = 0.00; Chi² = 4.17, df = 11 (P = 0.96); I² = 0%								
Test for overall effect: Z = 11.76 (P < 0.00001)								
Total (95% CI)			**1004**			**1004**	**100.0%**	**-0.69 [-0.78 , -0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 21.62, df = 24 (P = 0.60); I² = 0%								
Test for overall effect: Z = 15.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.64, df = 1 (P = 0.02), I² = 82.3%								



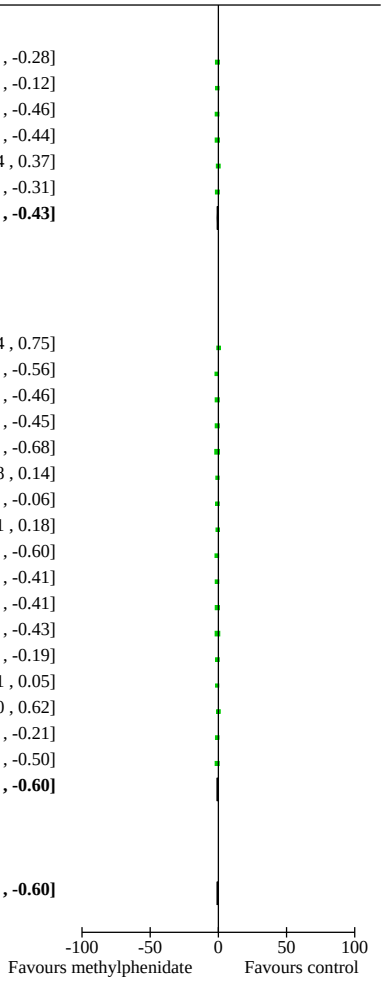
Analysis 9.8. Comparison 9: Teacher-rated general behaviour, Outcome 8: Subgroup analysis: all parallel-group trials and first-period cross-over trials (teacher-rated) versus cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.8.1 All parallel-group trials and first-period cross-over trials								
Findling 2006	2.3	2.7386	120	4.6	2.7478	39	5.8%	-0.84 [-1.21 , -0.46]
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	8.8%	-0.91 [-1.14 , -0.68]
Ialongo 1994	3.07	2.78	13	5.83	5	12	1.9%	-0.67 [-1.48 , 0.14]
Matthijssen 2019	-12.6	5.7786	37	-12.1	6.0411	38	4.6%	-0.08 [-0.54 , 0.37]
Tannock 2018	59	15.8	23	58.1	13.6	26	3.4%	0.06 [-0.50 , 0.62]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	2.9%	-0.84 [-1.46 , -0.21]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	5.7%	-0.88 [-1.25 , -0.50]
Subtotal (95% CI)			**451**			**341**	**33.2%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
9.8.2 Cross-over trials (endpoint data)								
Brown 1991	0.44	0.7	22	0.35	0.42	22	3.2%	0.15 [-0.44 , 0.75]
Chronis 2003	0.4	0.5	21	2.9	2.8	21	2.6%	-1.22 [-1.88 , -0.56]
Fabiano 2007	0.4	1.22	48	1.68	2.3	48	5.2%	-0.69 [-1.10 , -0.28]
Fitzpatrick 1992a	0.26	0.31	19	0.7	0.72	19	2.6%	-0.78 [-1.44 , -0.12]
Gadow 1995	1.4	2	34	4.3	3.7	34	4.0%	-0.96 [-1.47 , -0.46]
Gadow 2007	1.1	1.9	71	3.4	3.7	71	6.4%	-0.78 [-1.12 , -0.44]
Gadow 2011	1.6	2.1	54	4.2	3.8	54	5.5%	-0.84 [-1.24 , -0.45]
Kolko 1999	2.7	3.5	22	5.7	5.2	22	3.0%	-0.66 [-1.27 , -0.06]
Lufi 2007	8.59	9.73	19	14	12.68	19	2.8%	-0.47 [-1.11 , 0.18]
Pelham 1993a	0.4	1	31	4	4.3	31	3.6%	-1.14 [-1.68 , -0.60]
Pelham 1999	0.6	1	25	2.6	2.6	25	3.2%	-1.00 [-1.59 , -0.41]
Pelham 2001a	1.99	3.03	68	5.09	4.85	68	6.3%	-0.76 [-1.11 , -0.41]
Pelham 2002	0.5	1.1	133	1.9	2.7	133	8.5%	-0.68 [-0.92 , -0.43]
Pelham 2005	0.4	1.1	29	1.9	2.7	29	3.7%	-0.72 [-1.25 , -0.19]
Pelham 2011	4.7	4.3	10	9	5	10	1.5%	-0.88 [-1.81 , 0.05]
Smith 1998	0.6	1.2	45	2.5	3.4	45	4.9%	-0.74 [-1.17 , -0.31]
Subtotal (95% CI)			**651**			**651**	**66.8%**	**-0.75 [-0.87 , -0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 15.80, df = 15 (P = 0.40); I² = 5%								
Test for overall effect: Z = 12.51 (P < 0.00001)								
Total (95% CI)			**1102**			**992**	**100.0%**	**-0.72 [-0.84 , -0.60]**
Heterogeneity: Tau² = 0.03; Chi² = 34.65, df = 22 (P = 0.04); I² = 37%								
Test for overall effect: Z = 11.75 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%								



Analysis 9.9. Comparison 9: Teacher-rated general behaviour, Outcome 9: Subgroup analysis: all parallel-group trials and cross-over trials: vested interest

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.9.1 Low risk of vested interest								
Fabiano 2007	0.4	1.22	48	1.68	2.3	48	5.2%	-0.69 [-1.10 , -0.28]
Fitzpatrick 1992a	0.26	0.31	19	0.7	0.72	19	2.6%	-0.78 [-1.44 , -0.12]
Gadow 1995	1.4	2	34	4.3	3.7	34	4.0%	-0.96 [-1.47 , -0.46]
Gadow 2007	1.1	1.9	71	3.4	3.7	71	6.4%	-0.78 [-1.12 , -0.44]
Matthijssen 2019	-12.6	5.7786	37	-12.1	6.0411	38	4.6%	-0.08 [-0.54 , 0.37]
Smith 1998	0.6	1.2	45	2.5	3.4	45	4.9%	-0.74 [-1.17 , -0.31]
Subtotal (95% CI)			**254**			**255**	**27.7%**	**-0.67 [-0.90 , -0.43]**
Heterogeneity: Tau² = 0.03; Chi² = 8.34, df = 5 (P = 0.14); I² = 40%								
Test for overall effect: Z = 5.50 (P < 0.00001)								
9.9.2 High risk of vested interest								
Brown 1991	0.44	0.7	22	0.35	0.42	22	3.2%	0.15 [-0.44 , 0.75]
Chronis 2003	0.4	0.5	21	2.9	2.8	21	2.6%	-1.22 [-1.88 , -0.56]
Findling 2006	2.3	2.7386	120	4.6	2.7478	39	5.8%	-0.84 [-1.21 , -0.46]
Gadow 2011	1.6	2.1	54	4.2	3.8	54	5.5%	-0.84 [-1.24 , -0.45]
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	8.8%	-0.91 [-1.14 , -0.68]
Ialongo 1994	3.07	2.78	13	5.83	5	12	1.9%	-0.67 [-1.48 , 0.14]
Kolko 1999	2.7	3.5	22	5.7	5.2	22	3.0%	-0.66 [-1.27 , -0.06]
Lufi 2007	8.59	9.73	19	14	12.68	19	2.8%	-0.47 [-1.11 , 0.18]
Pelham 1993a	0.4	1	31	4	4.3	31	3.6%	-1.14 [-1.68 , -0.60]
Pelham 1999	0.6	1	25	2.6	2.6	25	3.2%	-1.00 [-1.59 , -0.41]
Pelham 2001a	1.99	3.03	68	5.09	4.85	68	6.3%	-0.76 [-1.11 , -0.41]
Pelham 2002	0.5	1.1	133	1.9	2.7	133	8.5%	-0.68 [-0.92 , -0.43]
Pelham 2005	0.4	1.1	29	1.9	2.7	29	3.7%	-0.72 [-1.25 , -0.19]
Pelham 2011	4.7	4.3	10	9	5	10	1.5%	-0.88 [-1.81 , 0.05]
Tannock 2018	59	15.8	23	58.1	13.6	26	3.4%	0.06 [-0.50 , 0.62]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	2.9%	-0.84 [-1.46 , -0.21]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	5.7%	-0.88 [-1.25 , -0.50]
Subtotal (95% CI)			**848**			**737**	**72.3%**	**-0.74 [-0.89 , -0.60]**
Heterogeneity: Tau² = 0.03; Chi² = 25.52, df = 16 (P = 0.06); I² = 37%								
Test for overall effect: Z = 10.19 (P < 0.00001)								
Total (95% CI)			**1102**			**992**	**100.0%**	**-0.72 [-0.84 , -0.60]**
Heterogeneity: Tau² = 0.03; Chi² = 34.65, df = 22 (P = 0.04); I² = 37%								
Test for overall effect: Z = 11.75 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%								

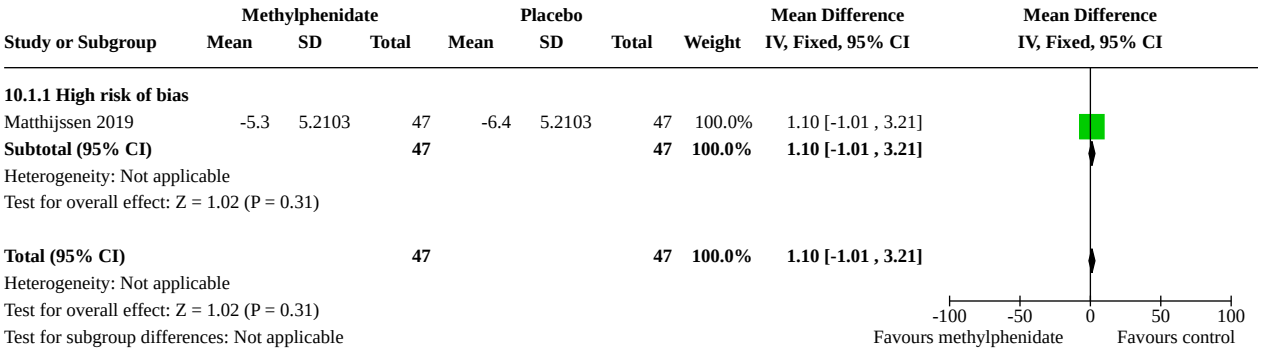


Comparison 10. Independent assessor-rated general behaviour

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 All parallel-group trials and first-period cross-over trials	1	94	Mean Difference (IV, Fixed, 95% CI)	1.10 [-1.01, 3.21]
10.1.1 High risk of bias	1	94	Mean Difference (IV, Fixed, 95% CI)	1.10 [-1.01, 3.21]
10.2 Cross-over trials (endpoint data)	9	987	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.39, -0.57]
10.2.1 High risk of bias	9	987	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.39, -0.57]

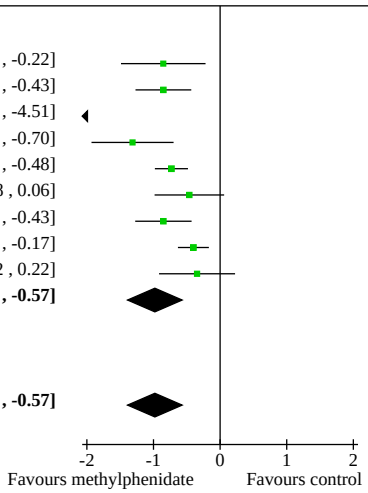
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Subgroup analysis: general behaviour, cross-over trials (endpoint data): dose	9	1319	Std. Mean Difference (IV, Random, 95% CI)	-1.02 [-1.39, -0.64]
10.3.1 Low dose	9	987	Std. Mean Difference (IV, Random, 95% CI)	-0.82 [-1.23, -0.41]
10.3.2 High dose	5	332	Std. Mean Difference (IV, Random, 95% CI)	-1.49 [-2.37, -0.61]
10.4 Subgroup analysis: all parallel-group trials and first-period cross-over trials (independent assessor-rated) compared with cross-over trials (endpoint data)	10	1081	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.27, -0.46]
10.4.1 Parallel-group trials and first-period cross-over trials	1	94	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.20, 0.61]
10.4.2 Cross-over trials (endpoint data)	9	987	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.39, -0.57]
10.5 Subgroup analysis: all parallel-group trials and cross-over trials: vested interest	9	1031	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.24, -0.39]
10.5.1 Low risk of vested interest	2	190	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-1.36, 0.72]
10.5.2 High risk of vested interest	6	799	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.77, -0.41]
10.5.3 Unclear risk of vested interest	1	42	Std. Mean Difference (IV, Random, 95% CI)	-5.99 [-7.46, -4.51]

Analysis 10.1. Comparison 10: Independent assessor-rated general behaviour, Outcome 1: All parallel-group trials and first-period cross-over trials



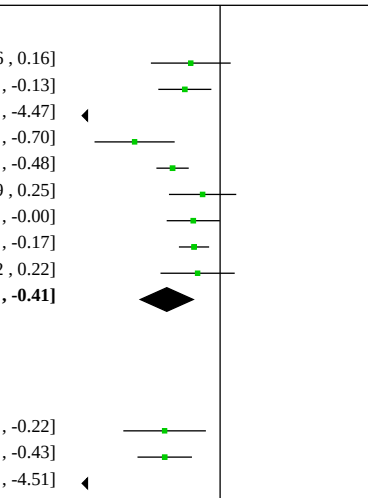
Analysis 10.2. Comparison 10: Independent assessor-rated general behaviour, Outcome 2: Cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
10.2.1 High risk of bias								
Chronis 2003	2.2	1.6	21	4.4	3.2	21	10.5%	-0.85 [-1.49 , -0.22]
Fabiano 2007	1.1	1.5	48	3.3	3.3	48	12.3%	-0.85 [-1.27 , -0.43]
Merrill 2021	1.83	0.42	21	8.8	1.56	21	5.0%	-5.99 [-7.46 , -4.51]
Pelham 1999	1.1	1.1	25	5.2	4.2	25	10.7%	-1.31 [-1.93 , -0.70]
Pelham 2002	1.7	1.3	133	3.3	2.8	133	13.4%	-0.73 [-0.98 , -0.48]
Pelham 2005	2	1.6	29	2.9	2.2	29	11.4%	-0.46 [-0.98 , 0.06]
Pelham 2014	1.1	1.5	47	3.3	3.3	47	12.2%	-0.85 [-1.27 , -0.43]
Schulz 2010	35.6	21	146	44.6	23.7	145	13.5%	-0.40 [-0.63 , -0.17]
Whalen 1990	3.25	4.81	24	4.79	3.9	24	11.1%	-0.35 [-0.92 , 0.22]
Subtotal (95% CI)			**494**			**493**	**100.0%**	**-0.98 [-1.39 , -0.57]**
Heterogeneity: Tau² = 0.31; Chi² = 63.08, df = 8 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 4.69 (P < 0.00001)								
Total (95% CI)			**494**			**493**	**100.0%**	**-0.98 [-1.39 , -0.57]**
Heterogeneity: Tau² = 0.31; Chi² = 63.08, df = 8 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 4.69 (P < 0.00001)								
Test for subgroup differences: Not applicable								



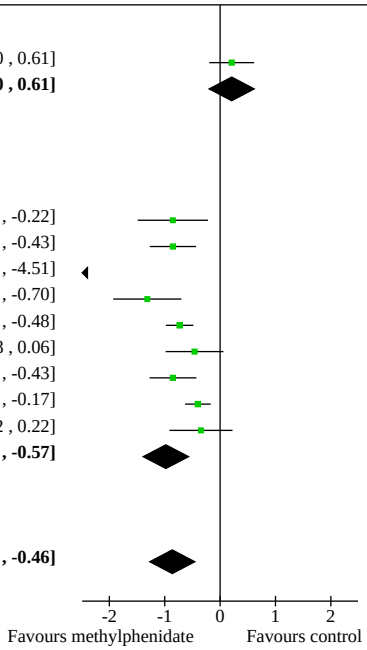
Analysis 10.3. Comparison 10: Independent assessor-rated general behaviour, Outcome 3: Subgroup analysis: general behaviour, cross-over trials (endpoint data): dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
10.3.1 Low dose								
Chronis 2003	3.1	2.4	21	4.4	3.2	21	7.1%	-0.45 [-1.06 , 0.16]
Fabiano 2007	1.7	2.5	48	3.3	3.3	48	8.0%	-0.54 [-0.95 , -0.13]
Merrill 2021	1.97	0.34	21	8.8	1.56	21	3.7%	-5.94 [-7.40 , -4.47]
Pelham 1999	1.1	1.1	25	5.2	4.2	25	7.1%	-1.31 [-1.93 , -0.70]
Pelham 2002	1.7	1.3	133	3.3	2.8	133	8.5%	-0.73 [-0.98 , -0.48]
Pelham 2005	2.3	2.2	29	2.9	2.2	29	7.5%	-0.27 [-0.79 , 0.25]
Pelham 2014	2.1	2.4	47	3.3	3.3	47	8.0%	-0.41 [-0.82 , -0.00]
Schulz 2010	35.6	21	146	44.6	23.7	145	8.5%	-0.40 [-0.63 , -0.17]
Whalen 1990	3.25	4.81	24	4.79	3.9	24	7.3%	-0.35 [-0.92 , 0.22]
Subtotal (95% CI)			**494**			**493**	**65.9%**	**-0.82 [-1.23 , -0.41]**
Heterogeneity: Tau² = 0.31; Chi² = 63.44, df = 8 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.96 (P < 0.0001)								
10.3.2 High dose								
Chronis 2003	2.2	1.6	21	4.4	3.2	21	7.0%	-0.85 [-1.49 , -0.22]
Fabiano 2007	1.1	1.5	48	3.3	3.3	48	8.0%	-0.85 [-1.27 , -0.43]
Merrill 2021	1.83	0.42	21	8.8	1.56	21	3.7%	-5.99 [-7.46 , -4.51]
Pelham 2005	2	1.6	29	2.9	2.2	29	7.5%	-0.46 [-0.98 , 0.06]
Pelham 2014	1.1	1.5	47	3.3	3.3	47	7.9%	-0.85 [-1.27 , -0.43]
Subtotal (95% CI)			**166**			**166**	**34.1%**	**-1.49 [-2.37 , -0.61]**
Heterogeneity: Tau² = 0.88; Chi² = 48.54, df = 4 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 3.31 (P = 0.0009)								
Total (95% CI)			**660**			**659**	**100.0%**	**-1.02 [-1.39 , -0.64]**
Heterogeneity: Tau² = 0.41; Chi² = 117.46, df = 13 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 5.36 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.83, df = 1 (P = 0.18), I² = 45.3%								

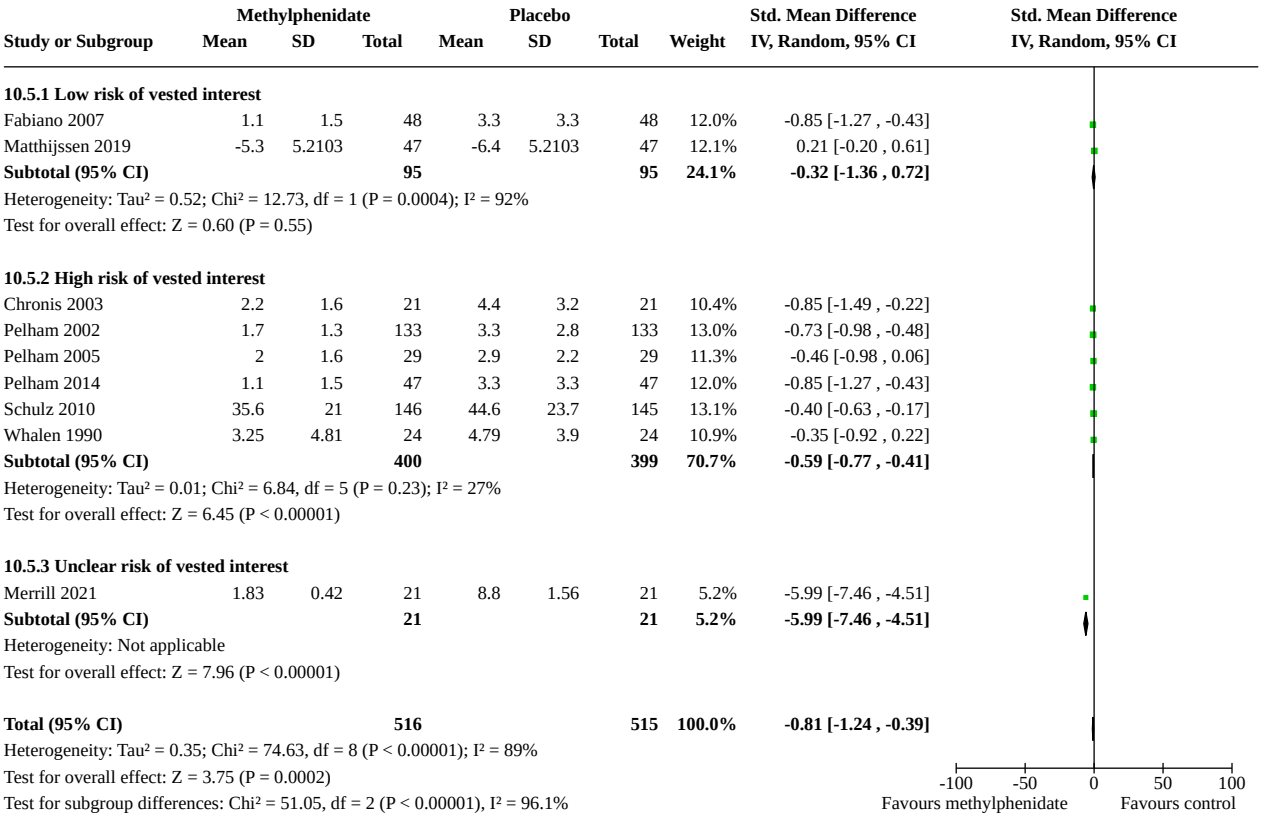


Analysis 10.4. Comparison 10: Independent assessor-rated general behaviour, Outcome 4: Subgroup analysis: all parallel-group trials and first-period cross-over trials (independent assessor-rated) compared with cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
10.4.1 Parallel-group trials and first-period cross-over trials								
Matthijssen 2019	-5.3	5.2103	47	-6.4	5.2103	47	10.9%	0.21 [-0.20 , 0.61]
Subtotal (95% CI)			**47**			**47**	**10.9%**	**0.21 [-0.20 , 0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.01 (P = 0.31)								
10.4.2 Cross-over trials (endpoint data)								
Chronis 2003	2.2	1.6	21	4.4	3.2	21	9.4%	-0.85 [-1.49 , -0.22]
Fabiano 2007	1.1	1.5	48	3.3	3.3	48	10.9%	-0.85 [-1.27 , -0.43]
Merrill 2021	1.83	0.42	21	8.8	1.56	21	4.7%	-5.99 [-7.46 , -4.51]
Pelham 1999	1.1	1.1	25	5.2	4.2	25	9.6%	-1.31 [-1.93 , -0.70]
Pelham 2002	1.7	1.3	133	3.3	2.8	133	11.7%	-0.73 [-0.98 , -0.48]
Pelham 2005	2	1.6	29	2.9	2.2	29	10.2%	-0.46 [-0.98 , 0.06]
Pelham 2014	1.1	1.5	47	3.3	3.3	47	10.8%	-0.85 [-1.27 , -0.43]
Schulz 2010	35.6	21	146	44.6	23.7	145	11.8%	-0.40 [-0.63 , -0.17]
Whalen 1990	3.25	4.81	24	4.79	3.9	24	9.9%	-0.35 [-0.92 , 0.22]
Subtotal (95% CI)			**494**			**493**	**89.1%**	**-0.98 [-1.39 , -0.57]**
Heterogeneity: Tau² = 0.31; Chi² = 63.08, df = 8 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 4.69 (P < 0.00001)								
Total (95% CI)			**541**			**540**	**100.0%**	**-0.86 [-1.27 , -0.46]**
Heterogeneity: Tau² = 0.35; Chi² = 80.01, df = 9 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 4.17 (P < 0.0001)								
Test for subgroup differences: Chi² = 16.36, df = 1 (P < 0.0001), I² = 93.9%								



Analysis 10.5. Comparison 10: Independent assessor-rated general behaviour, Outcome 5: Subgroup analysis: all parallel-group trials and cross-over trials: vested interest



Comparison 11. Parent-rated general behaviour

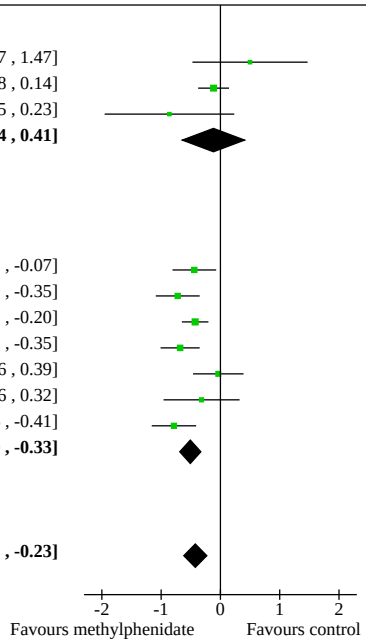
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 All parallel-group trials and first-period cross-over trials	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
11.1.1 Low risk of bias	3	386	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.64, 0.41]
11.1.2 High risk of bias	7	990	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-0.69, -0.33]
11.2 Subgroup analysis: types of scales	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
11.2.1 The Weekly Parent Ratings of Evening and Morning Behaviour (WPREMB) - Revised	2	167	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-1.32, 0.96]
11.2.2 Conners' Global Index (CGI) - Parent	2	352	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.63, -0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2.3 Swanson, Nolan and Pelham, Fourth Edition - Oppositional (SNAP-IV-Oppositional)	1	15	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.95, 0.23]
11.2.4 IOWA Conners' Rating Scale - Oppositional/Defiant (IOWA-I/O)	2	286	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.01, -0.49]
11.2.5 Conners' Early Childhood Behavior - Parent Short Response Scale	1	117	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.81, -0.07]
11.2.6 Strengths and Dificulties Questionnaire (SDQ)	1	85	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.46, 0.39]
11.2.7 Behaviour Rating Inventory of Executive Function (BRIEF)	1	354	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.38, 0.14]
11.3 Subgroup analysis: parallel-group trials compared with first-period cross-over trials	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
11.3.1 Parallel-group trials	9	1361	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.61, -0.21]
11.3.2 First-period cross-over trials	1	15	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.95, 0.23]
11.4 Subgroup analysis: duration of treatment	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
11.4.1 Short term (up to 6 months)	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
11.5 Subgroup analysis: dose	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
11.5.1 High dose	7	1052	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.54, -0.10]
11.5.2 Unknown dose	3	324	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-0.95, -0.47]
11.6 Cross-over trials (endpoint data)	6	384	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.05, -0.63]
11.6.1 High risk of bias	6	384	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.05, -0.63]
11.7 Subgroup analysis: cross-over trials (endpoint data): dose	6	550	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.93, -0.56]
11.7.1 Low dose	5	248	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-0.93, -0.38]

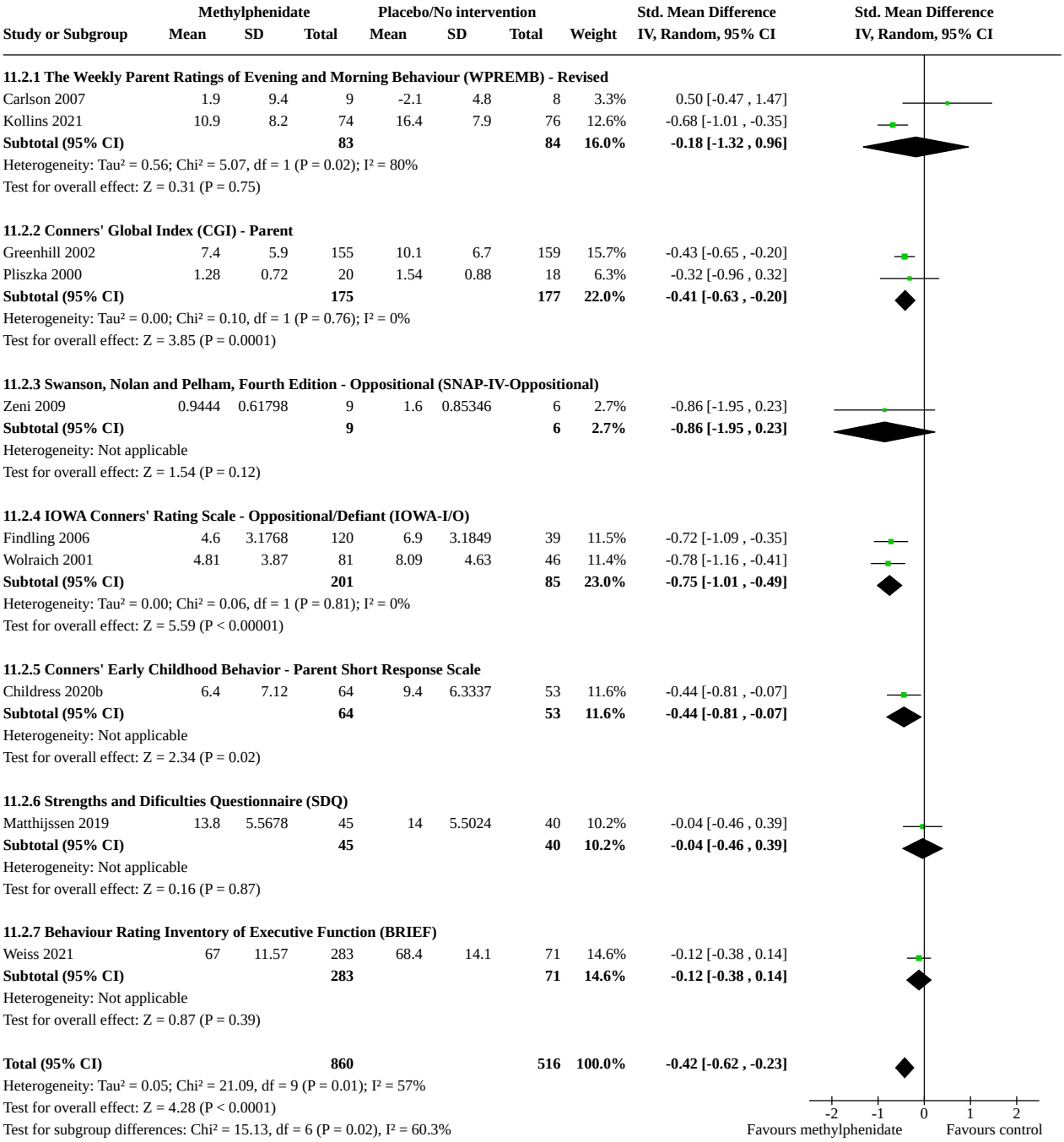
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.7.2 High dose	4	302	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.07, -0.60]
11.8 Subgroup analysis: all parallel-group trials and first-period cross-over trials (parent-rated) compared with cross-over trials (endpoint data)	16	1760	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.74, -0.39]
11.8.1 All parallel-group trials and first-period cross-over trials	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
11.8.2 Cross-over trials (endpoint data)	6	384	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.05, -0.63]
11.9 All parallel-group trials and cross-over trials: risk of bias	16	1760	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.74, -0.39]
11.9.1 Low risk of bias	3	386	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.64, 0.41]
11.9.2 High risk of bias	13	1374	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.78, -0.47]
11.10 Subgroup analysis: all parallel-group trials and cross-over trials: vested interest	16	1760	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.74, -0.39]
11.10.1 Low risk of vested interest	4	223	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-1.14, -0.10]
11.10.2 High risk of vested interest	12	1537	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.75, -0.38]

Analysis 11.1. Comparison 11: Parent-rated general behaviour, Outcome 1: All parallel-group trials and first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.1.1 Low risk of bias								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	3.3%	0.50 [-0.47 , 1.47]
Weiss 2021	67	11.57	283	68.4	14.1	71	14.6%	-0.12 [-0.38 , 0.14]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.7%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**301**			**85**	**20.7%**	**-0.12 [-0.64 , 0.41]**
Heterogeneity: Tau² = 0.10; Chi² = 3.32, df = 2 (P = 0.19); I² = 40%								
Test for overall effect: Z = 0.44 (P = 0.66)								
11.1.2 High risk of bias								
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	11.6%	-0.44 [-0.81 , -0.07]
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	11.5%	-0.72 [-1.09 , -0.35]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	15.7%	-0.43 [-0.65 , -0.20]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	12.6%	-0.68 [-1.01 , -0.35]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	10.2%	-0.04 [-0.46 , 0.39]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	6.3%	-0.32 [-0.96 , 0.32]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	11.4%	-0.78 [-1.16 , -0.41]
Subtotal (95% CI)			**559**			**431**	**79.3%**	**-0.51 [-0.69 , -0.33]**
Heterogeneity: Tau² = 0.02; Chi² = 10.09, df = 6 (P = 0.12); I² = 41%								
Test for overall effect: Z = 5.60 (P < 0.00001)								
Total (95% CI)			**860**			**516**	**100.0%**	**-0.42 [-0.62 , -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 21.09, df = 9 (P = 0.01); I² = 57%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.90, df = 1 (P = 0.17), I² = 47.5%								

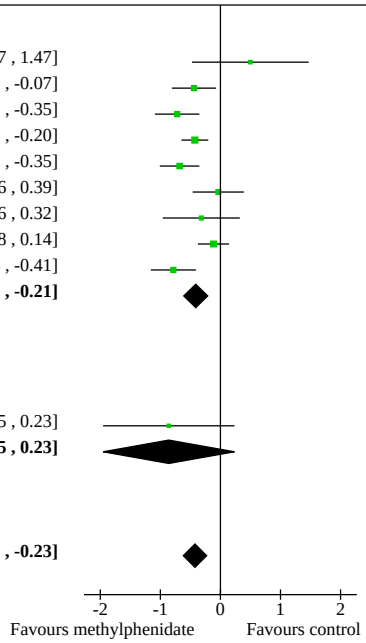


Analysis 11.2. Comparison 11: Parent-rated general behaviour, Outcome 2: Subgroup analysis: types of scales



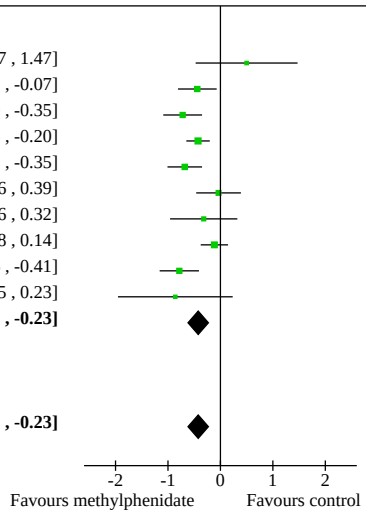
Analysis 11.3. Comparison 11: Parent-rated general behaviour, Outcome 3: Subgroup analysis: parallel-group trials compared with first-period cross-over trials

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.3.1 Parallel-group trials								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	3.3%	0.50 [-0.47 , 1.47]
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	11.6%	-0.44 [-0.81 , -0.07]
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	11.5%	-0.72 [-1.09 , -0.35]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	15.7%	-0.43 [-0.65 , -0.20]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	12.6%	-0.68 [-1.01 , -0.35]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	10.2%	-0.04 [-0.46 , 0.39]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	6.3%	-0.32 [-0.96 , 0.32]
Weiss 2021	67	11.57	283	68.4	14.1	71	14.6%	-0.12 [-0.38 , 0.14]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	11.4%	-0.78 [-1.16 , -0.41]
Subtotal (95% CI)			**851**			**510**	**97.3%**	**-0.41 [-0.61 , -0.21]**
Heterogeneity: Tau² = 0.05; Chi² = 20.46, df = 8 (P = 0.009); I² = 61%								
Test for overall effect: Z = 4.03 (P < 0.0001)								
11.3.2 First-period cross-over trials								
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.7%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**9**			**6**	**2.7%**	**-0.86 [-1.95 , 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.54 (P = 0.12)								
Total (95% CI)			**860**			**516**	**100.0%**	**-0.42 [-0.62 , -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 21.09, df = 9 (P = 0.01); I² = 57%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%								



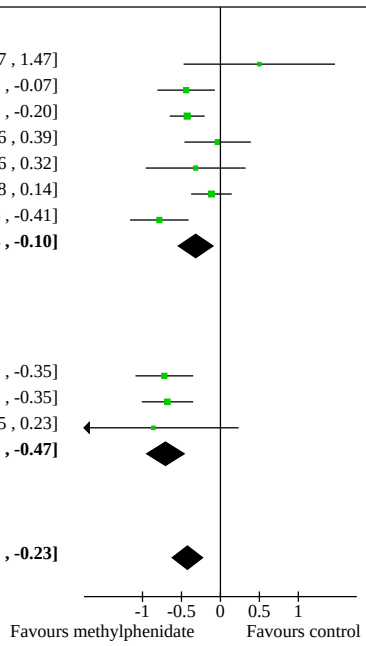
Analysis 11.4. Comparison 11: Parent-rated general behaviour, Outcome 4: Subgroup analysis: duration of treatment

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.4.1 Short term (up to 6 months)								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	3.3%	0.50 [-0.47 , 1.47]
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	11.6%	-0.44 [-0.81 , -0.07]
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	11.5%	-0.72 [-1.09 , -0.35]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	15.7%	-0.43 [-0.65 , -0.20]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	12.6%	-0.68 [-1.01 , -0.35]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	10.2%	-0.04 [-0.46 , 0.39]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	6.3%	-0.32 [-0.96 , 0.32]
Weiss 2021	67	11.57	283	68.4	14.1	71	14.6%	-0.12 [-0.38 , 0.14]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	11.4%	-0.78 [-1.16 , -0.41]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.7%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**860**			**516**	**100.0%**	**-0.42 [-0.62 , -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 21.09, df = 9 (P = 0.01); I² = 57%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Total (95% CI)			**860**			**516**	**100.0%**	**-0.42 [-0.62 , -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 21.09, df = 9 (P = 0.01); I² = 57%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Test for subgroup differences: Not applicable								



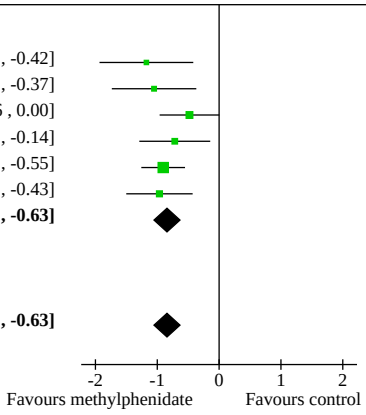
Analysis 11.5. Comparison 11: Parent-rated general behaviour, Outcome 5: Subgroup analysis: dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.5.1 High dose								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	3.3%	0.50 [-0.47 , 1.47]
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	11.6%	-0.44 [-0.81 , -0.07]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	15.7%	-0.43 [-0.65 , -0.20]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	10.2%	-0.04 [-0.46 , 0.39]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	6.3%	-0.32 [-0.96 , 0.32]
Weiss 2021	67	11.57	283	68.4	14.1	71	14.6%	-0.12 [-0.38 , 0.14]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	11.4%	-0.78 [-1.16 , -0.41]
Subtotal (95% CI)			**657**			**395**	**73.1%**	**-0.32 [-0.54 , -0.10]**
Heterogeneity: Tau² = 0.05; Chi² = 13.92, df = 6 (P = 0.03); I² = 57%								
Test for overall effect: Z = 2.81 (P = 0.005)								
11.5.2 Unknown dose								
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	11.5%	-0.72 [-1.09 , -0.35]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	12.6%	-0.68 [-1.01 , -0.35]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.7%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**203**			**121**	**26.9%**	**-0.71 [-0.95 , -0.47]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%								
Test for overall effect: Z = 5.76 (P < 0.00001)								
Total (95% CI)			**860**			**516**	**100.0%**	**-0.42 [-0.62 , -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 21.09, df = 9 (P = 0.01); I² = 57%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Test for subgroup differences: Chi² = 5.41, df = 1 (P = 0.02), I² = 81.5%								



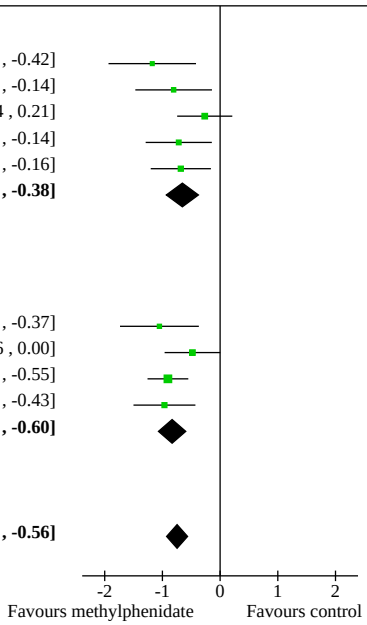
Analysis 11.6. Comparison 11: Parent-rated general behaviour, Outcome 6: Cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.6.1 High risk of bias								
Findling 2007	56	8	16	73.9	19.4	16	7.7%	-1.18 [-1.93 , -0.42]
Fitzpatrick 1992a	0.6	0.39	19	1.15	0.61	19	9.4%	-1.05 [-1.73 , -0.37]
Gadow 1995	1.5	1.7	34	2.4	2	34	18.9%	-0.48 [-0.96 , 0.00]
Pelham 1999	1.2	1.4	25	2.5	2.1	25	13.4%	-0.72 [-1.29 , -0.14]
Pelham 2001a	5.26	3.85	68	8.85	4.04	68	35.3%	-0.90 [-1.26 , -0.55]
Pelham 2005	0.8	1.1	30	2.5	2.2	30	15.3%	-0.96 [-1.50 , -0.43]
Subtotal (95% CI)			**192**			**192**	**100.0%**	**-0.84 [-1.05 , -0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 5 (P = 0.58); I² = 0%								
Test for overall effect: Z = 7.87 (P < 0.00001)								
Total (95% CI)			**192**			**192**	**100.0%**	**-0.84 [-1.05 , -0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 5 (P = 0.58); I² = 0%								
Test for overall effect: Z = 7.87 (P < 0.00001)								
Test for subgroup differences: Not applicable								



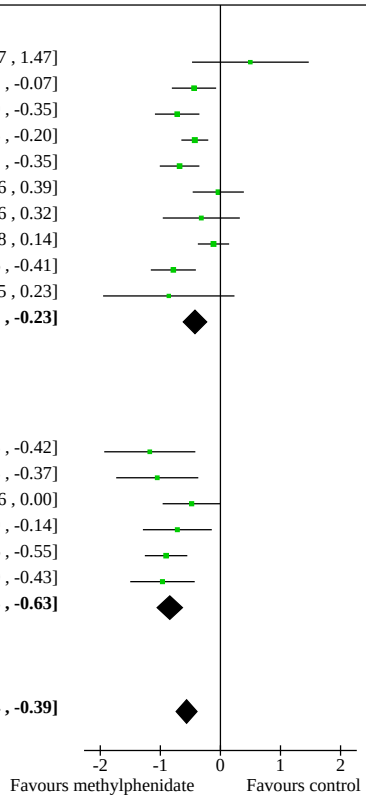
Analysis 11.7. Comparison 11: Parent-rated general behaviour, Outcome 7: Subgroup analysis: cross-over trials (endpoint data): dose

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.7.1 Low dose								
Findling 2007	56	8	16	73.9	19.4	16	5.5%	-1.18 [-1.93 , -0.42]
Fitzpatrick 1992a	0.68	0.53	19	1.15	0.61	19	7.2%	-0.81 [-1.47 , -0.14]
Gadow 1995	1.9	1.7	34	2.4	2	34	13.3%	-0.27 [-0.74 , 0.21]
Pelham 1999	1.2	1.4	25	2.5	2.1	25	9.5%	-0.72 [-1.29 , -0.14]
Pelham 2005	1.3	1.1	30	2.5	2.2	30	11.3%	-0.68 [-1.20 , -0.16]
Subtotal (95% CI)			**124**			**124**	**46.7%**	**-0.65 [-0.93 , -0.38]**
Heterogeneity: Tau² = 0.01; Chi² = 4.60, df = 4 (P = 0.33); I² = 13%								
Test for overall effect: Z = 4.61 (P < 0.00001)								
11.7.2 High dose								
Fitzpatrick 1992a	0.6	0.39	19	1.15	0.61	19	6.8%	-1.05 [-1.73 , -0.37]
Gadow 1995	1.5	1.7	34	2.4	2	34	13.0%	-0.48 [-0.96 , 0.00]
Pelham 2001a	5.26	3.85	68	8.85	4.04	68	22.8%	-0.90 [-1.26 , -0.55]
Pelham 2005	0.8	1.1	30	2.5	2.2	30	10.7%	-0.96 [-1.50 , -0.43]
Subtotal (95% CI)			**151**			**151**	**53.3%**	**-0.83 [-1.07 , -0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 3 (P = 0.42); I² = 0%								
Test for overall effect: Z = 6.90 (P < 0.00001)								
Total (95% CI)			**275**			**275**	**100.0%**	**-0.75 [-0.93 , -0.56]**
Heterogeneity: Tau² = 0.01; Chi² = 8.57, df = 8 (P = 0.38); I² = 7%								
Test for overall effect: Z = 8.05 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%								



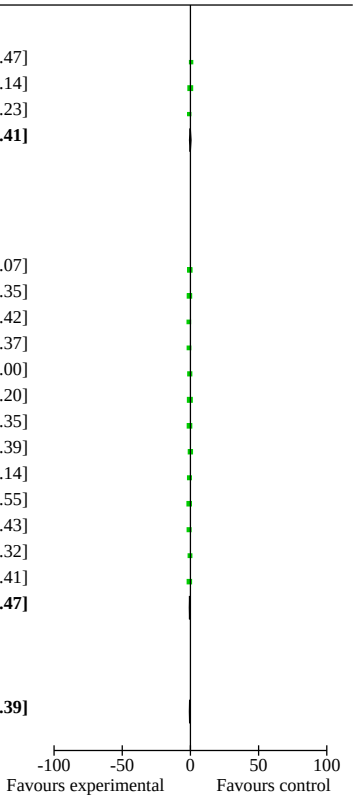
Analysis 11.8. Comparison 11: Parent-rated general behaviour, Outcome 8: Subgroup analysis: all parallel-group trials and first-period cross-over trials (parent-rated) compared with cross-over trials (endpoint data)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.8.1 All parallel-group trials and first-period cross-over trials								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	2.5%	0.50 [-0.47 , 1.47]
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	7.8%	-0.44 [-0.81 , -0.07]
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	7.8%	-0.72 [-1.09 , -0.35]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	10.0%	-0.43 [-0.65 , -0.20]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	8.4%	-0.68 [-1.01 , -0.35]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	7.0%	-0.04 [-0.46 , 0.39]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	4.5%	-0.32 [-0.96 , 0.32]
Weiss 2021	67	11.57	283	68.4	14.1	71	9.5%	-0.12 [-0.38 , 0.14]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	7.7%	-0.78 [-1.16 , -0.41]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.1%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**860**			**516**	**67.2%**	**-0.42 [-0.62 , -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 21.09, df = 9 (P = 0.01); I² = 57%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
11.8.2 Cross-over trials (endpoint data)								
Findling 2007	56	8	16	73.9	19.4	16	3.6%	-1.18 [-1.93 , -0.42]
Fitzpatrick 1992a	0.6	0.39	19	1.15	0.61	19	4.2%	-1.05 [-1.73 , -0.37]
Gadow 1995	1.5	1.7	34	2.4	2	34	6.2%	-0.48 [-0.96 , 0.00]
Pelham 1999	1.2	1.4	25	2.5	2.1	25	5.2%	-0.72 [-1.29 , -0.14]
Pelham 2001a	5.26	3.85	68	8.85	4.04	68	8.0%	-0.90 [-1.26 , -0.55]
Pelham 2005	0.8	1.1	30	2.5	2.2	30	5.6%	-0.96 [-1.50 , -0.43]
Subtotal (95% CI)			**192**			**192**	**32.8%**	**-0.84 [-1.05 , -0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 5 (P = 0.58); I² = 0%								
Test for overall effect: Z = 7.87 (P < 0.00001)								
Total (95% CI)			**1052**			**708**	**100.0%**	**-0.56 [-0.74 , -0.39]**
Heterogeneity: Tau² = 0.06; Chi² = 36.88, df = 15 (P = 0.001); I² = 59%								
Test for overall effect: Z = 6.38 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.26, df = 1 (P = 0.004), I² = 87.9%								



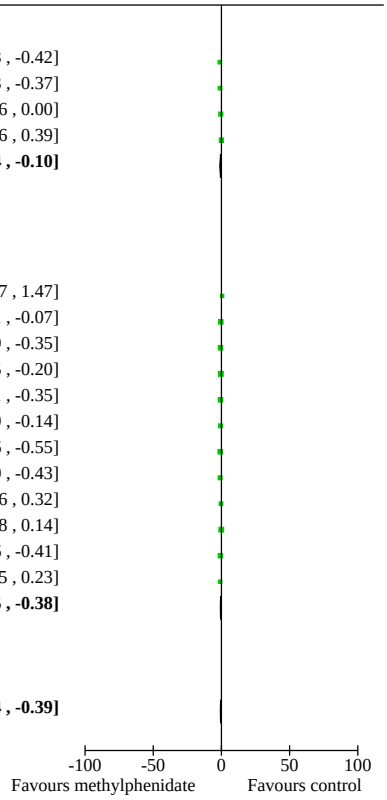
Analysis 11.9. Comparison 11: Parent-rated general behaviour, Outcome 9: All parallel-group trials and cross-over trials: risk of bias

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.9.1 Low risk of bias								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	2.5%	0.50 [-0.47 , 1.47]
Weiss 2021	67	11.57	283	68.4	14.1	71	9.5%	-0.12 [-0.38 , 0.14]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.1%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**301**			**85**	**14.0%**	**-0.12 [-0.64 , 0.41]**
Heterogeneity: Tau² = 0.10; Chi² = 3.32, df = 2 (P = 0.19); I² = 40%								
Test for overall effect: Z = 0.44 (P = 0.66)								
11.9.2 High risk of bias								
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	7.8%	-0.44 [-0.81 , -0.07]
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	7.8%	-0.72 [-1.09 , -0.35]
Findling 2007	56	8	16	73.9	19.4	16	3.6%	-1.18 [-1.93 , -0.42]
Fitzpatrick 1992a	0.6	0.39	19	1.15	0.61	19	4.2%	-1.05 [-1.73 , -0.37]
Gadow 1995	1.5	1.7	34	2.4	2	34	6.2%	-0.48 [-0.96 , 0.00]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	10.0%	-0.43 [-0.65 , -0.20]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	8.4%	-0.68 [-1.01 , -0.35]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	7.0%	-0.04 [-0.46 , 0.39]
Pelham 1999	1.2	1.4	25	2.5	2.1	25	5.2%	-0.72 [-1.29 , -0.14]
Pelham 2001a	5.26	3.85	68	8.85	4.04	68	8.0%	-0.90 [-1.26 , -0.55]
Pelham 2005	0.8	1.1	30	2.5	2.2	30	5.6%	-0.96 [-1.50 , -0.43]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	4.5%	-0.32 [-0.96 , 0.32]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	7.7%	-0.78 [-1.16 , -0.41]
Subtotal (95% CI)			**751**			**623**	**86.0%**	**-0.63 [-0.78 , -0.47]**
Heterogeneity: Tau² = 0.03; Chi² = 21.00, df = 12 (P = 0.05); I² = 43%								
Test for overall effect: Z = 7.88 (P < 0.00001)								
Total (95% CI)			**1052**			**708**	**100.0%**	**-0.56 [-0.74 , -0.39]**
Heterogeneity: Tau² = 0.06; Chi² = 36.88, df = 15 (P = 0.001); I² = 59%								
Test for overall effect: Z = 6.38 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.33, df = 1 (P = 0.07), I² = 69.9%								



Analysis 11.10. Comparison 11: Parent-rated general behaviour, Outcome 10: Subgroup analysis: all parallel-group trials and cross-over trials: vested interest

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
11.10.1 Low risk of vested interest								
Findling 2007	56	8	16	73.9	19.4	16	3.6%	-1.18 [-1.93 , -0.42]
Fitzpatrick 1992a	0.6	0.39	19	1.15	0.61	19	4.2%	-1.05 [-1.73 , -0.37]
Gadow 1995	1.5	1.7	34	2.4	2	34	6.2%	-0.48 [-0.96 , 0.00]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	7.0%	-0.04 [-0.46 , 0.39]
Subtotal (95% CI)			**114**			**109**	**21.0%**	**-0.62 [-1.14 , -0.10]**
Heterogeneity: Tau² = 0.19; Chi² = 10.10, df = 3 (P = 0.02); I² = 70%								
Test for overall effect: Z = 2.34 (P = 0.02)								
11.10.2 High risk of vested interest								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	2.5%	0.50 [-0.47 , 1.47]
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	7.8%	-0.44 [-0.81 , -0.07]
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	7.8%	-0.72 [-1.09 , -0.35]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	10.0%	-0.43 [-0.65 , -0.20]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	8.4%	-0.68 [-1.01 , -0.35]
Pelham 1999	1.2	1.4	25	2.5	2.1	25	5.2%	-0.72 [-1.29 , -0.14]
Pelham 2001a	5.26	3.85	68	8.85	4.04	68	8.0%	-0.90 [-1.26 , -0.55]
Pelham 2005	0.8	1.1	30	2.5	2.2	30	5.6%	-0.96 [-1.50 , -0.43]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	4.5%	-0.32 [-0.96 , 0.32]
Weiss 2021	67	11.57	283	68.4	14.1	71	9.5%	-0.12 [-0.38 , 0.14]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	7.7%	-0.78 [-1.16 , -0.41]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.1%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**938**			**599**	**79.0%**	**-0.56 [-0.75 , -0.38]**
Heterogeneity: Tau² = 0.06; Chi² = 26.69, df = 11 (P = 0.005); I² = 59%								
Test for overall effect: Z = 5.92 (P < 0.00001)								
Total (95% CI)			**1052**			**708**	**100.0%**	**-0.56 [-0.74 , -0.39]**
Heterogeneity: Tau² = 0.06; Chi² = 36.88, df = 15 (P = 0.001); I² = 59%								
Test for overall effect: Z = 6.38 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%								



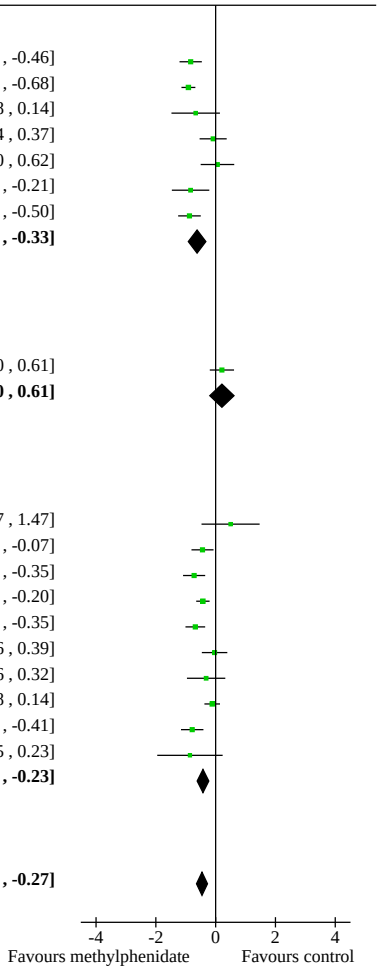
Comparison 12. Additional subgroup analyses of general behaviour

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Parallel-group trials and first-period cross-over trials: comparisons of raters	13	2262	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.64, -0.27]
12.1.1 Teacher-rated	7	792	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
12.1.2 Independent assessor-rated	1	94	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.20, 0.61]
12.1.3 Parent-rated	10	1376	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.23]
12.2 Parallel-group trials and first-period cross-over trials: comorbidity versus no comorbidity	8	696	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-0.90, -0.40]
12.2.1 ADHD with comorbidity	6	265	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.95, -0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2.2 ADHD without comorbidity	2	431	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.16, -0.24]
12.3 Cross-over trials: first-period data versus endpoint data in the same trials (teacher-, parent-, and independent assessor-rated)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.3.1 First-period data	1	16	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.75, 0.13]
12.3.2 Endpoint data	1	14	Mean Difference (IV, Random, 95% CI)	0.14 [-0.71, 1.00]

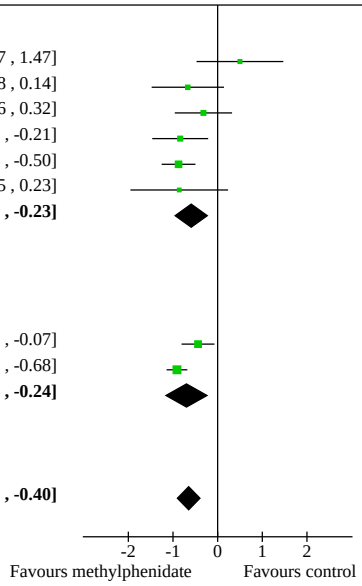
Analysis 12.1. Comparison 12: Additional subgroup analyses of general behaviour, Outcome 1: Parallel-group trials and first-period cross-over trials: comparisons of raters

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
12.1.1 Teacher-rated								
Findling 2006	2.3	2.7386	120	4.6	2.7478	39	6.4%	-0.84 [-1.21 , -0.46]
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	7.6%	-0.91 [-1.14 , -0.68]
Ialongo 1994	3.07	2.78	13	5.83	5	12	3.2%	-0.67 [-1.48 , 0.14]
Matthijssen 2019	-12.6	5.7786	37	-12.1	6.0411	38	5.7%	-0.08 [-0.54 , 0.37]
Tannock 2018	59	15.8	23	58.1	13.6	26	4.8%	0.06 [-0.50 , 0.62]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	4.3%	-0.84 [-1.46 , -0.21]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	6.3%	-0.88 [-1.25 , -0.50]
Subtotal (95% CI)			**451**			**341**	**38.2%**	**-0.62 [-0.91 , -0.33]**
Heterogeneity: Tau² = 0.10; Chi² = 18.77, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
12.1.2 Independent assessor-rated								
Matthijssen 2019	-5.3	5.2103	47	-6.4	5.2103	47	6.1%	0.21 [-0.20 , 0.61]
Subtotal (95% CI)			**47**			**47**	**6.1%**	**0.21 [-0.20 , 0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.01 (P = 0.31)								
12.1.3 Parent-rated								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	2.5%	0.50 [-0.47 , 1.47]
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	6.4%	-0.44 [-0.81 , -0.07]
Findling 2006	4.6	3.1768	120	6.9	3.1849	39	6.4%	-0.72 [-1.09 , -0.35]
Greenhill 2002	7.4	5.9	155	10.1	6.7	159	7.7%	-0.43 [-0.65 , -0.20]
Kollins 2021	10.9	8.2	74	16.4	7.9	76	6.8%	-0.68 [-1.01 , -0.35]
Matthijssen 2019	13.8	5.5678	45	14	5.5024	40	5.9%	-0.04 [-0.46 , 0.39]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	4.2%	-0.32 [-0.96 , 0.32]
Weiss 2021	67	11.57	283	68.4	14.1	71	7.4%	-0.12 [-0.38 , 0.14]
Wolraich 2001	4.81	3.87	81	8.09	4.63	46	6.4%	-0.78 [-1.16 , -0.41]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	2.1%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**860**			**516**	**55.7%**	**-0.42 [-0.62 , -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 21.09, df = 9 (P = 0.01); I² = 57%								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Total (95% CI)			**1358**			**904**	**100.0%**	**-0.46 [-0.64 , -0.27]**
Heterogeneity: Tau² = 0.10; Chi² = 61.97, df = 17 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 4.87 (P < 0.00001)								
Test for subgroup differences: Chi² = 10.89, df = 2 (P = 0.004), I² = 81.6%								



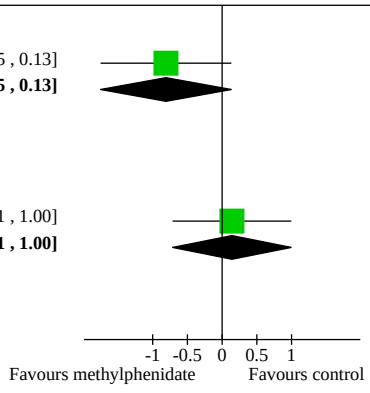
Analysis 12.2. Comparison 12: Additional subgroup analyses of general behaviour, Outcome 2: Parallel-group trials and first-period cross-over trials: comorbidity versus no comorbidity

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo/No intervention Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
12.2.1 ADHD with comorbidity								
Carlson 2007	1.9	9.4	9	-2.1	4.8	8	5.6%	0.50 [-0.47 , 1.47]
Ialongo 1994	3.07	2.78	13	5.83	5	12	7.4%	-0.67 [-1.48 , 0.14]
Pliszka 2000	1.28	0.72	20	1.54	0.88	18	10.3%	-0.32 [-0.96 , 0.32]
Van der Meere 1999a	37.8	5.8543	22	42.8	5.8543	21	10.7%	-0.84 [-1.46 , -0.21]
Wolraich 2001	1.78	2.99	81	5.21	5.12	46	18.3%	-0.88 [-1.25 , -0.50]
Zeni 2009	0.9444	0.61798	9	1.6	0.85346	6	4.6%	-0.86 [-1.95 , 0.23]
Subtotal (95% CI)			**154**			**111**	**56.8%**	**-0.59 [-0.95 , -0.23]**
Heterogeneity: Tau² = 0.08; Chi² = 8.25, df = 5 (P = 0.14); I² = 39%								
Test for overall effect: Z = 3.23 (P = 0.001)								
12.2.2 ADHD without comorbidity								
Childress 2020b	6.4	7.12	64	9.4	6.3337	53	18.7%	-0.44 [-0.81 , -0.07]
Greenhill 2002	4.9	4.66	155	10.3	6.92	159	24.5%	-0.91 [-1.14 , -0.68]
Subtotal (95% CI)			**219**			**212**	**43.2%**	**-0.70 [-1.16 , -0.24]**
Heterogeneity: Tau² = 0.09; Chi² = 4.49, df = 1 (P = 0.03); I² = 78%								
Test for overall effect: Z = 2.98 (P = 0.003)								
Total (95% CI)			**373**			**323**	**100.0%**	**-0.65 [-0.90 , -0.40]**
Heterogeneity: Tau² = 0.05; Chi² = 13.20, df = 7 (P = 0.07); I² = 47%								
Test for overall effect: Z = 5.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%								



Analysis 12.3. Comparison 12: Additional subgroup analyses of general behaviour, Outcome 3: Cross-over trials: first-period data versus endpoint data in the same trials (teacher-, parent-, and independent assessor-rated)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
12.3.1 First-period data								
Zeni 2009	0.8911	0.72428	9	1.7	1.0996	7	100.0%	-0.81 [-1.75 , 0.13]
Subtotal (95% CI)			**9**			**7**	**100.0%**	**-0.81 [-1.75 , 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								
12.3.2 Endpoint data								
Zeni 2009	1.06	0.78442	6	0.9188	0.83766	8	100.0%	0.14 [-0.71 , 1.00]
Subtotal (95% CI)			**6**			**8**	**100.0%**	**0.14 [-0.71 , 1.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								

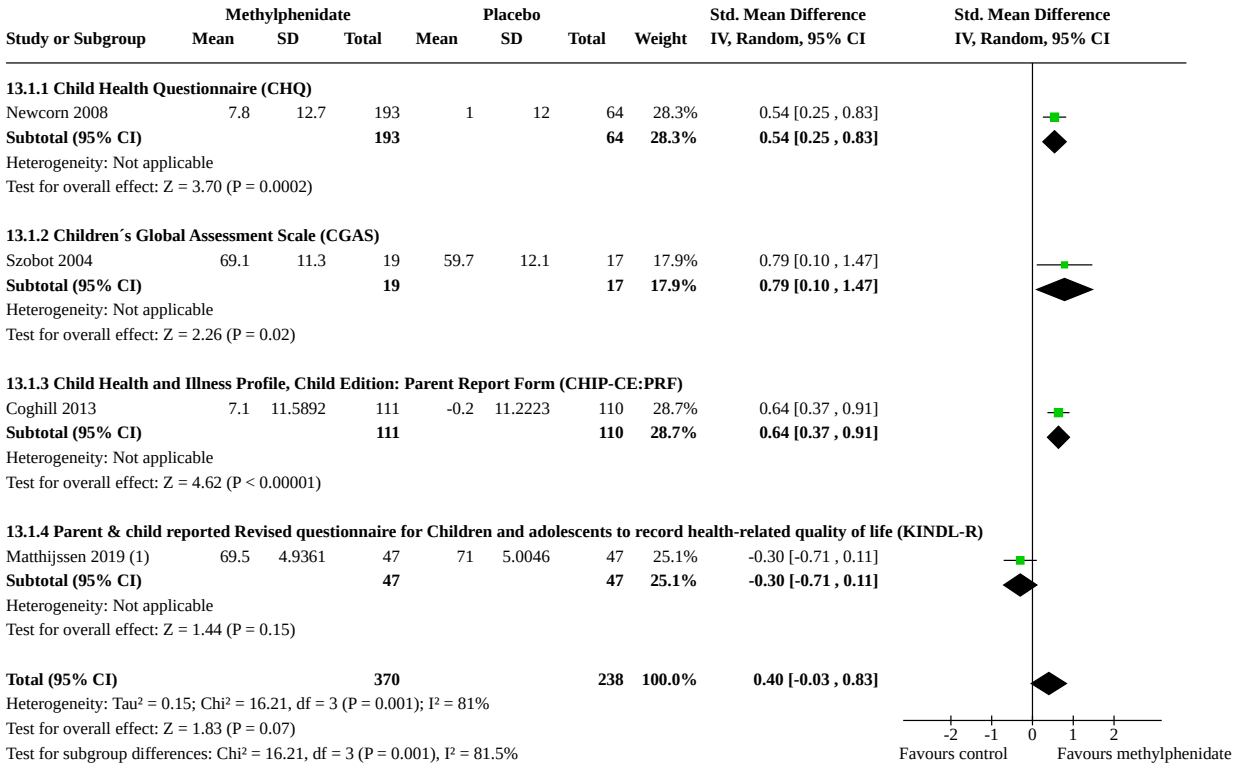


Comparison 13. Quality of life: parallel-group trials and first-period cross-over trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Subgroup analysis: types of scales	4	608	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.03, 0.83]
13.1.1 Child Health Questionnaire (CHQ)	1	257	Std. Mean Difference (IV, Random, 95% CI)	0.54 [0.25, 0.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1.2 Children´s Global Assessment Scale (CGAS)	1	36	Std. Mean Difference (IV, Random, 95% CI)	0.79 [0.10, 1.47]
13.1.3 Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP-CE:PRF)	1	221	Std. Mean Difference (IV, Random, 95% CI)	0.64 [0.37, 0.91]
13.1.4 Parent & child reported Revised questionnaire for Children and adolescents to record health-related quality of life (KINDL-R)	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.71, 0.11]

Analysis 13.1. Comparison 13: Quality of life: parallel-group trials and first-period cross-over trials, Outcome 1: Subgroup analysis: types of scales



Footnotes
(1) KINDL-R parent-rating

ADDITIONAL TABLES

Table 1. Vested interest of included studies

Study	Vested interest	Support for judgement

Table 1. Vested interest of included studies *(Continued)*

Abikoff 2009	High	Funding: investigator-initiated trial funded by a grant from Ortho-McNeil Janssen Scientific Affairs to Dr Abikoffx Conflicts of interest: Drs Abikoff and Gallagher have a contract with Multi-Health Systems to further develop the Children's Organizational Skills Scale (COSS) used in this trial. Dr Abikoff has served on the ADHD Advisory Board of Shire Pharmaceuticals and of Novartis Pharmaceuticals. Dr Boorady has served on the ADHD Advisory Board and Speakers' Bureau of Shire Pharmaceuticals. Other trial authors report no conflicts of interest
Ahmann 1993	Low	Funding: trial was funded by Marshfield Clinic grants Conflict of interest: not declared
Arnold 2004	High	Funding: trial was supported by the Celgene Corporation Conflicts of interest: Drs Arnold, Wigal and Bohan received research Funding from Celgene for the trial reported. Dr Wigal and Dr West are on the Advisory Panel and Speakers' Bureau for Novartis. Dr Arnold and Dr Bohan are on the Speakers' Bureau for Novartis. Dr Zeldis is Chief Medical Officer and Vice President of Medical Affairs at the Celgene Corporation.
Barkley 1989b	Low	Funding: trial was internally funded by the medical school Conflict of interest: not declared
Barkley 1991	Low	Funding: research was supported by the National Institute of Mental Health (NIMH) Conflicts of interest: not declared
Barkley 2000	Low	Funding: University of Massachusetts Medical School Conflict of interest: not declared
Barragán 2017	High	Funding: trial was funded by Vifor Pharma Conflict of interest: trial authors affiliated with the medical industry
Bedard 2008	Low	Funding: funding and operating grant from the Canadian Institute of Health Research and Funding from the Canada Research Chairs Programme Conflicts of interest: none
Bhat 2020	High	Funding: this work was supported in part by a grant from the Fond de Recherche du Québec and the Canadian Institutes of Health Research. Weam Fageera is a recipient of a PhD scholarship from the Ministry of Education of Saudi Arabia. Conflicts of interest: authors affiliated with medical industry
Biederman 2003b	High	Funding: received from Novartis Conflict of interest: not declared
Bliznakova 2007	Unclear	Funding: not declared Conflict of interest: not declared

Table 1. Vested interest of included studies *(Continued)*

Blum 2011	High	Funding: trial was supported by an investigator-initiated grant from Ortho McNeil Janssen Scientific Affairs, the manufacturer of OROS methylphenidate (Concerta) Conflict of interest: not declared
Borcherding 1990	Unclear	Funding: not declared Conflicts of interest: not declared
Brams 2008	High	Funding: sponsored by Novartis Pharmaceuticals Corporation Conflicts of interest: first trial author has been a speaker, consultant and advisory board member for Novartis and Shire
Brams 2012	High	Funding: Novartis Pharmaceuticals Corporation, with the following involvement reported: design and conduct of the trial; collection, management, analysis and interpretation of data; and preparation, review and approval of the manuscript. All trial authors are employees or consultants or have received research grants from pharmaceutical companies. Conflicts of interest: all trial authors are employees or consultants or have received research grants from pharmaceutical companies.
Brown 1984a	Unclear	Funding: funded by National institute of Mental Health and National institutes of Health. Placebo and methylphenidate were supplied by CIBA-GEIGY Corporation, Summit, New Jersey Conflicts of interest: not declared
Brown 1985	Unclear	Funding: research supported by US Public Health Services Grant from the National Institute of Mental Health (NIMH), and by the Biomedical Research Award from the National Institutes of Health (NIH). Methylphenidate provided by CIBA-GEIGY Corporation, Summit, New Jersey Conflicts of interest: not declared
Brown 1988	Low	Funding: Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health and Emory University Research Conflicts of interest: not declared
Brown 1991	Unclear	Funding: Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health, and by the Emory University Research Fund Conflicts of interest: not declared
Buitelaar 1995	Unclear	Funding: not declared Conflicts of interest: no affiliations with pharmaceutical companies were declared
Bukstein 1998	Unclear	Funding: no Funding declared Conflicts of interest: not declared
Butter 1983	Low	Funding: the Scientific Development Group, Organon International BV, Oss, the Netherlands Conflicts of interest: none

Table 1. Vested interest of included studies *(Continued)*

Carlson 1995	Unclear	Funding: not declared Conflict of interest: not declared
Carlson 2007	High	Funding: research was funded by Eli Lilly and Company, Indianapolis, Indiana Conflicts of interest: Dr Carlson has received research support or has consulted with the following companies: Abbott Laboratories, Cephalon, Eli Lilly and Company, Janssen, McNeil, Otsuka and Shire Pharmaceuticals. Dr Dunn has received research support or has served on Speakers' Bureaus of the following companies: AstraZeneca, Eli Lilly and Company, National Institues of Health, Otsuka and Pfizer Pharmaceuticals. Drs Kelsey, Ruff, Ball and Allen and Ms Ahrbecker are employees and/or shareholders of Eli Lilly and Company.
Castellanos 1997	Unclear	Funding: unclear Conflicts of interest: not declared
Chacko 2005	High	Funding: during the conduct of this research, Dr Pelham was supported by grants from the National Institute of Mental Health (NIMH) (MH48157, MH47390, MH45576, MH50467, MH53554, MH62946), NIAAA (AA06267, AA11873), National Institute on Drug Abuse (NIDA) (DA05605, DA12414), National Institute of Neurological Disorders and Stroke (NINDS) (NS39087), National Institute for Environmental Studies (NIES) (ES05015) and National Institute of Child Health and Human Development (NICHHD) (HD42080) Conflicts of interest: several trial authors have affiliations with medical companies
Childress 2009	High	Funding: Novartis Pharmaceuticals Corporation. Novartis Pharma has been helping with development of the manuscript. Conflicts of interest: several trial authors have received research support from, are speakers for, are consultants of, are on the Advisory Board, have served on the Speakers' Bureaus of or are employees of several pharmaceutical companies
Childress 2017	High	Funding: this trial was supported by funds from Neos Therapeutics, Inc, PI. Conflicts of interest: Carolyn R Sikes is affiliated with Neos Therapeutics, Inc.
Childress 2020a	High	Funding: trial was funded by Purdue Pharma Conflict of interest: trial authors affiliated with medical industry
Childress 2020b	High	Funding: trial funded by Ironshore Pharmaceuticals Conflict of interest: trial authors affiliated with the medical industry
Childress 2020c	High	Funding: trial funded by Rhodes Pharmaceuticals LP. Conflict of interest: authors affiliated with medical industry
Chronis 2003	High	Funding: supported by a grant from Shire-Richwood Pharmaceuticals, Incorporated - manufacturer of Adderall - and from the National Institute of Mental Health (NIMH) Conflict of interest: not declared
Coghill 2007	High	Funding: this work was supported by a local trust through a Tenovus Scotland initiative.

Table 1. Vested interest of included studies *(Continued)*

		Conflicts of interest: some trial authors have affiliations with different pharmaceutical companies
Coghill 2013	High	Funding: Shire Development LLC Conflicts of interest: C Anderson, R Civil, N Higgins, A Lyne and L Squires are employees of Shire and own stock/stock options. Some trial authors have received compensation for serving as consultants or speakers, or they or the institutions they work for have received research support or royalties from different companies or organisations.
Connor 2000	Low	Funding: supported by a UMMS (University of Massachusetts Medical School) Small Grants Project Award Conflicts of interest: not declared
Cook 1993	Low	Funding: supported by the Medical Center Rehabilitation Hospital Foundation and the School of Medicine, University North Dakota; the Veterans Hospital; the Dakota Clinic; and The Neuropsychiatric Institute, Fargo, North Dakota Conflicts of interest: not declared
Corkum 2008	Low	Funding: research was supported by a grant from the Izaak Walton Killam IWK Health Centre in Halifax, Nova Scotia Conflicts of interest: "none declared"
Corkum 2020	Low	Funding: the Canadian Institutes of Health Research Conflicts of interest: there were no conflicts of interest of any trial investigator with the pharmaceutical or equipment manufacturers.
Cox 2006	High	Funding: trial was supported by Funding from McNeil Pediatrics, a division of McNeil-PPC Incorporated Conflicts of interest: none declared
CRIT124US02	High	Funding: trial by Novartis Conflicts of interest: no information on investigators
Döpfner 2004	High	Funding: trial was conducted and sponsored by MEDICE Arzneimittel Pütter GmbH & Co. KG as part of the drug approval process for Medikinet-Retard Conflicts of interest: some trial authors have affiliations with medical companies
Douglas 1986	Low	Funding: research was supported by Grant Number MA 6913, from the Medical Research Council of Canada Conflicts of interest: not declared
Douglas 1995	Low	Funding: grants from the Medical Research Council of Canada and by William T Grant Foundation Faculty Scholar Program Conflicts of interest: none
DuPaul 1996	Unclear	Funding: unclear Conflict of interest: no conflicts of interest declared

Table 1. Vested interest of included studies *(Continued)*

Duric 2012	Low	Funding: the Child and Adolescent Psychiatry Department of Helse Fonna Hospital Haugesund, Helse Fonna Trust Haugesund, Norway Conflicts of interest: trial authors declare no potential conflicts of interests with regard to authorship or publication of this article.
Epstein 2011	Low	Funding: National Institutes of Health (NIH) and National Institute of Mental Health (NIMH) Conflicts of interest: no evidence of conflicts of interest
Fabiano 2007	Low	Funding: National Institute of Mental Health (NIMH) grant MH62946 Conflicts of interest: supported only by National Institutes
Findling 2006	High	Funding: provided by Celltech Americas Incorporated, currently part of UCB (Union Chimique Belge) Conflicts of interest: Drs Hatch and DeCory and Miss Cameron were employees of Celltech at the time of this trial. Dr Findling received research support, acted as a consultant and/or served on a Speakers' Bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Celltech-Medeva, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, New River, Novartis, Otsuka, Pfizer, Sanofi-Synthelabo, Shire, Solvay and Wyeth. Dr Quinn claims no competitive interests. Dr McDowell has consulted for Janssen-Cilag and Lilly.
Findling 2007	High	Funding: the Stanley Medical Research Institute Conflicts of interest: some trial authors have affiliations with pharmaceutical companies
Findling 2008	High	Funding: Shire Development Incorporated, Wayne, Pennsylvania Conflicts of interest: some trial authors received research support, acted as consultants and/or served on a Speakers' Bureau for several pharmaceutical companies.
Findling 2010	High	Funding: Shire Development Incorporated, which was involved in trial design, conduct and data analysis. The open-label trial was industry-sponsored. Conflicts of interest: Dr Findling has acted as consultant to, has served on Speakers' Bureaus of and/or has received research support from Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, KemPharm, Johnson & Johnson, Lundbeck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracor, Shire, Solvay, Supernus, Validus and Wyeth. Dr. Turnbow receives or has received research support, acted as a consultant and/or served on Speakers' Bureaus for Eli Lilly, Novartis US, Sanofi-Aventis, Shire and UCB (Union Chimique Belge). Dr Burnside has acted as consultant to, has served on Speakers' Bureaus of and/or has received research support from Eli Lilly, Johnson & Johnson, Shire and Wyeth. Dr Melmed has acted as consultant to, has served on Speakers' Bureaus of and/or has received research support from Bristol-Myers, Eli Lilly, McNeil, Novartis and Shire. Drs Civil and Li are full-time employees of Shire Development Incorporated.
Fine 1993	High	Funding: CIBA-GEIGY Canada Conflicts of interest: not declared
Firestone 1981	Low	Funding: Ministry of Health

Table 1. Vested interest of included studies *(Continued)*

		Conflicts of interest: not stated
Fitzpatrick 1992a	Low	Funding: National Institute of Mental Health (NIMH) grant MH38118 Conflicts of interest: not declared
Flapper 2008	Low	Funding: none (no funding was available). This double-blind placebo-controlled (DBPC) trial of methylphenidate was performed as a clinical treatment program as best clinical practice to determine the effects of methylphenidate and optimal dose compared with placebo. Conflicts of interest: no affiliations with pharmaceutical companies or similar declared.
NCT02039908	Low	Funding: Florida International University Conflicts of interest: nothing declared for trial investigators
Forness 1992	Low	Funding: National Institute of Mental Health (NIMH) grant MH38686 Conflicts of interest: no affiliations described
Froehlich 2011	High	Funding: National Institute of Mental Health (NIMH) and Cincinnati Children's Hospital Center for Education and Research Therapeutics Award Conflicts of interest: Dr Epstein receives Funding from Eli Lilly and Co. Dr Stein has received research support from Eli Lilly and Co., McNeil Pharmaceuticals, Novartis and Shire. He has served on a Speakers' Bureau for Novartis and has served as consultant to Novartis, Shire and Shinogi Pharmaceuticals.
Froehlich 2018	High	Funding: data collection for the project was supported by the National Institute of Mental Health (Bethesda, MD) by R01MH074770 [Epstein] and K23MH083881 [Froehlich], while investigators' time on the project was funded by National Institute of Mental Health K24MH064478 [Epstein], K23MH083027 [Brinkman], and R01MH070564 [Stein]). Conflicts of interest: trial authors are affiliated with the medical industry
Gadow 1990	Unclear	Funding: Ciba Pharmaceutical Company supplied methylphenidate placebo Conflicts of interest: not declared
Gadow 1995	Low	Funding: research grants from the Tourette Syndrome Association and the National Institute of Mental Health (NIMH) Conflicts of interest: not declared
Gadow 2007	Low	Funding: this trial was supported in part by a research grant from the Tourette Syndrome Association Incorporated, and by Public Health Service (PHS) grant number MH45358 from the National Institute of Mental Health (NIMH). Conflicts of interest: trial authors have no financial relationships to disclose.
Gadow 2011	Unclear	Funding: National Institute of Mental Health (NIMH) and the Tourette Syndrome Association Incorporated. CIBA Pharmaceutical Company supplied methylphenidate placebos. Novartis supplied immediate-release methylphenidate. Conflicts of interest: "Kenneth D. Gadow is a shareholder in Checkmate Plus, publisher of the Child Symptom Inventory-4"

Table 1. Vested interest of included studies *(Continued)*

Garfinkel 1983	Low	Funding: Ontario Mental Health Foundation Conflicts of interest: none
Gonzalez-Heydrich 2010	High	Funding: supported by National Institute of Mental Health (NIMH) Grant, Number K23 MH066835 Conflicts of interest: 4 trial authors are involved in the pharmaceutical sector.
Gorman 2006	Low	Funding: National Institute of Mental Health (NIMH) Conflicts of interest: trial authors have no financial relationships to declare
Green 2011	Low	Funding: the Basil O'Connor Starter Scholar Research Award of the March of Dimes, NARSAD (National Alliance for Research in Schizophrenia and Affective Disorders) Young Investigator Award, the Marguerite Stolz Award from the Sackler Faculty of Medicine and the National Institute on Drug Abuse (NIDA) Conflicts of interest: trial authors have had no institutional or corporate/commercial relationships for the past 36 months that might pose a conflict of interest.
Greenhill 2002	High	Funding: Celltech Pharmaceuticals Incorporated Conflicts of interest: Dr Greenhill is a consultant for Celltech-Medeva and a member of its medical advisory board. Drs Findling and Swanson are consultants for Celltech-Medeva.
Greenhill 2006	High	Funding: Novartis Conflicts of interest: 2 trial authors are employed by Novartis. Only Roberta R Ball has no conflicts of interest.
Gruber 2007	Low	Funding: this was not an industry-supported trial. Conflicts of interest: trial authors have indicated no financial conflicts of interest.
Hale 2011	Low	Funding: research part funded by the Neuropsychiatric Research Institute, Fargo, North Dakota, USA Conflicts of interest: trial authors disclose no conflicts of interest
Hawk 2018	Low	Funding: supported by grants from the National Institute of Mental Health (NIMH) and from the National Institute on Drug Abuse (NIDA) Conflicts of interest: no conflicts declared
Heriot 2008	Low	Funding: no funding to conduct the trial was received from any party. Conflicts of interest: none of the trial authors are affiliated with pharmaceutical companies.
Hicks 1985	Low	Funding: National Institutes of Health (NIH) Conflicts of interest: not declared
Hoeppner 1997	Unclear	Funding: not declared Conflicts of interest: not declared

Table 1. Vested interest of included studies *(Continued)*

Horn 1991	Unclear	Funding: not declared Conflicts of interest: not declared
Huang 2021	High	Funding: this work is supported by Orient Pharma Co, Ltd. Conflicts of interest: authors affiliated with medical industry
Ialongo 1994	Unclear	Funding: not declared Conflicts of interest: not declared
Jacobi-Polishook 2009	Unclear	Funding: not declared Conflicts of interest: not declared
Jensen 1999 (MTA)	High	Funding: this trial was supported by several grants from the National Institute of Mental Health, Bethesda, Maryland. Conflicts of interest: several trial authors have affiliations with medical companies.
Johnston 1988	Unclear	Funding: not declared. During the writing of this report, C Johnston was supported by a Doctoral Fellowship from the Social Sciences and Humanities Research Council of Canada. Conflicts of interest: not declared
Kaplan 1990	Unclear	Funding: not declared Conflicts of interest: not declared
Kelly 1989	Unclear	Funding: CIBA Geigy Pharmaceuticals provided placebos Conflicts of interest: not declared
Kent 1995	Low	Funding: this work was supported by the John and Maxine Bendheim Fellowship and by the Leon Lowenstein Foundation. Conflicts of interest: not declared
Kent 1999	High	Funding: Ms Kent was a summer medical student supported in part by the IWK Grace Research Foundation, Halifax, NovaScotia, and by the Pharmaceutical Manufacturers Association of Canada Studentship, Ottawa, Ontario Conflicts of interest: trial authors sponsored by Pharmaceutical Manufacturers' Association of Canada Studentship
Klorman 1990	Low	Funding: National Institute of Mental Health (NIMH) grant MH38118 Conflicts of interest: no corporate affiliations declared
Kolko 1999	Unclear	Funding: not declared Conflicts of interest: not declared
Kollins 2006 (PATS)	High	Funding: • Phase 5 (cross-over): sponsored by the National Institute of Mental Health, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical

Table 1. Vested interest of included studies *(Continued)*

		Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to JKG. Generic methylphenidate was purchased by grant funds. • Phase 6 (parallel-group): sponsored by the National Institute of Mental Health, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to JKG. Generic methylphenidate was purchased by grant funds. • Phase 8 (discontinuation): sponsored by the National Institute of Mental Health, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to JKG. Generic methylphenidate was purchased by grant funds. Conflicts of interest: • Phase 5 (cross-over): multiple trial authors had relationships with several pharmaceutical companies for the period 2000-2007. • Phase 6 (parallel-group): multiple trial authors had relationships with several pharmaceutical companies for the period 2000-2007. Placebo responders in phase 5 were excluded from phase 6. Participants with no clinical benefit any week were excluded from phase 6 (methylphenidate non-responders). • Phase 8 (discontinuation): multiple trial authors had relationships with several pharmaceutical companies for the period 2000-2007.
Kollins 2021	High	Funding: clinical research was funded by KemPharm, Inc. Funding for editorial and writing assistance in the form of proofreading, copyediting, and fact-checking was provided by Corium, Inc. Conflicts of interest: authors affiliated with medical industry
Konrad 2004	Low	Funding: the German Society for the Advancement of Scientific Research (DFG grant KFO112) Conflicts of interest: none declared
Konrad 2005	Low	Funding: provided through a grant from the German Research Foundation (DFG grant: KFO112–TP5) Conflicts of interest: none declared
Kortekaas-Rijlaarsdam 2017	High	Funding: unclear, but Shire was a collaborator Conflicts of interest: the second trial author has some affiliation to the medical industry.
Kritchman 2019	Low	Funding: Shalvata Mental Health Center Conflicts of interest: “The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.”
Leddy 2009	High	Funding: not declared Conflicts of interest: Dr Waxmonsky has served on the Speakers' Board for Novartis, received an honorarium from Shire and received research support from Shire and Eli Lilly. Dr Erbe has received educational and research support from

Table 1. Vested interest of included studies *(Continued)*

		Genzyme Corporation. Dr Pelham was paid an honorarium by Shire Pharmaceuticals.
Lehmkuhl 2002	High	Funding: Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, D-58638 Iserlohn Conflicts of interest: Dr Doepfner is a consultant for Lilly, Medice, Novartis and Union Chimique Belge; serves on the Advisory Boards of Lilly, Medice, Shire, Novartis and Union Chimique Belge; participates as a member of the Speakers' Bureaus of Lilly, Medice, Janssen-Cilag and Union Chimique Belge; and has research contracts with Lilly, Medice, Novartis, Union Chimique Belge, the German Research Foundation and the Federal Ministry of Health. Dr Lehmkuhl is on the Advisory Boards of Lilly and Medice. Dr Sinzig has no financial relationships to disclose.
Lijffijt 2006	Unclear	Funding: not declared Conflicts of interest: none declared
Lin 2014	High	Funding: Ely Lilly Conflicts of interest: 5 authors work for Lilly.
Lopez 2003	High	Funding: Novartis Conflicts of interest: Dr Silva is a consultant and a member of the Speakers' Bureau for Novartis. Dr Lopez is a consultant for Eli Lilly, Novartis and Shire. He is also a member of the Speakers' Bureaus for Novartis and Shire.
Lufi 1997	Unclear	Funding: not declared Conflits of interest: not declared
Lufi 2007	Unclear	Funding: not declared Conflicts of interest: not declared
Manos 1999	High	Funding: in part by from Shire Pharmaceutical Development Incorporated to Dr Faraone Conflicts of interest: trial authors acknowledge partial support to the second author from the National Institute on Drug Abuse (NIDA) (grants R01-DA07957 and MCJ-390592) and from the Maternal and Child Health Program, Health Resources and Service Administration, Department of Health and Human Services (grant 390715), and to the third author from the Stanley Foundation.
Martins 2004	Unclear	Funding: methylphenidate and placebo pills were supplied by Novartis Pharmaceuticals (São Paulo, Brazil) at no cost and without restrictions. No additional funding was requested or received from Novartis or any other commercial entity. Conflicts of interest: trial authors have reported no conflicts of interest
Matthijssen 2019	Low	Funding: The Netherlands Organization for Health Research and development (ZonMw, grant 836011014) Conflicts of interest: not declared
McBride 1988a	Unclear	Funding: not declared Conflicts of interest: not declared

Table 1. Vested interest of included studies *(Continued)*

McCracken 2016	High	Funding: National Institute of Mental Health (NIMH) Research Center grant P50MH077248, "Translational Research to Enhance Cognitive Control" Conflicts of interest: trial authors affiliated with the medical industry
McGough 2006	High	Funding: Shire US Inc Conflicts of interest: 2 medical writers acknowledged (Amy M Horton & Michelle Roberts) but were unclear about where they came from or what their role was in the publication.
McInnes 2007	High	Funding: the Psychiatric Endowment Fund Conflicts of interest: trial authors had received Funding from Eli Lilly, Shire Pharmaceuticals, Janssen-Ortho and McNeil Pharmaceuticals
Merrill 2021	Unclear	Funding: not stated Conflicts of interest: trial authors declare that they have no conflict of interest
Moshe 2012	Low	Funding: none Conflicts of interest: none declared
Muniz 2008	High	Funding: "This study was funded by Novartis Pharmaceuticals Corporation and reports the following involvement: design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, and approval of the manuscript" Conflicts of interest: Dr Muniz is an employee of Novartis Pharmaceuticals Corporation. He has no other relationships to disclose. Dr Brams reports the following relationships: serves as speaker, consultant and Advisory Board member for Novartis and Shire; receives grant research support from Novartis, Shire and Eli Lilly. Dr Mao reports the following relationships: speaker for Novartis, Eli Lilly, Bristol-Myers Squibb, AstraZeneca and Shire; consultant for Eli Lilly, Novartis and Shire; receives grant research support from Novartis. Mr McCague is an employee of Novartis Pharmaceuticals Corporation. He has no other relationships to disclose. Ms Pestreich is an employee of Novartis Pharmaceuticals Corporation. She has no other relationships to disclose. Dr Silva reports the following relationships: none since 15 December 2006; before that, she was a speaker for Novartis, AstraZeneca and Janssen; received grant/research support from Novartis and Celgene.
Murray 2011	High	Funding: Ortho-McNeil Janssen Scientific Affairs, LLC Conflicts of interest: several trial authors had affiliations with pharmaceutical companies producing methylphenidate
Musten 1997	Low	Funding: Health Canada grant Conflicts of interest: none declared
NCT00409708	High	Funding: Novartis Conflicts of interest: no information on investigators
NCT02293655	Unclear	Funding: Children's Hospital Medical Center, Cincinnati Conflicts of interest: not stated
NCT02536105	High	Funding: Massachusetts General Hospital

Table 1. Vested interest of included studies *(Continued)*

		Conflicts of interest: trial investigators affiliated with the medical industry
Newcorn 2008	High	Funding: Eli Lilly and Company Conflicts of interest: Dr Newcorn receives grant support from Eli Lilly and McNeil; is a consultant and/or advisor for Eli Lilly, McNeil, Shire, Novartis and Sanofi-Aventis; and is a member of Speakers' Bureaus for Eli Lilly and Novartis. Dr Kratochvil receives grant support from Abbott, Cephalon, Eli Lilly, McNeil, Pfizer, Shire and Somerset; receives from Eli Lilly trial medication for an NIMH (National Institute of Mental Health)-funded trial; is a consultant for Abbott, AstraZeneca, Eli Lilly and Pfizer; and is a member of the Eli Lilly Speakers' Bureau. Dr Casat receives research Funding from Eli Lilly, Novartis and Abbott, and serves on an advisory board for Eli Lilly. Dr Allen and Dr Ruff are employees and shareholders of Eli Lilly. Dr Michelson and Dr Moore are former employees of Eli Lilly.
Newcorn 2017a (flexible dose)	High	Funding: Shire Conflicts of interest: trial authors affiliated with pharmaceutical companies
Newcorn 2017b (forced dose)	High	Funding: Shire Conflicts of interest: trial authors heavily affiliated with pharmaceutical companies
Nikles 2006	Low	Funding: the General Practice Evaluation Program, the Department of Health and Aged Care, Queensland Medical Laboratory, and the Royal Australian College of General Practitioners Conflicts of interest: trial authors have indicated that they have no financial relationships relevant to this article to disclose
Oesterheld 1998	Low	Funding: University of South Dakota/USF-Mini Grant Conflicts of interest: none declared
Overtoom 2003	Low	Funding: Netherlands Organisation for Scientific Research (NWO) Grant 575-63-082 Conflicts of interest: not declared
Palumbo 2008	High	Funding: NIH (National Institutes of Health) and NINDS (National Institute of Neurological Disorders and Stroke) Conflicts of interest: some trial authors are on the ADHD Advisory Board and the Speakers' Bureau of; are scientific consultants or principal or site investigators for; and/or have received educational or funding support from several pharmaceutical companies.
Pearson 2013	Low	Funding: grant number MH072263 from National Institute of Mental Health (NIMH) Conflicts of interest: none declared
Pelham 1989	Unclear	Funding: not declared Conflicts of interest: not declared
Pelham 1990a	Unclear	Funding: not declared Conflicts of interest: not declared

Table 1. Vested interest of included studies *(Continued)*

Pelham 1993a	Unclear	Funding: not declared Conflicts of interest: not declared
Pelham 1999	High	Funding: grants from the Shire Richwood Pharmaceutical Company and National Institute of Mental Health (Grants MH53554, MH45576 and MH50467) Conflicts of interest: not declared
Pelham 2001a	High	Funding: ALZA Corporation, the manufacturers of Concerta Conflicts of interest: Dr Pelham is a member of the ALZA advisory committee on Concerta and its development. Drs Hoffman and Lock are members of the ALZA paediatric advisory board.
Pelham 2002	High	Funding: NIMH (Grant MH48157) Conflicts of interest: Pelham served as an advisor for ALZA Corporation (see Pelham 2001a)
Pelham 2005	High	Funding: Noven Pharmaceuticals. Furthermore, Dr Pelham was supported by grants from NIAAA, NIDA, NIMH and NINDS. Conflicts of interest: several trial authors have received consulting fees and research funding and have been consultants and/or served on the Speakers' Bureaus of several pharmaceutical companies in the past year.
Pelham 2011	High	Funding: grant from Noven Pharmaceuticals Conflicts of interest: Dr Pelham has served as a consultant for Shire, McNeil, Noven, Celltech/Medeva, Novartis and Abbott Laboratories; has received honoraria from Shire and Janssen and research support from Shire, Alza, Eli Lilly, Noven and Cephalon; and holds common stock in Abbott Laboratories. Dr Waxmonsky has served on the Speakers' Bureau for Novartis and has received research support from Eli Lilly and Shire Incorporated. Dr Hoffman has served on the advisory board and Speakers' Bureau for Shire Pharmaceuticals and on the Speakers' Bureau for McNeil. Dr Ballow has received research support from GlaxoSmithKline, Panacos, Boehringer Ingelheim, Pharmasset, Jacobus and Pharmena. Dr Schentag has served as a consultant for or received support from Noven, Wyeth, Daiichi, Targanta Therapeutics and Astellas. Dr Gonzalez is a full-time employee of P'Kinetics International Incorporated. No other conflicts of interest are known.
Pelham 2014	Low	Funding: grant from the National Institute of Mental Health (MH62946). Dr Pelham was funded by grants from the National Institutes of Health (MH62946, MH69614, MH53554, MH69434, MH65899, MH78051, MH062946, NS39087, AA11873, DA12414, HD42080) and the Institute of Education Sciences (L03000665A). Dr Fabiano was supported in part by a Ruth S Kirschstein National Research Service Award Predoctoral Fellowship (1F31MH064243-01A1) and by the Department of Education, Institute of Education Sciences (R324J06024, R324B06045). Conflicts of interest: not declared
Perez-Alvarez 2009	Low	Funding: none. Research was part of the work day, participants were voluntary and no funding was needed to implement the trial Conflicts of interest: none. Investigators are staff members at institutions (affiliations) reported in the paper.
Pliszka 1990	Low	Funding: National Institute of Mental Health (NIMH)

Table 1. Vested interest of included studies *(Continued)*

		Conflicts of interest: not declared
Pliszka 2000	High	Funding: Shire Richwood Incorporated Conflicts of interest: Dr Browne is currently with Watson Pharmaceuticals, Corona, California
Pliszka 2007	High	Funding: National Institute of Mental Health Grant R01 MH63986 Conflicts of interest: Pliszka received honoraria and research support from Shire and MacNeil and research support from Ely Lilly and Cephalon
Pliszka 2017	High	Funding: Ironshore Pharmaceuticals Conflicts of interest: trial authors affiliated with the medical industry
Quinn 2004	High	Funding: Celgene Conflicts of interest: all trial authors disclosed that they have past and present affiliations with the pharmaceutical industry.
Ramtvedt 2013	High	Funding: the first phase was conducted as part of ordinary clinical practice at Neuropsychiatric Unit, Østfold Hospital Trust. The second and third phases, data analysis and preparation of manuscript were sponsored by South-Eastern Norway Regional Health Authority, and also by Østfold Hospital Trust and National Resource Centre for ADHD, both under the umbrella of South-Eastern Norway Regional Health Authority. Conflicts of interest: Henning Aabech is a member of the Strattera Advisory Board, Eli Lilly, Norway.
Rapport 1985	Unclear	Funding: not declared Conflicts of interest: not declared
Rapport 1987	Low	Funding: none, neither external nor internal. This project was supported in part by a Biomedical Research Support Grant (no. S07 RR05712), which was awarded to the first trial author by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health. Conflicts of interest: not declared
Rapport 2008	Low	Funding: none Conflicts of interest: no financial, corporate or commercial relationships to disclose
Reitman 2001	Unclear	Funding: not declared Conflict of interest: none
Riggs 2011	High	Funding: OROS methylphenidate and matching placebo were supplied to the Clinical Trials Network contract pharmacy (EMINENT Services Corporation) by McNeil Consumer and Specialty Pharmaceuticals (distributor for Concerta), at no cost. Principal investigators are not employed by the organisation sponsoring the trial. No agreement between principal investigators and trial sponsor (or its agents) restricts the principal investigator's rights to discuss or publish trial results after the trial is complete

Table 1. Vested interest of included studies *(Continued)*

		Conflicts of interest: some trial authors have received research support from, served on Speakers' Bureaus of or acted as consultants for pharmaceutical companies.
Rubinsten 2008	Low	Funding: the research was completed while Dr Rubinsten was a post-doctoral fellow at the Hospital for Sick Children (HSC), in Toronto, Canada, and was supported by the Rothschild Fellowship from Israel. It was undertaken, in part, through funding received from the Canadian Institutes of Health (CIHR: grant #MOP 64312), a CIHR post-doctoral fellowship, and the Canada Research Chairs Program (RT). Conflicts of interest: not declared
Samuels 2006	Unclear	Funding: not declared Conflicts of interest: not declared
Schachar 1997a	High	Funding: Medical Research Council of Canada, National Health Research Development Program of Canada and the Department of Psychiatry, The Hospital for Sick Children, Toronto. Placebo pills were provided by Ciba Geigy, Canada, Ltd Conflicts of interest: 2 trial authors have reported working as consultants for pharmaceutical companies, and 1 has furthermore received industry-sponsored research grants.
Schachar 2008	High	Funding: Purdue Pharma (Canada) Conflicts of interest: some trial authors are working for Purdue Pharma
Schrantee 2016	Low	Funding: this trial was funded by faculty resources of the Academic Medical Center, University of Amsterdam, and by grant 11.32050.26 from the European Research Area Network Priority Medicines for Children (Sixth Framework Programme). Dr Rombouts was supported by Vici (Netherlands Organisation for Scientific Research), and Dr Andersen was supported by grant DA-015403 from the National Institute on Drug Abuse Conflicts of interest: Dr Niessen reported being cofounder, shareholder, and part-time scientific officer of Quantib BV. No other disclosures were reported. Through personal correspondence it was clarified that Dr Niessen did not facilitate any part of the trial, but was involved in the data-analysis of MRI imaging sequence technique used (arterial spin labelling).
Schulz 2010	High	Funding: Novartis Pharma GmbH, Germany. Trial aimed at showing efficacy of Ritalin LA with purpose of obtaining marketing authorisation Conflicts of interest: almost all trial authors have received grants, research support or other kinds of financial support from the medical industry.
Schwartz 2004	High	Funding: grants from Le Fonds de la Recherche en Santé du Québec and the Canadian Institutes of Health Research Conflicts of interest: yes. Dr Joober is a principal investigator on a clinical trial not related to this trial that is sponsored by AstraZeneca Canada Incorporated, and receives no direct compensation for this trial. Dr Boivin has the following industry financial ties: The Litebook Company Ltd., Medicine Hat, Alberta, Canada; and Pulsar Informatics Inc., Vancouver, British Columbia, Canada.
Sharp 1999	Unclear	Funding: not declared Conflicts of interest: not declared

Table 1. Vested interest of included studies *(Continued)*

Shiels 2009	High	Funding: National Institute of Mental Health Conflicts of interest: "In the past 3 years, James G. Waxmonsky has served on the Speakers Bureau for Novartis, received honoraria from Scepter, and received research support from Eli Lilly"
Silva 2005a	High	Funding: Novartis Pharmaceuticals Corporation Conflicts of interest: all trial authors have been consultants, have received honoraria or have worked for Novartis.
Silva 2006	High	Funding: Novartis Conflicts of interest: some trial authors have affiliations with medical companies
Silva 2008	High	Funding: Novartis Conflicts of interest: some trial authors have affiliations with medical companies
Smith 1998	Low	Funding: grants from the National Institute on Drug Abuse, the National Institute of Mental Health, the National Institute on Alcohol Abuse and Alcoholism and the National Institute of Child Health and Human Development Conflicts of interest: not declared
Smith 2004	Unclear	Funding: not declared Conflicts of interest: not declared
Smithee 1998	Low	Funding: National Institute of Mental Health (NIMH) Grant MH 38228; Rafael Klorman Conflicts of interest: not declared
Solanto 2009	High	Funding: the National Institute of Mental Health Conflicts of interest: 3 trial authors have served or received grants from pharmaceutical companies in the past.
Soleimani 2017	Low	Funding: Guilan University of Medical Sciences Conflicts of interest: none declared
Stein 1996	Low	Funding: the work was supported by the Smart Family Foundation. Conflicts of interest: no affiliations with pharmaceutical companies stated
Stein 2003	High	Funding: the National Institute of Mental Health, the General Clinical Research Center Program of the National Center for Research Resources and the National Institutes of Health, Department of Health and Human Services Conflicts of interest: Drs Stein, Robb, Conlon and Newcorn participate in the Speakers' Bureau for McNeil Consumer and Specialty Pharmaceuticals, and Drs Stein and Newcorn are members of the Concerta National Advisory Committee.
Stein 2011	High	Funding: investigator-initiated trial sponsored by Novartis Pharmaceuticals, with additional support provided by the University of Illinois at Chicago (UIC) Center for Clinical and Translational Science (CCTS)

Table 1. Vested interest of included studies *(Continued)*

		Conflicts of interest: some trial authors are affiliated with pharmaceutical companies
Stoner 1994	Low	Funding: National Association of School Psychologists Conflicts of interest: not declared
Sumner 2010	Unclear	Funding: it was not clear who sponsored the trial, but someone did (see authors' affiliations). Conflicts of interest: Calvin R Sumner is an employee of and an equity holder for the trial sponsor. Virginia S Haynes, PhD, is an employee of 3i Global (Basking Ridge, NJ) and a paid consultant for the trial sponsor. Martin H Teicher, MD, PhD, served as paid consultant and clinical investigator for the sponsor. Jeffrey H Newcorn, MD, serves as advisor and consultant for Lilly, Ortho-McNeil Janssen, Schering-Plough and Shire. He receives research support from Lilly, Ortho-McNeil Janssen and Shire.
Sunohara 1999	High	Funding: RESTRACOM graduate studentship for The Hospital for Sick Children Research Institute and Novartis Pharmaceuticals Conflicts of interest: not declared
Swanson 1998	High	Funding: grant from Richwood Pharmaceutical Company Conflicts of interest: not declared
Swanson 1999	High	Funding: ALZA Corporation, Palo Alto, California Conflicts of interest: not declared
Swanson 2002a	High	Funding: ALZA Corporation Conflicts of interest: not declared
Swanson 2002b	High	Funding: ALZA Corporation Conflicts of interest: not declared
Swanson 2004b	High	Funding: Celltech Pharmaceuticals Incorporated Conflicts of interest: some trial authors are consultants for pharmaceutical companies
Symons 2007	Unclear	Funding: A McKnight Land-Grant Professorship to the first author Conflicts of interest: this work was supported, in part, by a McKnight Land-Grant Professorship to Frank Symons.
Szobot 2004	High	Funding: research funds from Hospital de Clínicas de Porto Alegre, FAPERGS and NOVARTIS Conflicts of interest: not declared
Szobot 2008	High	Funding: "The ADHD outpatient program receives research support from Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag and Novartis" Conflicts of interest: trial authors are consultants and speakers for various companies

Table 1. Vested interest of included studies *(Continued)*

Tannock 1989	Low	Funding: jointly funded by Ontario Mental Health Foundation (Grant No. 963-86/88) and Health and Welfare Canada (Grant No. 6606-3166-42) Conflict of interest: not declared
Tannock 1992	Low	Funding: grant from the Canadian Psychiatric Research Foundation and a post-doctoral fellowship by the Ontario Mental Health Foundation Conflicts of interest: not declared
Tannock 1993	Low	Funding: the Canadian Psychiatric Research Foundation and the Medical Research Council of Canada Conflicts of interest: not declared
Tannock 1995a	Low	Funding: Medical Research Council of Canada and Health and Welfare Canada Conflicts of interest: nothing to declare
Tannock 1995b	Low	Funding: in part, by the Ontario Mental Health Foundation and the National Health Research and Development Program, Health Canada Conflicts of interest: not declared
Tannock 2018	Unclear	Funding: an operating grant from the Canadian Institutes of Health Research (Grant # MT 13366), and by the donation of placebo medication from Novartis Pharmaceuticals Conflict of interest: none declared
Taylor 1987	High	Funding: partially funded by grant from CIBA Ltd., which provided medicine and placebo Conflicts of interest: Dr Schachar was supported during this period by a fellowship from the Medical Research Council of Canada.
Taylor 1993	Unclear	Funding: not declared Conflicts of interest: not declared
Tervo 2002	Unclear	Funding: not declared Conflicts of interest: no conflicts of interest have been disclosed
Tirosh 1993a	Unclear	Funding: none Conflicts of interest: not declared
Tirosh 1993b	Unclear	Funding: not declared Conflicts of interest: not declared
Tourette's Syndrome Study Group 2002	Unclear	Funding: National Institute of Neurological Disorders and Stroke, the General Clinical Research Center, the National Center for Research Resources, the Tourette Syndrome Association Boeringer Ingelheim Inc. (particularly Dr Virgil Dias), for supplying clonidine and matching placebo; Bausch and Lomb, Inc., for supplying small gifts for our trial participants Conflicts of interest: none declared
Tucker 2009	High	Funding: Novartis Pharmaceuticals Corporation

Table 1. Vested interest of included studies *(Continued)*

		Conflicts of interest: some trial authors were employed by Novartis (5 of 8 had a Novartis email address)
Ullmann 1985	Unclear	Funding: National Institutes of Mental Health (NIMH). Ciba-Geigy provided medication and placebo Conflicts of interest: not declared
Ullmann 1986	Unclear	Funding: in part by a National Institute of Mental Health (NIMH) grant. Ciba-Geigy provided medication and placebo Conflicts of interest: not declared
Urman 1995	Low	Funding: in part by funds from the Medical Research Council of Canada and the Research Institute of the Hospital for Sick Children Conflicts of interest: not declared
Van der Meere 1999a	High	Funding: grants from the Sophia Foundation for Medical Research and Boehringer Ingelheim BV, the Netherlands Conflicts of interest: not declared
Wallace 1994	Low	Funding: The Veterans Administration Medical Center, Vermont Conflicts of interest: not declared
Wallander 1987	Low	Funding: in part by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) grants and the University of Southern California Faculty Research and Innovation Fund Conflicts of interest: not declared
Waxmonsky 2008	High	Funding: National Institute of Mental Health (NIMH) Grant MH62946 and a Klingenstein Third Generation Foundation Fellowship in Child and Adolescent Depression Research Conflicts of interest: several authors have affiliations with pharmaceutical companies
Weiss 2021	High	Funding: Rhodes Pharmaceuticals, LP Conflict of interest: the trial authors are affiliated with the medical industry.
Whalen 1990	Unclear	Funding: not declared Conflicts of interest: not declared
Wigal 2003	High	Funding: Celltech Americas Incorporated Conflicts of interest: some trial authors are working for Celltech Americas Incorporated
Wigal 2004	High	Funding: Celgene Corporation Conflicts of interest: Dr Wigal reports extensive disclosure.
Wigal 2011	High	Funding: Ortho-McNeil-Janssen Scientific Affairs, LLC. Phase IV trial Conflicts of interest: several trial authors had affiliations with pharmaceutical companies producing methylphenidate

Table 1. Vested interest of included studies *(Continued)*

Wigal 2013	High	Funding: trial received funds from NextWave Pharmaceutics (Belden and Berry are with NextWave) Conflicts of interest: all trial authors are affiliated with NextWave Pharmaceuticals.
Wigal 2014	High	Funding: Rhodes Pharmaceuticals LP Conflicts of interest: several trial authors work for, or have received grant and research support or both from pharmaceutical companies
Wigal 2015	High	Funding: Rhodes Pharmaceuticals […]. Medical writing assistance was provided by Linda Wagner, PharmD, from Excel Scientific Solutions and funded by Rhodes Pharmaceuticals LP Conflicts of interest: not declared
Wigal 2017	High	Funding: the research was sponsored by NextWave Pharmaceuticals, a wholly owned subsidiary of Pfizer, Inc. Conflicts of interest: trial authors are affiliated with the medical industry
Wilens 2006b	High	Funding: McNeil Consumer and Specialty Pharmaceuticals Conflicts of interest: several trial authors have had commitments (e.g. speakers, consultants, advisors) with various pharmaceutical companies
Wilens 2008	High	Funding: Shire Development Incorporated Conflicts of interest: several trial authors have affiliations with medical companies
Wilens 2010	High	Funding: trial and medication/placebo were funded by a grant through Shire Pharmaceuticals. Shire had no role in design, collection, analysis, interpretation, writing or decision to submit Conflicts of interest: some trial authors have received research support from medical companies
Wilkison 1995	Low	Funding: a University of Utah Biomedical Sciences research grant and a grant from the University Research Committee Conflicts of interest: no corporate affiliations described
Wodrich 1998	Unclear	Funding: not declared Conflicts of interest: not declared
Wolraich 2001	High	Funding: ALZA Corporation Conflicts of interest: trial authors are part of the Concerta Study Group
Zeiner 1999	Low	Funding: the Norwegian Medical Research Council, the Norwegian Public Health Association and the Legacy of Haldis and Josef Andresen Conflicts of interest: not declared
Zeni 2009	High	Funding: research grants from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq, Brazil) (Grant 471761=03-6) and Hospital de Clinicas de Porto Alegre (GPPG 03-325). Aripiprazole was provided by Bristol-Myers Squibb without restriction.

Table 1. Vested interest of included studies *(Continued)*

	Conflicts of interest: stated, "this is an independent investigator trial"; however some study authors have affiliations with medical companies.

ADHD: Attention deficit hyperactivity disorder; **BV:** besloten vennootschap (corresponding to a private limited liability company (LLC) in the USA); **DFG:** Deutsche Forschungsgemeinschaft; **NIH:** National Institutes of Health; **Inc.:** Incorporated; **IWK:** Izaak Walton Killam; **LA:** Long acting; **Ldt.:** Limited liability; **LLC:** Limited liability company; **LP:** Limited partnership; **MRI:** Magnetic resonance imaging; **NIAAA:** National Institute on Alcohol Abuse and Alcoholism; **NIDA:** National Institute on Drug Abuse; **NIMH:** National Institute of Mental Health; **NINDS:** National institute of Neurological Disorders and Stroke; **OROS:** osmotic-release oral system; **PI:** Primary Investigator; **ZonMw:** Organisation for Health Research and Development in the Netherlands

Table 2. Key demographics of included studies

Key demographics	Number of trials	Cross-over trials	Parallel trials
Sample size			
Sample size above 100 participants	49	17 trials: Ahmann 1993; Bedard 2008; Bhat 2020; Brams 2012; CRIT124US02; Froehlich 2011; Froehlich 2018; Huang 2021; Kollins 2006 (PATS); Manos 1999; NCT02039908; Pelham 2002; Schulz 2010; Swanson 2004b; Ullmann 1986; Waxmonsky 2008; Wilens 2008	33 trials: Biederman 2003b; Childress 2009; Childress 2020a; Childress 2020b; Coghill 2013; Findling 2006; Findling 2008; Findling 2010; Greenhill 2002; Greenhill 2006; Horn 1991; Jensen 1999 (MTA); Kollins 2006 (PATS); Kollins 2021; Lin 2014; Matthijssen 2019; McCracken 2016; NCT00409708; NCT02293655; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Perez-Alvarez 2009; Pliszka 2017; Riggs 2011; Tourette's Syndrome Study Group 2002; Tucker 2009; Weiss 2021; Wigal 2004; Wigal 2015; Wilens 2006b; Wolraich 2001
Risk of bias			
Trials with low risk of bias	21	13 trials: Cook 1993; DuPaul 1996; Flapper 2008; Kollins 2006 (PATS); McGough 2006; Moshe 2012; Rapport 2008; Soleimani 2017; Stein 1996; Stein 2011; Waxmonsky 2008; Wilkison 1995; Zeni 2009	9 trials: Childress 2020a; Jacobi-Polishook 2009; Kollins 2006 (PATS); Lehmkuhl 2002; Pliszka 2017; Riggs 2011; Schrantee 2016; Tourette's Syndrome Study Group 2002; Weiss 2021
Setting			
Outpatient	186	134 trials: Abikoff 2009; Ahmann 1993; Barkley 1989b; Barkley 1991; Barkley 2000; Bedard 2008; Bhat 2020; Blum 2011; Borcherding 1990; Brams 2008; Brams 2012; Brown 1984a; Brown 1988; Buitelaar 1995; Bukstein 1998; Castellanos 1997; Chacko 2005; Chronis 2003;	52 trials: Arnold 2004; Barragán 2017; Biederman 2003b; Butter 1983; Carlson 2007; Childress 2009; Childress 2017; Childress

Table 2. Key demographics of included studies *(Continued)*

		Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; Cox 2006; Döpfner 2004; Douglas 1986; Douglas 1995; DuPaul 1996; Epstein 2011; Fabiano 2007; Findling 2007; Fine 1993; Fitzpatrick 1992a; Flapper 2008; Forness 1992; Froehlich 2011; Froehlich 2018; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Gorman 2006; Gruber 2007; Hale 2011; Hawk 2018; Hoeppner 1997; Huang 2021; Johnston 1988; Kelly 1989; Kent 1999; Klorman 1990; Kollins 2006 (PATS); Kortekaas-Rijlaarsdam 2017; Kritchman 2019; Leddy 2009; Lijffijt 2006; Lopez 2003; Lufi 1997; Lufi 2007; Manos 1999; McBride 1988a; McGough 2006; McInnes 2007; Merrill 2021; Moshe 2012; Muniz 2008; Murray 2011; Musten 1997; NCT02039908; NCT02536105; Nikles 2006; Oesterheld 1998; Overtoom 2003; Pearson 2013; Pelham 1989; Pelham 1990a; Pelham 1999; Pelham 2001a; Pelham 2005; Pelham 2011; Pelham 2014; Pliszka 1990; Quinn 2004; Ramtvedt 2013; Rapport 1985; Rapport 1987; Rapport 2008; Reitman 2001; Rubinsten 2008; Samuels 2006; Schachar 2008; Schulz 2010; Schwartz 2004; Sharp 1999; Shiels 2009; Silva 2006; Silva 2008; Smith 1998; Smith 2004; Smithee 1998; Soleimani 2017; Stein 1996; Stein 2003; Stein 2011; Sumner 2010; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Szobot 2008; Tannock 1989; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1987; Taylor 1993; Tervo 2002; Tirosh 1993a; Tirosh 1993b; Ullmann 1986; Waxmonsky 2008; Whalen 1990; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010; Wilkison 1995; Wodrich 1998; Zeiner 1999; Zeni 2009	2020a; Childress 2020b; Childress 2020c; Coghill 2013; Connor 2000; Duric 2012; Findling 2006; Findling 2008; Findling 2010; Firestone 1981; Greenhill 2002; Greenhill 2006; Heriot 2008; Horn 1991; Ialongo 1994; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kollins 2006 (PATS); Kollins 2021; Lehmkuhl 2002; Lin 2014; Martins 2004; Matthijssen 2019; NCT00409708; NCT02293655; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Perez-Alvarez 2009; Pliszka 2000; Pliszka 2017; Riggs 2011; Schrantee 2016; Szobot 2004; Tannock 2018; Tourette's Syndrome Study Group 2002; Tucker 2009; Van der Meere 1999a; Weiss 2021; Wigal 2004; Wigal 2015; Wigal 2017; Wilens 2006b; Wolraich 2001
Inpatient	9	9 trials: Brown 1991; Carlson 1995; Gonzalez-Heydrich 2010; Kent 1995; Konrad 2005; Pelham 1993a; Pelham 2002; Solanto 2009; Wallace 1994	0 trials
Both outpatient and inpatient	8	7 trials: Garfinkel 1983; Hicks 1985; Kaplan 1990; Kolko 1999; Konrad 2004; Tannock 1992; Wallander 1987	1 trial: Green 2011
Laboratory classroom	21	17 trials: Brams 2008; Brams 2012; Lopez 2003; Murray 2011; Oesterheld 1998; Schachar 2008; Sharp 1999; Silva 2005a; Silva 2006; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Wigal 2003; Wigal 2011; Wigal 2014; Wilens 2008	4 trials: Childress 2017; Childress 2020a; Childress 2020b; Kollins 2021
Naturalistic school setting	3	1 trial: Ullmann 1986	2 trials: Biederman 2003b; Greenhill 2006
Summer school/summer treatment camp/summer treatment programme/summer research programme	21	21 trials: Bukstein 1998; Chacko 2005; Chronis 2003; Fabiano 2007; Johnston 1988; Kolko 1999; Leddy 2009; Merrill 2021; NCT02039908; Pelham 1989; Pelham 1990a; Pelham 1993a; Pelham 2001a; Pelham 2002; Pelham 2005; Pelham 2014; Reitman 2001; Shiels 2009; Smith 1998; Waxmonsky 2008; Whalen 1990	0 trials
Not stated	8	6 trials: Bliznakova 2007; CRIT124US02; Pliszka 2007; Stoner 1994; Ullmann 1985; Urman 1995	2 trials: Brown 1985; McCracken 2016

Table 2. Key demographics of included studies *(Continued)*

Research unit at hospital	0	0 trials	1 trial: Schachar 1997a
Psychiatric comorbidities (if specific data on participant comorbidities were available, we used this information for the table. If not, but some psychiatric comorbidities were part of the inclusion/exclusion criteria, we used them for the table). Learning disorders are not included in this table.			
Only ODD and/or CD and/or ODD and/or socially aggressive and/or disturbance in social behavior	52	39 trials: Brown 1988; Brown 1991; Bukstein 1998; Chacko 2005; Chronis 2003; Corkum 2008; Corkum 2020; Döpfner 2004; Douglas 1995; DuPaul 1996; Findling 2007[b]; Forness 1992; Hawk 2018; Johnston 1988; Kelly 1989; Kent 1995; Leddy 2009; McGough 2006; Merrill 2021; Musten 1997; Pelham 1989; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2001a; Pelham 2002; Pelham 2011; Pliszka 2007; Schulz 2010; Shiels 2009; Smith 1998; Solanto 2009; Stein 1996; Sunohara 1999; Tannock 1989; Tannock 1995a; Taylor 1987; Waxmonsky 2008; Zeiner 1999	13 trials: Carlson 2007; Findling 2008; Heriot 2008; Horn 1991; Ialongo 1994; Lin 2014; Martins 2004; McCracken 2016; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Tannock 2018
Only ODD and/or CD and/or OCD and/or anxiety disorder and/or specific developmental disorders and/or mood disorders and/or adjustment disorder and/or depression/dysthymia and/or sleep disorders and/or communication disorders and/or Asperger syndrome and/or trichotillomania and/or tic disorder	57	46 trials: Abikoff 2009; Bedard 2008; Bhat 2020; Blum 2011 Buitelaar 1995; Carlson 1995; Castellanos 1997; Coghill 2007; Epstein 2011; Fitzpatrick 1992a; NCT02039908; Froehlich 2011; Froehlich 2018; Gadow 1995; Gadow 2007; Gorman 2006; Gruber 2007; Gadow 2011; Hale 2011; Klorman 1990[c]; Kolko 1999; Konrad 2004; Kortekaas-Rijlaarsdam 2017; Lijffijt 2006; McInnes 2007; Murray 2011; NCT02536105; Overtoom 2003; Pearson 2013; Pliszka 1990; Ramtvedt 2013; Schwartz 2004; Sharp 1999; Smithee 1998; Stein 2003; Stein 2011; Swanson 2004b; Szobot 2008; Tannock 1992; Tannock 1993; Tannock 1995b; Urman 1995[d]; Wigal 2013; Wigal 2014; Wilens 2010; Zeni 2009[e]	11 trials: Duric 2012; Green 2011; Jensen 1999 (MTA); Lehmkuhl 2002; Pliszka 2000; Riggs 2011; Schachar 1997a; Szobot 2004; Tourette's Syndrome Study Group 2002; Van der Meere 1999a; Wolraich 2001
All had ODD and/or CD/and or disruptive behavior disorder	4	3 trials: Carlson 1995; Gadow 1990; Kaplan 1990[f]	1 trial: Connor 2000
All had Tourette's syndrome or chronic motor tics	5	4 trials: Castellanos 1997; Gadow 1995; Gadow 2007; Gadow 2011	1 trial: Tourette's Syndrome Study Group 2002
All had bipolar disorder or borderline personality	2	2 trials: Findling 2007; Zeni 2009	0 trials
All had a non-nicotine substance use disorder	2	1 trial: Szobot 2008	1 trial: Riggs 2011
Some psychiatric comorbidities excluded	20	11 trials: Barkley 1989b; Barkley 1991; Cook 1993; Douglas 1986; Gadow 1990; Gonzalez-Heydrich 2010; Konrad 2005; Oesterheld 1998; Silva 2006; Silva 2008; Wodrich 1998	9 trials: Barragán 2017; Brown 1985; Childress 2020c; Firestone 1981;Jacobi-Polishook 2009; Matthijssen 2019;

Table 2. Key demographics of included studies *(Continued)*

			NCT02293655; Wigal 2015; Wilens 2006b
Some psychiatric comorbidities and substance use excluded	23	11 trials: Borcherding 1990; Brams 2008; Brams 2012; Kaplan 1990; Kritchman 2019; Lopez 2003; Murray 2011; Silva 2005a; Sumner 2010; Wigal 2003; Wigal 2011	12 trials: Arnold 2004; Biederman 2003b; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Findling 2006; Kollins 2021; Pliszka 2017; Schrantee 2016; Weiss 2021; Wigal 2004
Substance use excluded	2	0 trials	2 trials: Coghill 2013; Findling 2010
Psychiatric comorbidities allowed	6	5 trials: Cox 2006; Gadow 2011; Kent 1999; Kollins 2006 (PATS); Symons 2007	2 trials: Coghill 2013; Kollins 2006 (PATS)
No psychiatric comorbidities	21	15 trials: Flapper 2008; Garfinkel 1983; Huang 2021; Lufi 1997; Moshe 2012; Muniz 2008; Quinn 2004; Schachar 2008; Soleimani 2017; Swanson 1998; Swanson 2002a; Tirosh 1993a; Tirosh 1993b; Wilens 2008; Wilkison 1995	6 trials: Findling 2010; Greenhill 2002; Greenhill 2006; Perez-Alvarez 2009; Tucker 2009; Wigal 2017
Not stated or unclear	35	33 trials: Ahmann 1993; Barkley 2000; Bliznakova 2007; Brown 1984a; CRIT124US02; Fabiano 2007; Fine 1993; Hicks 1985; Hoeppner 1997; Lufi 2007; Manos 1999; McBride 1988a; Merrill 2021; Nikles 2006; Pelham 2005; Pelham 2014; Rapport 1985; Rapport 1987; Rapport 2008; Reitman 2001; Rubinsten 2008; Samuels 2006; Smith 2004; Stoner 1994; Swanson 1999; Swanson 2002b; Taylor 1993; Tervo 2002; Ullmann 1985; Ullmann 1986; Wallace 1994; Wallander 1987; Whalen 1990	2 trials: Butter 1983; NCT00409708
Comedication (some** trials **in more than one category)			
None allowed	35	27 trials: Brown 1988; Bukstein 1998; Gadow 1995; Garfinkel 1983; Gorman 2006; Gruber 2007; Klorman 1990; Kollins 2006 (PATS); Konrad 2004; Konrad 2005; Leddy 2009; Lufi 1997; Lufi 2007; Moshe 2012; Muniz 2008; NCT02536105; Pliszka 1990; Ramtvedt 2013; Rubinsten 2008; Schulz 2010; Schwartz 2004; Solanto 2009; Swanson 1998; Tirosh 1993a; Tirosh 1993b; Wigal 2003; Wilkison 1995	9 trials: Carlson 2007; Childress 2017; Heriot 2008; Ialongo 1994; Jacobi-Polishook 2009; Kollins 2006 (PATS); Perez-Alvarez 2009; Tucker 2009; Wigal 2017
No medication for chronic conditions or no long-term use of any medicine	2	1 trial: Pliszka 2007	1 trial: Barragán 2017
Allergy medication allowed	2	1 trial: Brown 1991	1 trial: Childress 2009
Non-sedating antihistamines; acetaminophen (paracetamol); ibuprofen; antibiotics for treatment of a minor ill-	1	0 trials	1 trial: Childress 2020c

Table 2. Key demographics of included studies *(Continued)*

ness; and vitamins allowed			
Haloperidol allowed	1	1 trial: Castellanos 1997	0 trials
Comedication allowed with few or no exceptions	3	2 trials: McBride 1988a; Pelham 1989	1 trial: Matthijssen 2019
CNS medications excluded	9	6 trials: Abikoff 2009; Barkley 1991; Corkum 2008; McGough 2006; Pelham 2001a; Stein 2011	3 trials: Arnold 2004; Findling 2008; McCracken 2016
CNS medications excluded except for bronchodilators	3	1 trial: Wigal 2011	2 trials: Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose)
No concurrent treatment with other psychoactive drugs; or currently receiving psychotropic medication; or no other psychotropic medication during the trial/psychotropic medication had to be discontinued for > 6/3 weeks prior to screening; or no psychiatric medication for the past 6 months; or no prior psychotropic medication use; or no use of other medication for ADHD; or no current medication; or no current or previous use of medication that influences the dopamine system	43	26 trials: Blum 2011; Brams 2008; Brams 2012; Corkum 2008; DuPaul 1996; NCT02039908; Forness 1992; Froehlich 2018; Hawk 2018; Huang 2021; Oesterheld 1998; Pelham 2001a; Pelham 2011; Quinn 2004; Rapport 1985; Rapport 1987; Schachar 2008; Shiels 2009; Silva 2006; Smithee 1998; Stein 2003; Stein 2011; Taylor 1987; Waxmonsky 2008; Wigal 2013; Zeiner 1999	17 trials: Arnold 2004; Biederman 2003b; Brown 1985; Findling 2008; Green 2011; Greenhill 2006; Lehmkuhl 2002; Martins 2004; Newcorn 2008; Palumbo 2008; Riggs 2011; Schrantee 2016; Szobot 2004; Tourette's Syndrome Study Group 2002; Van der Meere 1999a; Wigal 2015; Wolraich 2001
Exclusion of some specified medications including some psychostimulants and or other medication	15	7 trials: Findling 2007; McGough 2006; Pearson 2013; Silva 2006; Silva 2008; Sumner 2010; Wigal 2014	8 trials: Findling 2010; Greenhill 2002; NCT02293655; Pliszka 2017; Weiss 2021; Wigal 2004; Wigal 2015; Wilens 2006b
Washout for some psychotropic medications specified	1	1 trial: Gadow 2007	0 trials
Comedication for comorbidities allowed	2	1 trial: Buitelaar 1995	1 trial: Van der Meere 1999a

Table 2. Key demographics of included studies *(Continued)*

Stable psychotropic medication was continued throughout the trial	1	1 trial: Gonzalez-Heydrich 2010	0 trials
Comedication as part of the trial design	10	6 trials: Carlson 1995; Findling 2007; Gonzalez-Heydrich 2010; Kaplan 1990; Szobot 2008[g]; Zeni 2009	4 trials: Carlson 2007; Connor 2000; McCracken 2016; Riggs 2011[g]
Not stated	98	82 trials: Ahmann 1993; Barkley 1989b; Barkley 2000; Bhat 2020; Bliznakova 2007; Borcherding 1990; Brown 1984a; Chacko 2005; Chronis 2003; Coghill 2007; Cook 1993; Corkum 2020; Cox 2006; CRIT124US02; Döpfner 2004; Douglas 1986; Douglas 1995; Epstein 2011; Fabiano 2007; Fine 1993; Fitzpatrick 1992a; Flapper 2008; Froehlich 2011; Gadow 1990; Gadow 2011; Hale 2011; Hicks 1985; Hoeppner 1997; Johnston 1988; Kelly 1989; Kent 1995; Kent 1999; Kolko 1999; Kortekaas-Rijlaarsdam 2017; Kritchman 2019; Lijffijt 2006; Lopez 2003; Manos 1999; McInnes 2007; Merrill 2021; Murray 2011; Musten 1997; Nikles 2006; Overtoom 2003; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2002; Pelham 2005; Pelham 2014; Rapport 2008; Reitman 2001; Samuels 2006; Sharp 1999; Silva 2005a; Smith 1998; Smith 2004; Soleimani 2017; Stein 1996; Stoner 1994; Sunohara 1999; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1993; Tervo 2002; Ullmann 1985; Ullmann 1986; Urman 1995; Wallace 1994; Wallander 1987; Whalen 1990; Wilens 2008; Wilens 2010; Wodrich 1998	16 trials: Butter 1983; Childress 2020a; Childress 2020b; Coghill 2013; Connor 2000; Duric 2012[h]; Findling 2006; Firestone 1981; Horn 1991; Jensen 1999 (MTA); Kollins 2021; Lin 2014; NCT00409708; Pliszka 2000; Schachar 1997a; Tannock 2018
Cotherapy			
Cognitive training/behavioral therapy/parent training as part of the intervention	15	5 trials: Döpfner 2004; Fabiano 2007; Kolko 1999; Pelham 2014; Waxmonsky 2008	10 trials: Brown 1985; Firestone 1981; Heriot 2008; Horn 1991[i]; Jensen 1999 (MTA); NCT00409708; Palumbo 2008; Perez-Alvarez 2009; Riggs 2011; Tucker 2009
Ongoing behavioral therapy permitted; but new therapy was not allowed to be initiated	1	0 trials	1 trial: Biederman 2003b
Only psychotherapy initiated > 3 months before screening allowed	3	1 trial: Brams 2012	2 trials: Childress 2009; Greenhill 2006
Not allowed to start psychosocial therapy	1	0 trials	1 trial: Matthijssen 2019

Table 2. Key demographics of included studies *(Continued)*

No psychotherapy initiated within 3 months before screening	3	3 trials: Muniz 2008; Silva 2006; Silva 2008	0 trials
Behaviour management treatment/uncontrolled parent training prior to medication phase as part of the trial design	2	1 trial: Kollins 2006 (PATS)	2 trials: Childress 2020c; Kollins 2006 (PATS)
No current behavioral intervention allowed	3	2 trials: Froehlich 2018; Lufi 1997	1 trial: NCT02293655;
Not stated	184	145 trials: Abikoff 2009; Ahmann 1993; Barkley 1989b; Barkley 1991; Barkley 2000; Bedard 2008; Bhat 2020; Bliznakova 2007; Blum 2011; Borcherding 1990; Brams 2008; Brown 1984a; Brown 1988; Brown 1991; Buitelaar 1995; Bukstein 1998; Carlson 1995; Castellanos 1997; Chacko 2005; Chronis 2003; Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; Cox 2006; CRIT124US02; Douglas 1986; Douglas 1995; DuPaul 1996; Epstein 2011; Findling 2007; Fine 1993; Fitzpatrick 1992a; Flapper 2008; Forness 1992; Froehlich 2011; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Gonzalez-Heydrich 2010; Gorman 2006; Gruber 2007; Hale 2011; Hawk 2018; Hicks 1985; Hoeppner 1997; Huang 2021; Johnston 1988; Kaplan 1990; Kelly 1989; Kent 1995; Kent 1999; Klorman 1990; Konrad 2004; Konrad 2005; Kortekaas-Rijlaarsdam 2017; Kritchman 2019; Leddy 2009; Lijffijt 2006; Lopez 2003; Lufi 2007; Manos 1999; McBride 1988a; McGough 2006; McInnes 2007; Merrill 2021; Moshe 2012; Murray 2011; Musten 1997; NCT02039908; NCT02536105; Nikles 2006; Oesterheld 1998; Overtoom 2003; Pearson 2013; Pelham 1989; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2001a; Pelham 2002; Pelham 2005; Pelham 2011; Pliszka 1990; Pliszka 2007; Quinn 2004; Ramtvedt 2013; Rapport 1985; Rapport 1987; Rapport 2008; Reitman 2001; Rubinsten 2008; Samuels 2006; Schachar 2008; Schulz 2010; Schwartz 2004; Sharp 1999; Shiels 2009; Silva 2005a; Smith 1998; Smith 2004; Smithee 1998; Solanto 2009; Soleimani 2017; Stein 1996; Stein 2003; Stein 2011; Stoner 1994; Sumner 2010; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Szobot 2008; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1987; Taylor 1993; Tervo 2002; Tirosh 1993a; Tirosh 1993b; Ullmann 1985; Ullmann 1986; Urman 1995; Wallace 1994; Wallander 1987; Whalen 1990; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010; Wilkinson 1995; Wodrich 1998; Zeiner 1999; Zeni 2009	39 trials: Arnold 2004; Barragán 2017; Butter 1983; Carlson 2007; Childress 2017; Childress 2020a; Childress 2020b; Coghill 2013; Connor 2000; Duric 2012[h]; Findling 2006; Findling 2008; Findling 2010; Green 2011; Greenhill 2002; Ialongo 1994; Jacobi-Polishook 2009; Kollins 2021; Lehmkuhl 2002; Lin 2014; Martins 2004; McCracken 2016; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Pliszka 2000; Pliszka 2017; Schachar 1997a; Schrantee 2016; Szobot 2004; Tannock 2018; Tourette's Syndrome Study Group 2002; Van der Meere 1999a; Weiss 2021; Wigal 2004; Wigal 2015; Wigal 2017; Wilens 2006b; Wolraich 2001
Participant mean age			

Table 2. Key demographics of included studies *(Continued)*

2-6 years	6	4 trials: Chacko 2005; Kollins 2006 (PATS); Musten 1997; Reitman 2001	3 trials: Childress 2020c; Heriot 2008; Kollins 2006 (PATS)
7-11 years	172	128 trials: Abikoff 2009; Barkley 1989b; Barkley 1991; Bedard 2008; Bhat 2020; Blum 2011; Borcherding 1990; Brams 2008; Brams 2012; Brown 1984a; Buitelaar 1995; Bukstein 1998; Castellanos 1997; Chronis 2003; Cook 1993; Corkum 2020; Döpfner 2004; Douglas 1986; Douglas 1995; DuPaul 1996; Epstein 2011; Fabiano 2007; Findling 2007; Fine 1993; Fitzpatrick 1992a; Flapper 2008; Forness 1992; Froehlich 2011; Froehlich 2018; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Gonzalez-Heydrich 2010; Gorman 2006; Gruber 2007; Hale 2011; Hawk 2018; Hicks 1985; Hoeppner 1997; Huang 2021; Johnston 1988; Kelly 1989; Kent 1995; Kolko 1999; Konrad 2004; Konrad 2005; Kortekaas-Rijlaarsdam 2017; Kritchman 2019; Lijffijt 2006; Lopez 2003; Lufi 1997; Lufi 2007; Manos 1999; McBride 1988a; McGough 2006; McInnes 2007; Merrill 2021; Moshe 2012; Muniz 2008; Murray 2011; NCT02536105; Nikles 2006; Oesterheld 1998; Overtoom 2003; Pearson 2013; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2001a; Pelham 2002; Pelham 2005; Pelham 2011; Pelham 2014; Pliszka 1990; Ramtvedt 2013; Rapport 1985; Rapport 2008; Rubinsten 2008; Schachar 2008; Schulz 2010; Schwartz 2004; Sharp 1999; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Smith 2004; Smithee 1998; Soleimani 2017; Stein 1996; Stein 2003; Stein 2011; Stoner 1994; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1987; Taylor 1993; Tervo 2002; Tirosh 1993a; Tirosh 1993b; Ullmann 1985; Ullmann 1986; Urman 1995; Wallace 1994; Wallander 1987; Waxmonsky 2008; Whalen 1990; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010; Wilkison 1995; Wodrich 1998; Zeiner 1999; Zeni 2009	44 trials: Barragán 2017; Biederman 2003b; Brown 1985; Carlson 2007; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Coghill 2013; Connor 2000; Duric 2012; Findling 2006; Findling 2008; Firestone 1981; Green 2011; Greenhill 2002; Greenhill 2006; Horn 1991; Ialongo 1994; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kollins 2021; Lehmkuhl 2002; Lin 2014; Martins 2004; McCracken 2016; NCT00409708; NCT02293655; Newcorn 2008; Palumbo 2008; Perez-Alvarez 2009; Pliszka 2000; Pliszka 2017; Schachar 1997a; Schrantee 2016; Szobot 2004; Tannock 2018; Tourette's Syndrome Study Group 2002; Tucker 2009; Van der Meere 1999a; Wigal 2004; Wigal 2015; Wigal 2017; Wolraich 2001
12-18 years	17	10 trials: Barkley 2000; Bliznakova 2007; Brown 1988; Brown 1991; Cox 2006; CRIT124US02; Kaplan 1990; Pliszka 2007; Smith 1998; Szobot 2008	7 trials: Findling 2010; Matthijssen 2019; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Riggs 2011; Weiss 2021; Wilens 2006b
Not stated	17	15 trials: Ahmann 1993; Carlson 1995; Coghill 2007; Corkum 2008; Gadow 1990; Kent 1999; Klorman 1990; Leddy 2009; NCT02039908; Pelham 1989; Quinn 2004; Rapport 1987; Samuels 2006; Solanto 2009; Sumner 2010	2 trials: Arnold 2004; Butter 1983
Sex			
Only male participants	35	30 trials: Bliznakova 2007; Borcherding 1990; Brown 1984a; Brown 1988; Brown 1991; Carlson 1995; Castellanos 1997; Coghill 2007; Cook 1993; Forness 1992; Gadow 1990; Garfinkel 1983; Johnston 1988; Kaplan 1990; Kolko 1999; Merrill 2021; Moshe 2012; Overtoom 2003; Pelham 1990a; Pelham 1993a; Pelham 2002; Pelham	5 trials: Butter 1983; Connor 2000; Martins 2004; Schrantee 2016; Szobot 2004

Table 2. Key demographics of included studies *(Continued)*

		2011; Quinn 2004; Smith 2004; Stein 1996; Stoner 1994; Szobot 2008; Taylor 1987; Wilkison 1995; Zeiner 1999	
Only female participants	2	2 trials: CRIT124US02; Sharp 1999	0 trials
Both male and female participants	167	119 trials: Abikoff 2009; Ahmann 1993; Barkley 1989b; Barkley 1991; Barkley 2000; Bedard 2008; Bhat 2020; Blum 2011; Brams 2008; Brams 2012; Buitelaar 1995; Bukstein 1998; Chacko 2005; Chronis 2003; Corkum 2008; Corkum 2020; Cox 2006; Döpfner 2004; Douglas 1986; Douglas 1995; DuPaul 1996; Fabiano 2007; Findling 2007; Fitzpatrick 1992a; Flapper 2008; Froehlich 2011; Froehlich 2018; Gadow 1995; Gadow 2007; Gadow 2011; Gonzalez-Heydrich 2010; Gorman 2006; Gruber 2007; Hale 2011; Hawk 2018; Hicks 1985; Hoeppner 1997; Huang 2021; Kelly 1989; Kent 1995; Kent 1999; Klorman 1990; Kollins 2006 (PATS); Konrad 2004; Konrad 2005; Kortekaas-Rijlaarsdam 2017; Kritchman 2019; Leddy 2009; Lijffijt 2006; Lopez 2003; Lufi 1997; Lufi 2007; Manos 1999; McBride 1988a; McGough 2006; McInnes 2007; Muniz 2008; Murray 2011; Musten 1997; NCT02039908; NCT02536105; Nikles 2006; Oesterheld 1998; Pearson 2013; Pelham 1989; Pelham 1999; Pelham 2001a; Pelham 2005; Pelham 2014; Pliszka 1990; Pliszka 2007; Ramtvedt 2013; Rapport 1985; Rapport 1987; Rapport 2008; Reitman 2001; Rubinsten 2008; Schachar 2008; Schulz 2010; Schwartz 2004; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Smith 1998; Smithee 1998; Soleimani 2017; Stein 2003; Stein 2011; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1993; Tervo 2002; Tirosh 1993a; Tirosh 1993b; Ullmann 1985; Ullmann 1986; Urman 1995; Wallander 1987; Waxmonsky 2008; Whalen 1990; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010; Wodrich 1998; Zeni 2009	49 trial: Arnold 2004; Barragán 2017; Biederman 2003b; Carlson 2007; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Duric 2012; Findling 2006; Findling 2008; Findling 2010; Firestone 1981; Green 2011; Greenhill 2002; Greenhill 2006; Heriot 2008; Horn 1991; Ialongo 1994; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kollins 2006 (PATS); Kollins 2021; Lehmkuhl 2002; Lin 2014; Matthijssen 2019; McCracken 2016; NCT00409708; NCT02293655; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Perez-Alvarez 2009; Pliszka 2017; Riggs 2011; Schachar 1997a; Tannock 2018; Tourette's Syndrome Study Group 2002; Tucker 2009; Van der Meere 1999a; Weiss 2021; Wigal 2004; Wigal 2015; Wigal 2017; Wilens 2006b; Wolraich 2001
Not stated	8	6 trials: Epstein 2011; Fine 1993; Samuels 2006; Solanto 2009; Sumner 2010; Wallace 1994	2 trials: Brown 1985; Pliszka 2000
Diagnostic classification			
DSM-III	30	27 trials: Borcherding 1990; Brown 1984a; Brown 1988; Cook 1993; Douglas 1986; Douglas 1995; Fitzpatrick 1992a; Gadow 1990; Garfinkel 1983; Hicks 1985; Kaplan 1990; Kelly 1989; Klorman 1990; McBride 1988a; Pelham 1989; Pliszka 1990; Rapport 1985; Rapport 1987; Tannock 1989; Tannock 1992; Tannock 1993; Taylor 1987; Tirosh 1993a; Tirosh 1993b; Ullmann 1985; Ullmann 1986; Wallander 1987	3 trials: Brown 1985; Butter 1983; Firestone 1981
DSM-III-R	42	37 trials: Ahmann 1993; Barkley 1989b; Barkley 1991; Brown 1991; Buitelaar 1995; Bukstein 1998; Castellanos 1997; Chacko 2005; Douglas 1995; DuPaul 1996; Fine 1993; Forness 1992; Gadow 1995; Gadow 2007; Gadow 2011; Hoeppner 1997; Johnston 1988; Kent 1995; Kolko	5 trials: Connor 2000; Horn 1991; Ialongo 1994; Schachar 1997a; Van der Meere 1999a

Table 2. Key demographics of included studies *(Continued)*

		1999; Musten 1997; Overtoom 2003; Pelham 1990a; Pelham 1993a; Pelham 2002; Smith 1998; Stein 1996; Stoner 1994; Sunohara 1999; Tannock 1995a; Tannock 1995b; Taylor 1993; Urman 1995; Wallace 1994; Whalen 1990; Wilkison 1995; Wodrich 1998; Zeiner 1999	
DSM-IV	105	77 trials: Abikoff 2009; Barkley 2000; Bedard 2008; Bhat 2020; Brams 2008; Brams 2012; Carlson 1995; Chronis 2003; Coghill 2007; Corkum 2008; Cox 2006; Döpfner 2004; Epstein 2011; Fabiano 2007; Findling 2007; Flapper 2008; Froehlich 2011; Froehlich 2018; Gadow 2011; Gorman 2006; Gruber 2007; Hawk 2018; Kent 1999; Kollins 2006 (PATS); Konrad 2004; Konrad 2005; Kortekaas-Rijlaarsdam 2017; Leddy 2009; Lijffijt 2006; Lopez 2003; Lufi 1997; Lufi 2007; Manos 1999; Moshe 2012; Muniz 2008; Nikles 2006; Oesterheld 1998; Pearson 2013; Pelham 1999; Pelham 2001a; Pelham 2005; Pelham 2011; Pelham 2014; Pliszka 2007; Quinn 2004; Rapport 2008; Rubinsten 2008; Samuels 2006; Schachar 2008; Schulz 2010; Schwartz 2004; Sharp 1999; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Smith 2004; Smithee 1998; Solanto 2009; Stein 2003; Stein 2011; Sumner 2010; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Szobot 2008; Tervo 2002; Waxmonsky 2008; Wigal 2003; Wigal 2013; Wilens 2008; Wilens 2010; Zeiner 1999; Zeni 2009	29 trials: Arnold 2004; Biederman 2003b; Carlson 2007; Childress 2009; Childress 2017; Findling 2006; Findling 2010; Greenhill 2002; Greenhill 2006; Heriot 2008; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kollins 2006 (PATS); Lehmkuhl 2002; Martins 2004; McCracken 2016; NCT00409708; Newcorn 2008; Palumbo 2008; Pliszka 2000; Riggs 2011; Schrantee 2016; Szobot 2004; Tannock 2018; Tourette's Syndrome Study Group 2002; Tucker 2009; Wigal 2004; Wilens 2006b; Wolraich 2001
DSM-IV-TR	21	12 trials: Blum 2011; Corkum 2020; NCT02039908; Gonzalez-Heydrich 2010; Hale 2011; McGough 2006; McInnes 2007; Murray 2011; Ramtvedt 2013; Soleimani 2017; Wigal 2011; Wigal 2014	9 trials: Barragán 2017; Coghill 2013; Findling 2008; Green 2011; Lin 2014; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Perez-Alvarez 2009; Wigal 2015
DSM-5	10	3 trials: Gadow 2007; Huang 2021; NCT02536105	7 trials: Childress 2020a; Childress 2020b; Childress 2020c; Kollins 2021; NCT02293655; Pliszka 2017; Weiss 2021
ICD-10	3	2 trials: Bliznakova 2007; Döpfner 2004	1 trial: Duric 2012
Not stated	6	4 trials: CRIT124US02; Kritchman 2019; Merrill 2021; Reitman 2001	2 trials: Matthijssen 2019; Wigal 2017
Attention deficit hyperactivity disorder subtype			
Combined type only	14	12 trials: Blum 2011; Coghill 2007; Cook 1993; Douglas 1995; Konrad 2005; Overtoom 2003; Pliszka 2007; Rapport 2008; Schachar 2008; Soleimani 2017; Symons 2007; Tannock 1989	2 trials: Connor 2000; Jensen 1999 (MTA)
Hyperactive type only	2	2 trials: Bliznakova 2007; Forness 1992	0 trials
Multiple subtypes	101	64 trials: Abikoff 2009; Barkley 1991; Bedard 2008; Bhat 2020; Brams 2008; Brams 2012; Corkum 2008; Corkum 2020; Cox 2006; CRIT124US02; Döpfner 2004; Epstein	38 trials: Arnold 2004; Barragán 2017; Biederman 2003b; Carlson 2007;

Table 2. Key demographics of included studies *(Continued)*

		2011; Findling 2007; Fitzpatrick 1992a; Flapper 2008; Froehlich 2011; Froehlich 2018; Gonzalez-Heydrich 2010; Gorman 2006; Gruber 2007; Hale 2011; Huang 2021; Kollins 2006 (PATS); Konrad 2004; Leddy 2009; Lijffijt 2006; Manos 1999; McBride 1988a; McGough 2006; McInnes 2007; Moshe 2012; Muniz 2008; Murray 2011; Oesterheld 1998; Pearson 2013; Pelham 1989; Pelham 2011; Quinn 2004; Ramtvedt 2013; Rubinsten 2008; Schulz 2010; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Smithee 1998; Solanto 2009; Stein 1996; Stein 2003; Stein 2011; Swanson 2002a; Swanson 2002b; Swanson 2004b; Szobot 2008; Tervo 2002; Tirosh 1993a; Ullmann 1985; Waxmonsky 2008; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010; Zeni 2009	Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Findling 2006; Findling 2008; Green 2011; Greenhill 2002; Greenhill 2006; Heriot 2008; Kollins 2006 (PATS); Kollins 2021; Lehmkuhl 2002; Lin 2014; Martins 2004; McCracken 2016; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Perez-Alvarez 2009; Pliszka 2017; Riggs 2011; Schrantee 2016; Szobot 2004; Tourette's Syndrome Study Group 2002; Weiss 2021; Wigal 2004; Wigal 2015; Wigal 2017; Wolraich 2001
Not stated	95	79 trials: Ahmann 1993; Barkley 1989b; Barkley 2000; Borcherding 1990; Brown 1984a; Brown 1988; Brown 1991; Buitelaar 1995; Bukstein 1998; Carlson 1995; Castellanos 1997; Chacko 2005; Chronis 2003; Douglas 1986; DuPaul 1996; Fabiano 2007; Fine 1993; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Hawk 2018; Hicks 1985; Hoeppner 1997; Johnston 1988; Kaplan 1990; Kelly 1989; Kent 1995; Kent 1999; Klorman 1990; Kolko 1999; Kortekaas-Rijlaarsdam 2017; Kritchman 2019; Lopez 2003; Lufi 1997; Lufi 2007; Merrill 2021; Musten 1997; NCT02039908; NCT02536105; Nikles 2006; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2001a; Pelham 2002; Pelham 2005; Pelham 2014; Pliszka 1990; Rapport 1985; Rapport 1987; Reitman 2001; Samuels 2006; Schwartz 2004; Sharp 1999; Smith 1998; Smith 2004; Stoner 1994; Sumner 2010; Sunohara 1999; Swanson 1998; Swanson 1999; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1987; Taylor 1993; Tirosh 1993b; Ullmann 1986; Urman 1995; Wallace 1994; Wallander 1987; Whalen 1990; Wigal 2003; Wilkison 1995; Wodrich 1998; Zeiner 1999	16 trials: Brown 1985; Butter 1983; Duric 2012; Findling 2010; Firestone 1981; Horn 1991; Ialongo 1994; Jacobi-Polishook 2009; Matthijssen 2019; NCT00409708; NCT02293655; Pliszka 2000; Tannock 2018; Schachar 1997a;Tucker 2009; Van der Meere 1999a; Wilens 2006b
***Methylphenidate**-naive*			
100%	35	29 trials: Abikoff 2009; Buitelaar 1995; Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; Epstein 2011; Fine 1993; Flapper 2008; Forness 1992; Froehlich 2011; Froehlich 2018; Kelly 1989; Kollins 2006 (PATS); Konrad 2004; Lufi 1997; Moshe 2012; Oesterheld 1998; Ramtvedt 2013; Rapport 1987; Stoner 1994; Sunohara 1999; Szobot 2008; Taylor 1987; Tirosh 1993a; Tirosh 1993b; Urman 1995; Wallander 1987; Zeiner 1999	8 trials: Barragán 2017; Heriot 2008; Kollins 2006 (PATS); Perez-Alvarez 2009; Schachar 1997a; Schrantee 2016; Tucker 2009; Van der Meere 1999a
50%-99%	38	23 trials: Barkley 1989b; Bedard 2008; Douglas 1986; Douglas 1995; Fitzpatrick 1992a; Gadow 1990; Gadow 1995; Gadow 2011; Garfinkel 1983; Gorman 2006; Kaplan	15 trials: Arnold 2004; Biederman 2003b; Childress 2009; Coghill 2013; Connor

Table 2. Key demographics of included studies *(Continued)*

		1990; Kent 1995; Klorman 1990; McBride 1988a; McInnes 2007; Murray 2011; Musten 1997; Pearson 2013; Pliszka 2007; Smithee 1998; Stein 2003; Tannock 1992; Tannock 1995a	2000; Findling 2008; Findling 2010; Green 2011; Ialongo 1994; Jensen 1999 (MTA); Kollins 2021; Lin 2014; Weiss 2021; Wigal 2004; Wigal 2015
1%-49%	27	17 trials: Borcherding 1990; Carlson 1995; Chronis 2003; Hawk 2018; Leddy 2009; McGough 2006; Nikles 2006; Pelham 2005; Schachar 2008; Schwartz 2004; Smith 1998; Solanto 2009; Stein 1996; Stein 2011; Tannock 1989; Taylor 1993; Wilens 2010	10 trials: Carlson 2007; Greenhill 2002; Greenhill 2006; Lehmkuhl 2002; Newcorn 2008; Palumbo 2008; Pliszka 2000; Tourette's Syndrome Study Group 2002; Wilens 2006b; Wolraich 2001
0%	35	29 trials: Bliznakova 2007; Brams 2008; Brams 2012; Döpfner 2004; Kortekaas-Rijlaarsdam 2017; Lijffijt 2006; Lopez 2003; Lufi 2007; Muniz 2008; Overtoom 2003; Pelham 2001a; Pelham 2011; Quinn 2004; Reitman 2001; Rubinsten 2008; Schulz 2010; Silva 2005a; Silva 2006; Silva 2008; Smith 2004; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Whalen 1990; Wigal 2013; Wigal 2014; Wilkison 1995	6 trials: Childress 2017; Childress 2020b; Findling 2006; Jacobi-Polishook 2009; Matthijssen 2019; Pliszka 2017
Not stated or unclear	76	59 trials: Ahmann 1993; Barkley 1991; Barkley 2000; Bhat 2020j; Blum 2011; Brown 1984a; Brown 1988; Brown 1991; Bukstein 1998; Castellanos 1997; Chacko 2005; Cox 2006; CRIT124US02; DuPaul 1996; Fabiano 2007; Findling 2007; Gadow 2007; Gonzalez-Heydrich 2010; Gruber 2007; Hale 2011; Hicks 1985; Hoeppner 1997; Huang 2021; Johnston 1988; Kent 1999; Kolko 1999; Konrad 2005; Kritchman 2019; Manos 1999; Merrill 2021; NCT02039908; NCT02536105; Pelham 1989; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2002; Pelham 2014; Pliszka 1990; Rapport 1985; Rapport 2008; Samuels 2006; Sharp 1999; Shiels 2009; Soleimani 2017; Sumner 2010; Symons 2007; Tannock 1993; Tannock 1995b; Tervo 2002; Ullmann 1985; Ullmann 1986; Wallace 1994; Waxmonsky 2008; Wigal 2003; Wigal 2011; Wilens 2008; Wodrich 1998; Zeni 2009	17 trials: Brown 1985; Butter 1983; Childress 2020a; Childress 2020c; Duric 2012; Firestone 1981; Horn 1991; Martins 2004; McCracken 2016; NCT00409708; NCT02293655; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Riggs 2011; Szobot 2004; Tannock 2018; Wigal 2017
Methylphenidate release			
Extended-release and/or modified-release	61	32 trials: Abikoff 2009; Blum 2011; Brams 2008; Brams 2012; Corkum 2020; Cox 2006; CRIT124US02; Epstein 2011; Froehlich 2011; Froehlich 2018; Gonzalez-Heydrich 2010; Hawk 2018; Huang 2021; Kortekaas-Rijlaarsdam 2017; Lopez 2003; Muniz 2008; Murray 2011; NCT02039908; NCT02536105; Schulz 2010; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Stein 2003; Stein 2011; Sumner 2010; Swanson 2004b; Szobot 2008; Wigal 2011; Wigal 2013; Wigal 2014	29 trials: Barragán 2017; Biederman 2003b; Carlson 2007; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Greenhill 2002; Greenhill 2006; Kollins 2021; Lehmkuhl 2002; Lin 2014; Matthijssen 2019; McCracken 2016; NCT00409708; NCT02293655; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Perez-Al-

Table 2. Key demographics of included studies *(Continued)*

			varez 2009; Pliszka 2017[k]; Riggs 2011; Tucker 2009; Weiss 2021; Wigal 2015; Wigal 2017; Wilens 2006b
Immediate-release	101	83 trials: Ahmann 1993; Barkley 1989b; Barkley 1991; Barkley 2000; Bhat 2020; Borcherding 1990; Brown 1984a; Brown 1988; Brown 1991; Buitelaar 1995; Bukstein 1998; Carlson 1995; Castellanos 1997; Chacko 2005; Chronis 2003; Coghill 2007; Corkum 2008; Douglas 1986; DuPaul 1996; Fabiano 2007; Findling 2007; Forness 1992; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Gorman 2006; Gruber 2007; Hale 2011; Hicks 1985; Hoeppner 1997; Kaplan 1990; Kelly 1989; Kent 1995; Kent 1999; Klorman 1990; Kolko 1999; Kollins 2006 (PATS); Konrad 2004; Konrad 2005; Kritchman 2019; Leddy 2009; Manos 1999; McBride 1988a; Merrill 2021; Moshe 2012; Musten 1997; Nikles 2006; Oesterheld 1998; Pelham 1989; Pelham 1993a; Pelham 1999; Pelham 2002; Pelham 2014; Pliszka 1990; Pliszka 2007; Ramtvedt 2013; Rapport 2008; Schwartz 2004; Sharp 1999; Smith 1998; Smith 2004; Smithee 1998; Solanto 2009; Soleimani 2017; Stein 1996; Sunohara 1999; Swanson 1999; Swanson 2002a[l]; Tannock 1989; Tannock 1993; Tannock 1995a; Taylor 1993; Tervo 2002; Tirosh 1993a; Tirosh 1993b; Wallander 1987; Waxmonsky 2008; Whalen 1990; Wodrich 1998; Zeiner 1999; Zeni 2009	19 trials: Arnold 2004; Brown 1985; Connor 2000; Duric 2012; Firestone 1981; Green 2011; Heriot 2008; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kollins 2006 (PATS); Martins 2004; Palumbo 2008; Pliszka 2000; Schachar 1997a; Szobot 2004; Tannock 2018; Tourette's Syndrome Study Group 2002; Van der Meere 1999a; Wigal 2004
Transdermal patch	5	4 trials: McGough 2006; Pelham 2005; Wilens 2008; Wilens 2010	1 trial: Findling 2010
Both immediate-release and transdermal patch administered during the trial	1	1 trial: Pelham 2011	0 trials
Both Immediate-release and extended-release and/or modified-release administered during the trial	11	9 trials: Döpfner 2004; Fitzpatrick 1992a; Johnston 1988; Pearson 2013; Pelham 1990a; Pelham 2001a; Schachar 2008; Swanson 2002b; Wigal 2003	2 trials: Findling 2006; Wolraich 2001
Both transdermal patch and extended-release administered during the trial	1	0 trials	1 trial: Findling 2008
Not stated or unclear	32	28 trials: Bedard 2008; Bliznakova 2007; Cook 1993; Douglas 1995; Fine 1993; Flapper 2008; Lijffijt 2006; Lufi 1997; Lufi 2007; McInnes 2007; Overtoom 2003; Quinn 2004; Rapport 1985; Rapport 1987; Reitman 2001; Rubinsten 2008; Samuels 2006; Stoner 1994; Swanson 1998; Symons 2007; Tannock 1992; Tannock 1995b; Taylor 1987; Ullmann 1985; Ullmann 1986; Urman 1995; Wallace 1994; Wilkison 1995	4 trials: Butter 1983; Horn 1991; Ialongo 1994; Schrantee 2016

Table 2. Key demographics of included studies *(Continued)*

Dosage			
Low dose (≤ 20 mg/d or ≤ 0.6 mg/kg/d)	51	43 trials: Barkley 2000; Bhat 2020; Brams 2008; Brown 1984a; Brown 1991; Buitelaar 1995; Cook 1993; Douglas 1986; Garfinkel 1983; Gruber 2007; Hale 2011; Kaplan 1990; Kelly 1989; Kent 1995; Konrad 2004; Kritchman 2019; Lufi 1997; Lufi 2007; McGough 2006; McInnes 2007; Moshe 2012; Oesterheld 1998; Overtoom 2003; Pelham 1989; Pelham 1990a; Pelham 2002; Quinn 2004; Rapport 1985; Rapport 1987; Rapport 2008; Reitman 2001; Rubinsten 2008; Schulz 2010; Silva 2006; Silva 2008; Smith 2004; Stoner 1994; Symons 2007; Tervo 2002; Whalen 1990; Wilens 2010; Wilkison 1995; Zeiner 1999	8 trials: Brown 1985; Butter 1983; Green 2011; Heriot 2008; Jacobi-Polishook 2009; Kollins 2006 (PATS)[m]; McCracken 2016; Van der Meere 1999a
Moderate/high dose (> 20 mg/day or > 0.6 mg/kg/d)	57	29 trials: Abikoff 2009; Ahmann 1993; Barkley 1989b; Blum 2011; Borcherding 1990; Bukstein 1998; Castellanos 1997; Corkum 2020; Cox 2006; Döpfner 2004; Epstein 2011; Forness 1992; Gonzalez-Heydrich 2010; Gorman 2006; Hawk 2018; Huang 2021; Klorman 1990; McBride 1988a; Murray 2011; Pelham 2011; Ramtvedt 2013; Schachar 2008; Schwartz 2004; Sharp 1999; Shiels 2009; Smithee 1998; Wigal 2011; Wigal 2013; Wigal 2014	28 trials: Barragán 2017; Carlson 2007; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Connor 2000; Firestone 1981; Greenhill 2002; Greenhill 2006; Jensen 1999 (MTA); Matthijssen 2019; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Pliszka 2000; Pliszka 2017; Riggs 2011; Schachar 1997a; Schrantee 2016; Szobot 2004; Tourette's Syndrome Study Group 2002; Weiss 2021; Wigal 2017; Wilens 2006b; Wolraich 2001
Both low and moderate/high dose were given in a cross-over design or in different arms in a parallel trial	75	68 trials: Barkley 1991; Bedard 2008; Brams 2012; Brown 1988; Carlson 1995; Chacko 2005; Chronis 2003; Coghill 2007; Corkum 2008; Douglas 1995; DuPaul 1996; Fabiano 2007; Findling 2007; Fine 1993; Fitzpatrick 1992a; Flapper 2008; Froehlich 2011; Froehlich 2018; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Hicks 1985; Hoeppner 1997; Johnston 1988; Kent 1999; Kolko 1999; Kollins 2006 (PATS)[n]; Konrad 2005; Leddy 2009; Lijffijt 2006; Lopez 2003; Manos 1999; Merrill 2021; Muniz 2008; Musten 1997; Pearson 2013; Pelham 1993a; Pelham 1999; Pelham 2005; Pliszka 1990; Pliszka 2007; Silva 2005a; Smith 1998; Solanto 2009; Soleimani 2017; Stein 1996; Stein 2003; Stein 2011; Sumner 2010; Sunohara 1999; Swanson 2004b; Szobot 2008; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1993; Tirosh 1993a; Ullmann 1985; Ullmann 1986; Urman 1995; Wallander 1987; Waxmonsky 2008; Wigal 2003; Wodrich 1998; Zeni 2009	7 trials: Childress 2009; Horn 1991; Ialongo 1994; Lin 2014; Martins 2004; Wigal 2004; Wigal 2015
Not stated or unclear	30	17 trials: Bliznakova 2007; CRIT124US02; Kortekaas-Rijlaarsdam 2017; NCT02039908; NCT02536105; Nikles 2006; Pelham 2001a; Pelham 2014; Samuels 2006; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson	13 trials: Arnold 2004; Biederman 2003b; Duric 2012; Findling 2006; Findling 2008; Findling 2010; Kollins 2021; Lehmkuhl

Table 2. Key demographics of included studies *(Continued)*

		2002b; Taylor 1987; Tirosh 1993b; Wallace 1994; Wilens 2008	2002; NCT00409708; NCT02293655; Perez-Alvarez 2009; Tannock 2018; Tucker 2009
Duration of intervention			
Single day/single dosage	9	7 trials: Kritchman 2019; Lopez 2003; Murray 2011; Overtoom 2003; Samuels 2006; Wigal 2011; Wilkison 1995	2 trials: Green 2011; Jacobi-Polishook 2009
2-14 days	104	92 trials: Ahmann 1993; Barkley 1989b[o]; Barkley 2000; Bedard 2008; Bhat 2020; Bliznakova 2007; Blum 2011; Brams 2008; Brams 2012; Brown 1984a; Brown 1991; Bukstein 1998; Chacko 2005; Chronis 2003; Corkum 2008; Corkum 2020; Döpfner 2004; Douglas 1986; Douglas 1995; Epstein 2011; Fine 1993; Gonzalez-Heydrich 2010[p]; Gruber 2007; Hawk 2018; Hoeppner 1997; Huang 2021; Johnston 1988; Kent 1995; Kent 1999; Klorman 1990; Kolko 1999; Konrad 2004; Konrad 2005; Kortekaas-Rijlaarsdam 2017; Lijffijt 2006; McBride 1988a; McGough 2006; McInnes 2007; Moshe 2012; NCT02039908; Nikles 2006; Oesterheld 1998; Pelham 1989; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2001a; Pelham 2002; Pelham 2005; Pelham 2011; Pelham 2014; Pliszka 1990; Quinn 2004; Ramtvedt 2013; Reitman 2001; Rubinsten 2008; Schachar 2008; Schulz 2010; Schwartz 2004; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Smith 2004; Smithee 1998; Stoner 1994; Sumner 2010; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1993; Tervo 2002; Tirosh 1993a; Tirosh 1993b; Urman 1995; Wallace 1994; Whalen 1990; Wigal 2003; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010; Wodrich 1998; Zeni 2009	12 trials: Arnold 2004; Biederman 2003b; Butter 1983; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Kollins 2021; Szobot 2004; Wigal 2015; Wigal 2017; Wilens 2006b
15 days-6 months	93	56 trials: Abikoff 2009; Barkley 1991; Borcherding 1990; Brown 1988; Buitelaar 1995; Carlson 1995; Castellanos 1997; Coghill 2007; Cook 1993; Cox 2006; CRIT124US02; DuPaul 1996; Fabiano 2007; Findling 2007; Fitzpatrick 1992a; Flapper 2008; Forness 1992; Froehlich 2011; Froehlich 2018; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Gorman 2006; Hale 2011; Hicks 1985[q]; Kaplan 1990; Kollins 2006 (PATS); Leddy 2009; Lufi 1997; Lufi 2007; Manos 1999; Merrill 2021; Muniz 2008; Musten 1997; NCT02536105; Pearson 2013; Pliszka 2007; Rapport 1985; Rapport 1987; Rapport 2008; Sharp 1999; Smith 1998; Solanto 2009; Soleimani 2017; Stein 1996; Stein 2003; Stein 2011; Szobot 2008; Taylor 1987; Ullmann 1985; Ullmann 1986; Wallander 1987; Waxmonsky 2008; Zeiner 1999	38 trials: Brown 1985; Carlson 2007; Childress 2009; Coghill 2013; Connor 2000; Duric 2012; Findling 2006; Findling 2008; Findling 2010; Firestone 1981; Greenhill 2002; Greenhill 2006; Heriot 2008; Horn 1991; Ialongo 1994; Kollins 2006 (PATS); Lehmkuhl 2002; Lin 2014; Martins 2004; Matthijssen 2019; McCracken 2016; NCT00409708; NCT02293655; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Pliszka 2000; Pliszka 2017; Riggs 2011; Schrantee 2016; Tourette's Syndrome Study Group 2002; Tannock 2018; Tucker 2009; Van der Meere

Table 2. Key demographics of included studies *(Continued)*

			1999a; Weiss 2021; Wigal 2004; Wolraich 2001
More than 6 months	4	0 trials	4 trials: Barragán 2017; Jensen 1999 (MTA); Perez-Alvarez 2009; Schachar 1997a
Not stated or unclear	2	2 trials: Kelly 1989; Tannock 1989	0 trials
Titration period			
After randomisation	36	13 trials: Abikoff 2009; Borcherding 1990; Castellanos 1997; Cook 1993; Cox 2006; Gadow 1990; Gorman 2006; Ramtvedt 2013; Sharp 1999; Stein 1996; Taylor 1987; Ullmann 1985; Wilens 2010	23 trials: Barragán 2017; Carlson 2007; Childress 2009; Coghill 2013; Connor 2000; Findling 2008; Findling 2010; Firestone 1981; Greenhill 2006; Jensen 1999 (MTA); Lehmkuhl 2002; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Pliszka 2017; Schachar 1997a; Schrantee 2016; Szobot 2004; Tannock 2018; Tourette's Syndrome Study Group 2002; Weiss 2021; Tucker 2009; Wigal 2004
Before randomisation	32	20 trials: Blum 2011; Brown 1991; Döpfner 2004; Epstein 2011; Huang 2021; Kent 1995; Kollins 2006 (PATS); Konrad 2004; Konrad 2005; Lopez 2003; McGough 2006; Murray 2011; NCT02039908; NCT02536105; Pearson 2013; Wallace 1994; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008	13 trials: Arnold 2004; Biederman 2003b; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Kollins 2006 (PATS); Kollins 2021; NCT02293655; Riggs 2011; Wigal 2017; Wilens 2006b; Wolraich 2001
None	139	120 trials: Ahmann 1993; Barkley 1989b; Barkley 1991; Barkley 2000; Bedard 2008; Bhat 2020; Bliznakova 2007; Brams 2008; Brams 2012; Brown 1984a; Brown 1988; Buitelaar 1995; Bukstein 1998; Carlson 1995; Castellanos 1997; Chronis 2003; Coghill 2007; Corkum 2008; Corkum 2020; Douglas 1986; Douglas 1995; DuPaul 1996; Fabiano 2007; Findling 2007; Fine 1993; Fitzpatrick 1992a; Flapper 2008; Forness 1992; Froehlich 2011; Froehlich 2018; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Gonzalez-Heydrich 2010; Gruber 2007; Hale 2011; Hawk 2018; Hicks 1985; Hoeppner 1997; Johnston 1988; Kaplan 1990; Kelly 1989; Kent 1999; Klorman 1990; Kolko 1999; Kortekaas-Rijlaarsdam 2017; Kritchman 2019; Leddy 2009; Lijffijt 2006; Lufi 1997; Lufi 2007; Manos 1999; McBride 1988a; McInnes 2007; Merrill 2021; Moshe 2012; Muniz 2008; Musten 1997; Nikles 2006; Oesterheld 1998; Overtoom 2003; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2001a; Pelham 2002; Pelham 2005; Pelham 2011; Pelham 2014; Pliszka 1990; Pliszka 2007; Quinn	19 trials: Brown 1985; Butter 1983; Findling 2006; Green 2011; Greenhill 2002; Heriot 2008; Horn 1991; Ialongo 1994; Jacobi-Polishook 2009; Lin 2014; Martins 2004; Matthijssen 2019; McCracken 2016; NCT00409708; Newcorn 2008; Perez-Alvarez 2009; Pliszka 2000; Van der Meere 1999a; Wigal 2015

Table 2. Key demographics of included studies *(Continued)*

		2004; Rapport 1985; Rapport 1987; Rapport 2008; Reitman 2001; Rubinsten 2008; Samuels 2006; Schachar 2008; Schulz 2010; Schwartz 2004; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Smith 1998; Smith 2004; Smithee 1998; Soleimani 2017; Stein 2003; Stein 2011; Stoner 1994; Sumner 2010; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Symons 2007; Szobot 2008; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1993; Tervo 2002; Tirosh 1993a; Ullmann 1986; Urman 1995; Wallander 1987; Waxmonsky 2008; Whalen 1990; Wigal 2003; Wilkison 1995; Wodrich 1998; Zeiner 1999; Zeni 2009	
Unclear	5	4 trials: Chacko 2005; CRIT124US02; Pelham 1989; Solanto 2009	1 trial: Duric 2012
Funding			
Funded by grants from universities; authorities or research foundations	82	70 trials: Ahmann 1993; Barkley 1991; Barkley 2000; Bedard 2008; Bhat 2020; Brown 1988; Brown 1991; Chacko 2005; Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; Cox 2006; Douglas 1986; Douglas 1995; Epstein 2011; Fabiano 2007; Findling 2007; Fitzpatrick 1992a; Forness 1992; Froehlich 2011; Froehlich 2018; Gadow 1995; Gadow 2007; Garfinkel 1983; Gonzalez-Heydrich 2010; Gorman 2006; Hale 2011; Hawk 2018; Hicks 1985; Kent 1995; Klorman 1990; Kollins 2006 (PATS); Konrad 2004; Konrad 2005; Kritchman 2019; McInnes 2007; Musten 1997; NCT02039908; NCT02536105; Nikles 2006; Oesterheld 1998; Overtoom 2003; Pearson 2013; Pelham 2002; Pelham 2014; Pliszka 1990; Pliszka 2007; Ramtvedt 2013; Rubinsten 2008; Schwartz 2004; Shiels 2009; Smith 1998; Smithee 1998; Soleimani 2017; Stein 1996; Stein 2003; Stoner 1994; Symons 2007; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Urman 1995; Wallace 1994; Wallander 1987; Waxmonsky 2008; Wilkison 1995; Zeiner 1999	12 trials: Butter 1983; Connor 2000; Duric 2012; Firestone 1981; Green 2011; Jensen 1999 (MTA); Kollins 2006 (PATS); Matthijssen 2019; McCracken 2016; NCT02293655; Palumbo 2008; Schrantee 2016
Funded or partially funded by pharmaceutical industry	87	48 trials: Abikoff 2009; Blum 2011; Brams 2008; Brams 2012; Brown 1984a; Chronis 2003; CRIT124US02; Döpfner 2004; Fine 1993; Gadow 1990; Gadow 2011; Huang 2021; Kelly 1989; Kent 1999; Kortekaas-Rijlaarsdam 2017; Lopez 2003; Manos 1999; McGough 2006; Muniz 2008; Murray 2011; Pelham 1999; Pelham 2001a; Pelham 2005; Pelham 2011; Quinn 2004; Schachar 2008; Schulz 2010; Silva 2005a; Silva 2006; Silva 2008; Stein 2011; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Szobot 2008; Taylor 1987; Ullmann 1985; Ullmann 1986; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010; Zeni 2009	39 trials: Arnold 2004; Barragán 2017; Biederman 2003b; Brown 1985; Carlson 2007; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Findling 2006; Findling 2008; Findling 2010; Greenhill 2002; Greenhill 2006; Kollins 2021; Lehmkuhl 2002; Lin 2014; Martins 2004; NCT00409708; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Pliszka 2000; Pliszka 2017; Riggs 2011; Schachar 1997a; Szobot 2004; Tannock 2018; Tourette's Syndrome

Table 2. Key demographics of included studies *(Continued)*

			Study Group 2002; Tucker 2009; Van der Meere 1999a; Weiss 2021; Wigal 2004; Wigal 2015; Wigal 2017; Wilens 2006b; Wolraich 2001
No funding received	8	6 trials: Barkley 1989b; Flapper 2008; Moshe 2012; Rapport 1987; Rapport 2008; Tirosh 1993a	2 trials: Heriot 2008; Perez-Alvarez 2009
Unclear funding	36	33 trials: Bliznakova 2007; Borcherding 1990; Buitelaar 1995; Bukstein 1998; Carlson 1995; Castellanos 1997; DuPaul 1996; Gruber 2007r; Hoeppner 1997; Johnston 1988; Kaplan 1990; Kolko 1999; Leddy 2009; Lijffijt 2006; Lufi 1997; Lufi 2007; McBride 1988a; Merrill 2021; Pelham 1989; Pelham 1990a; Pelham 1993a; Rapport 1985; Reitman 2001; Samuels 2006; Sharp 1999; Smith 2004; Solanto 2009; Sumner 2010; Taylor 1993; Tervo 2002; Tirosh 1993b; Whalen 1990; Wodrich 1998	3 trials: Horn 1991; Ialongo 1994; Jacobi-Polishook 2009
Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation			
Yes	88	60 trials: Barkley 1991; Barkley 2000; Blum 2011; Brams 2008; Brams 2012; Brown 1991; Cox 2006; Döpfner 2004; Fabiano 2007; Gonzalez-Heydrich 2010; Gruber 2007; Huang 2021; Kent 1995; Klorman 1990; Kollins 2006 (PATS); Konrad 2004; Konrad 2005; Kortekaas-Rijlaarsdam 2017; Lijffijt 2006; Lopez 2003; Manos 1999; McGough 2006; Muniz 2008; Murray 2011; NCT02039908; NCT02536105; Nikles 2006; Overtoom 2003; Pearson 2013; Pelham 2001a; Pelham 2011; Pelham 2014; Quinn 2004; Reitman 2001; Samuels 2006; Schachar 2008; Schulz 2010; Schwartz 2004; Silva 2005a; Silva 2006; Silva 2008; Stein 2011; Sumner 2010; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Tannock 1992; Tannock 1995a; Tannock 1995b; Wallace 1994; Waxmonsky 2008; Whalen 1990; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2014; Wilens 2008; Wilens 2010	29 trials: Arnold 2004; Biederman 2003b; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Findling 2006; Findling 2008; Findling 2010; Greenhill 2002; Greenhill 2006; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kollins 2006 (PATS); Kollins 2021; Matthijssen 2019; NCT02293655; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Pliszka 2017; Tannock 2018; Weiss 2021; Wigal 2004; Wigal 2015; Wigal 2017; Wilens 2006b; Wolraich 2001
No	112	86 trials: Abikoff 2009; Ahmann 1993; Barkley 1989b; Bedard 2008; Bhat 2020; Bliznakova 2007; Borcherding 1990; Brown 1984a; Brown 1988; Buitelaar 1995; Bukstein 1998; Carlson 1995; Castellanos 1997; Chronis 2003; Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; CRIT124US02; Douglas 1986; Douglas 1995; DuPaul 1996; Epstein 2011; Findling 2007; Fine 1993; Flapper 2008; Forness 1992; Froehlich 2011; Froehlich 2018; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Gorman 2006; Hale 2011; Hawk 2018; Hicks 1985; Hoeppner 1997; Kaplan 1990; Kelly 1989; Kent 1999; Kolko 1999; Kritchman 2019; Lufi 1997; McBride 1988a; McInnes 2007; Moshe 2012; Musten 1997; Oesterheld 1998; Pelham 1990a; Pelham 1993a; Pelham 1999; Pelham 2002; Pelham 2005; Pliszka 1990; Pliszka 2007; Ramtvedt 2013; Rapport 1985; Rapport 1987; Rapport	26 trials: Barragán 2017; Brown 1985; Butter 1983; Carlson 2007; Childress 2009; Connor 2000; Duric 2012; Firestone 1981; Green 2011; Heriot 2008; Horn 1991; Ialongo 1994; Lehmkuhl 2002; Lin 2014; Martins 2004; McCracken 2016; NCT00409708; Palumbo 2008; Perez-Alvarez 2009; Pliszka 2000; Schachar 1997a; Schrantee 2016; Szobot 2004; Tourette's Syndrome

Table 2. Key demographics of included studies *(Continued)*

		2008; Rubinsten 2008; Sharp 1999; Shiels 2009; Smith 1998; Smith 2004; Smithee 1998; Soleimani 2017; Stein 1996; Stein 2003; Stoner 1994; Szobot 2008; Tannock 1989; Taylor 1987; Taylor 1993; Tervo 2002; Tirosh 1993a; Tirosh 1993b; Ullmann 1985; Ullmann 1986; Urman 1995; Wallander 1987; Wilkison 1995; Wodrich 1998; Zeiner 1999; Zeni 2009	Study Group 2002; Tucker 2009; Van der Meere 1999a
Not stated or unclear	12	11 trials: Chacko 2005; Fitzpatrick 1992a; Johnston 1988; Leddy 2009; Lufi 2007; Merrill 2021; Pelham 1989; Solanto 2009; Sunohara 1999; Symons 2007; Tannock 1993	1 trial: Riggs 2011
Withdrawals due to adverse events			
Yes	68	36 trials: Ahmann 1993; Barkley 1989b; Bhat 2020; Castellanos 1997; Fabiano 2007; Findling 2007; Hawk 2018; Huang 2021; Kolko 1999; Kollins 2006 (PATS); Kortekaas-Rijlaarsdam 2017; Lijffijt 2006; Manos 1999; Murray 2011; Nikles 2006; Pelham 1999; Pelham 2011; Pelham 2014; Silva 2006; Silva 2008; Solanto 2009; Stein 1996; Stein 2003; Stein 2011; Swanson 2004b; Szobot 2008; Tannock 1992; Taylor 1987; Tervo 2002; Tirosh 1993b; Waxmonsky 2008; Wigal 2014; Wilens 2008; Wilens 2010; Wodrich 1998; Zeni 2009	33 trials: Barragán 2017; Biederman 2003b; Carlson 2007; Childress 2009; Childress 2020c; Coghill 2013; Findling 2006; Findling 2008; Findling 2010; Firestone 1981; Greenhill 2002; Greenhill 2006; Horn 1991; Ialongo 1994; Jensen 1999 (MTA); Kollins 2006 (PATS); Lehmkuhl 2002; Lin 2014; Matthijssen 2019; McCracken 2016; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Pliszka 2000; Pliszka 2017; Schachar 1997a; Schrantee 2016; Weiss 2021; Wigal 2004; Wigal 2015; Wilens 2006b; Wolraich 2001
No	116	101 trials: Abikoff 2009; Barkley 1991; Barkley 2000; Bedard 2008; Bliznakova 2007; Blum 2011; Borcherding 1990; Brams 2008; Brams 2012; Brown 1984a; Brown 1988; Brown 1991; Buitelaar 1995; Bukstein 1998; Carlson 1995; Chacko 2005; Chronis 2003; Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; Cox 2006; CRIT124US02; Döpfner 2004; Douglas 1995; DuPaul 1996; Fine 1993; Flapper 2008; Froehlich 2011; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Garfinkel 1983; Gonzalez-Heydrich 2010; Gruber 2007; Hicks 1985; Hoeppner 1997; Johnston 1988; Kaplan 1990; Kelly 1989; Kent 1995; Kent 1999; Konrad 2004; Kritchman 2019; Lopez 2003; Lufi 1997; Lufi 2007; McBride 1988a; McGough 2006; McInnes 2007; Merrill 2021; Moshe 2012; Muniz 2008; NCT02536105; Oesterheld 1998; Overtoom 2003; Pearson 2013; Pelham 1990a; Pelham 1993a; Pelham 2001a; Pelham 2002; Pelham 2005; Pliszka 2007; Quinn 2004; Ramtvedt 2013; Rapport 1985; Rapport 2008; Reitman 2001; Rubinsten 2008; Schachar 2008; Schulz 2010; Schwartz 2004; Sharp 1999; Shiels 2009; Silva 2005a; Smith 1998; Smith 2004; Soleimani 2017; Stoner 1994; Sunohara 1999; Swanson 1998; Swanson	15 trials: Arnold 2004; Brown 1985; Butter 1983; Childress 2017; Childress 2020a; Childress 2020b; Connor 2000; Green 2011; Jacobi-Polishook 2009; Kollins 2021; Martins 2004; Perez-Alvarez 2009; Szobot 2004; Tucker 2009; Van der Meere 1999a

Table 2. Key demographics of included studies *(Continued)*

		2002a; Swanson 2002b; Symons 2007; Tannock 1989; Tannock 1993; Tannock 1995a; Tannock 1995b; Taylor 1993; Tirosh 1993a; Ullmann 1985; Ullmann 1986; Urman 1995; Wallace 1994; Wallander 1987; Whalen 1990; Wigal 2003; Wigal 2011; Wigal 2013; Zeiner 1999	
Not stated or unclear	28	20 trials: Douglas 1986; Epstein 2011; Fitzpatrick 1992a; NCT02039908; Forness 1992; Froehlich 2018; Gorman 2006; Hale 2011; Klorman 1990; Konrad 2005; Leddy 2009; Musten 1997; Pelham 1989; Pliszka 1990; Rapport 1987; Samuels 2006; Smithee 1998; Sumner 2010; Swanson 1999; Wilkison 1995	8 trials: Duric 2012; Heriot 2008; NCT00409708; NCT02293655; Riggs 2011; Tannock 2018; Tourette's Syndrome Study Group 2002; Wigal 2017
Availability for quantitative analyses			
No usable data	47	41 trials: Ahmann 1993; Bliznakova 2007; Douglas 1995; Forness 1992; Froehlich 2011; Gruber 2007; Hale 2011; Hicks 1985; Johnston 1988; Kelly 1989; Kent 1999; Leddy 2009; Lijffijt 2006; Lopez 2003; McInnes 2007; Nikles 2006; Oesterheld 1998; Pliszka 2007; Rubinsten 2008; Samuels 2006; Shiels 2009; Soleimani 2017; Stoner 1994; Sumner 2010; Sunohara 1999; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Symons 2007; Tannock 1992; Tannock 1995b; Taylor 1993; Tervo 2002; Ullmann 1985; Wallace 1994; Wallander 1987; Waxmonsky 2008; Wigal 2003; Wilkison 1995; Wodrich 1998	6 trials: Connor 2000; Heriot 2008; Horn 1991; Martins 2004; Perez-Alvarez 2009; Szobot 2008

ADHD: attention deficit hyperactivity disorder; **CD:** conduct disorder; **CNS:** central nervous system; **ODD: Oppositional defiant disorder**;**DSM:***Diagnostic and Statistical Manual of Mental Disorders*; **DSM-III:***Diagnostic and Statistical Manual of Mental Disorders Third Edition*; **DSM-III-R:***Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised*; **DSM-IV:***Diagnostic and Statistical Manual of Mental Disorders Fourth Edition*; **DSM-IV-TR:***Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision*; **DSM-5:***Diagnostic and Statistical Manual of Mental Disorders Fifth Edition*; **ICD-10:***International Statistical Classification of Diseases and Related Health Problems 10th Revision;* **OCD:** obsessive compulsive disorder; **ODD:** oppositional defiant disorder

[a]Research unit at a hospital.
[b]In addition to bipolar disorder, which was an inclusion criterion for this trial.
[c]2 participants also had drug or alcohol abuse.
[d]Participants were grouped to be with or without anxiety.
[e]50% also suffered from psychosis. All participants had either bipolar disorder or borderline personality disorder.
[f]Aggressive conduct disorder.
[g]Drug/alcohol use.
[h]Neurofeedback was part of the intervention.
[i]For the review, we used data from arms with no behavioural intervention.
[j]Different reporting across different articles, ranging between 39% and 63%.
[k]Delayed-release and extended-release methylphenidate.
[l]Given 3 times a day as well as an experimental delivery, to evaluate the effect of applying an osmotically driven, continuous delivery system.
[m]For the parallel trial.
[n]For the cross-over trial.
[o]In this cross-over trial, children received methylphenidate twice for 7-10 days, resulting in a full methylphenidate intervention period of 14-20 days.
[p]Between 7-21 days depending on group size. The mean intervention period considered 14 days for this review.
[q]Twelve days for the 20 inpatients, 19 days for the 24 outpatients.
[r]It is only stated that this trial was not industry-funded.

Table 3. Key inclusion and exclusion criteria

Criteria	Number of trials	Trials
Inclusion criteria of special interest		
A diagnosis of ODD or CD or disruptive behavior disorder	4	Brown 1991; Bukstein 1998; Connor 2000; Gadow 1990
A diagnosis of bipolar disorder and treated with a stable dose of mood stabilisers or either bipolar disorder or borderline disorder	2	Findling 2007; Zeni 2009
A diagnosis of Tourette's syndrome or motor tic disorder	5	Castellanos 1997; Gadow 1995; Gadow 2007; Gadow 2011; Tourette's Syndrome Study Group 2002
A diagnosis of developmental co-ordination disorder	2	Flapper 2008; Soleimani 2017
A diagnosis of epilepsy	1	Gonzalez-Heydrich 2010
A diagnosis of velocardiofacial syndrome	1	Green 2011
A diagnosis of cerebral palsy	1	Symons 2007
Non-nicotine substance use disorder	2	Riggs 2011; Szobot 2008
Positive response to methylphenidate prior to screening or being on a stable dose of methylphenidate before screening/entering trial or familiar with methylphenidate intake for at least 2 weeks-2 years	27	Childress 2017; Childress 2020b; Cox 2006; Döpfner 2004; Findling 2006; Findling 2008; Kortekaas-Rijlaarsdam 2017; Lijffijt 2006; Matthijssen 2019; Muniz 2008; Nikles 2006; Pelham 2001a; Pelham 2011; Pliszka 2017; Samuels 2006; Schulz 2010; Silva 2005a; Silva 2006; Silva 2008; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b; Tannock 2018; Wigal 2003; Wilkison 1995
Most common exclusion criteria and exclusion criteria of special interest		
Intellectual disability, or estimated/measured IQ < 60-85, or deemed by investigators to have below-average cognitive capacity, or history of neurological impairment, or history of significant developmental delay, or to be home-schooled, or intellectual disability	126	Ahmann 1993; Barkley 1989b; Barkley 1991; Barragán 2017; Bedard 2008; Bhat 2020; Blum 2011; Brams 2008; Brams 2012; Brown 1984a; Brown 1988; Brown 1991; Butter 1983; Carlson 1995; Carlson 2007; Castellanos 1997; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Coghill 2007; Coghill 2013; Cook 1993; Corkum 2008; Corkum 2020; Döpfner 2004; Douglas 1995; DuPaul 1996; Duric 2012; Epstein 2011; Findling 2006; Findling 2007; Findling 2008; Findling 2010; Fine 1993; Firestone 1981; Flapper 2008; Forness 1992; Froehlich 2011; Froehlich 2018; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Gonzalez-Heydrich 2010; Gorman 2006; Greenhill 2002; Gruber 2007; Hale 2011; Heriot 2008; Horn 1991; Huang 2021; Ialongo 1994; Jensen 1999 (MTA); Kelly 1989; Klorman 1990; Kollins 2006 (PATS); Kollins 2021; Konrad 2004; Kortekaas-Rijlaarsdam 2017; Led-

Table 3. Key inclusion and exclusion criteria *(Continued)*

		dy 2009; Lehmkuhl 2002; Lufi 1997; Martins 2004; Matthijssen 2019; McCracken 2016; McGough 2006; McInnes 2007; Murray 2011; NCT00409708; NCT02039908; NCT02293655; NCT02536105; Oesterheld 1998; Palumbo 2008; Pearson 2013; Pelham 1989; Pelham 2001a; Pelham 2011; Pelham 2014; Pliszka 2007; Pliszka 2017; Quinn 2004; Ramtvedt 2013; Reitman 2001; Rubinsten 2008; Schachar 2008; Schrantee 2016; Schwartz 2004; Sharp 1999; Shiels 2009; Silva 2005a; Silva 2008; Smith 1998; Smithee 1998; Solanto 2009; Soleimani 2017; Stein 1996; Stein 2003; Stein 2011; Sunohara 1999; Swanson 1998; Swanson 2004b; Szobot 2004; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Tannock 2018; Taylor 1987; Taylor 1993; Tourette's Syndrome Study Group 2002; Tucker 2009; Van der Meere 1999a; Waxmonsky 2008; Weiss 2021; Wigal 2004; Wigal 2011; Wigal 2013; Wigal 2014; Wigal 2015; Wilens 2008; Wilens 2010; Wolraich 2001; Zeiner 1999; Zeni 2009
Learning disability, or not having an age-appropriate academic level, or at least an average learning score	17	Abikoff 2009; Biederman 2003b; Childress 2009; Coghill 2007; Cook 1993; CRIT124US02; Froehlich 2018; Greenhill 2006; Moshe 2012[a]; Muniz 2008; Murray 2011; NCT02293655; Pelham 2001a; Pliszka 2007; Rubinsten 2008; Wigal 2011; Wilkison 1995
Any psychiatric disorder that could contraindicate treatment or confound efficacy or safety assessments, or any psychiatric comorbidity, or any concurrent significant psychiatric illness, or any psychiatric disorder with few specified exceptions, or any comorbid axis I psychiatric disorder requiring treatment, or any psychiatric comorbidity requiring treatment	54	Biederman 2003b; Borcherding 1990; Brams 2008; Brams 2012; Carlson 2007; Castellanos 1997[b]; Childress 2020c; Corkum 2008; Corkum 2020; Duric 2012; Findling 2006; Findling 2008; Findling 2010; Flapper 2008; NCT02039908; Greenhill 2002; Greenhill 2006; Jacobi-Polishook 2009; Kollins 2006 (PATS); Konrad 2004; Kortekaas-Rijlaarsdam 2017; Lopez 2003; Lufi 1997; Matthijssen 2019; McGough 2006; Moshe 2012; Muniz 2008; Murray 2011; NCT02536105; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Pelham 2011; Perez-Alvarez 2009; Pliszka 2017; Quinn 2004; Schachar 2008; Schrantee 2016; Schulz 2010; Silva 2005a; Silva 2006; Silva 2008; Soleimani 2017; Swanson 1998; Szobot 2008; Taylor 1987; Waxmonsky 2008; Weiss 2021; Wigal 2013; Wigal 2014; Wigal 2015; Wigal 2017; Wilens 2006b; Wilens 2010; Wilkison 1995
Psychiatric disorders that might be the primary cause of ADHD symptoms	2	Froehlich 2011; Wodrich 1998
Significant neurological history, or other significant CNS disorders, or gross sensory or motor deficits/impairment, or brain damage/traumatic brain injury, or head injury requiring hospitalisation, or major organic brain dysfunction, or history of electroencephalographic abnormalities	74	Ahmann 1993; Arnold 2004; Barkley 1989b; Barkley 2000; Barragán 2017; Bedard 2008; Blum 2011; Borcherding 1990; Brown 1984a; Brown 1985; Brown 1988; Brown 1991; Castellanos 1997; Childress 2020c; Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; Douglas 1986; DuPaul 1996; Duric 2012; Findling 2007; Firestone 1981; Froehlich 2011; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Gorman 2006; Hale 2011; Hawk 2018; Heriot 2008; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kelly 1989; Klorman 1990; Kortekaas-Rijlaarsdam 2017; Leddy 2009; Lin 2014; Martins 2004; Moshe 2012; Murray 2011; Musten 1997; NCT02293655; Oesterheld 1998; Pearson 2013; Pelham 1989; Pliszka 2007; Quinn 2004; Ramtvedt 2013; Rapport 1985; Rapport 1987; Rapport 2008; Schachar 2008; Schrantee 2016; Sharp 1999; Shiels 2009; Smithee 1998; Solanto 2009; Soleimani 2017; Sumner 2010; Szobot 2004; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Tannock 2018; Tirosh 1993a; Tirosh 1993b; Waxmonsky 2008; Weiss 2021; Wigal 2004; Zeiner 1999
History of epilepsy or seizures	60	Ahmann 1993; Barkley 1989b; Barragán 2017; Blum 2011; Brams 2008; Brams 2012; Carlson 2007; Childress 2009; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Cook 1993; Corkum 2008; Corkum 2020; DuPaul 1996; Findling 2008; Findling 2010; Firestone 1981; Gadow 1990;

Table 3. Key inclusion and exclusion criteria *(Continued)*

		Gadow 1995; Gadow 2007; Gadow 2011; Greenhill 2002; Greenhill 2006; Hale 2011; Hawk 2018; Huang 2021; Leddy 2009; Lehmkuhl 2002; Lin 2014; McGough 2006; Moshe 2012; Muniz 2008; NCT00409708; NCT02536105; NCT02293655; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Oesterheld 1998; Pliszka 2017; Ramtvedt 2013; Schrantee 2016; Sharp 1999; Shiels 2009; Soleimani 2017; Stein 2003; Swanson 2004b; Tannock 1989; Tucker 2009; Waxmonsky 2008; Weiss 2021; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2015; Wigal 2017; Wilens 2006b; Wilens 2010; Wolraich 2001
History or diagnosis of and/or family history of Tourette's syndrome or tic disorders	62	Ahmann 1993; Abikoff 2009; Barkley 1989b; Barkley 1991; Barkley 2000; Bhat 2020; Blum 2011; Borcherding 1990; Brams 2008; Brams 2012; Buitelaar 1995; Childress 2009; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; DuPaul 1996; Findling 2008; Fine 1993; Greenhill 2002; Gruber 2007; Heriot 2008; Huang 2021; Jensen 1999 (MTA); Kent 1995; Kollins 2006 (PATS); Kollins 2021; Lehmkuhl 2002; Lin 2014; McCracken 2016; McGough 2006; Moshe 2012; Muniz 2008; Murray 2011; NCT02536105; Newcorn 2008; Overtoom 2003; Palumbo 2008; Pearson 2013; Pliszka 2000; Pliszka 2017; Riggs 2011; Schachar 1997a; Schrantee 2016; Schwartz 2004; Silva 2005a; Silva 2006; Silva 2008; Solanto 2009; Stein 2003; Stein 2011; Sumner 2010; Swanson 2004b; Tannock 1989; Wigal 2003; Wigal 2004; Wigal 2011; Wigal 2013; Wigal 2017; Wilens 2006b; Wilens 2010; Wolraich 2001
History or diagnosis of autism or pervasive development disorder or Asperger's disorder	49	Abikoff 2009; Barkley 1989b; Barragán 2017; Bhat 2020; Blum 2011; Buitelaar 1995; Carlson 2007; Corkum 2008; Döpfner 2004; DuPaul 1996; Findling 2007; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Gorman 2006; Gruber 2007; Hawk 2018; Heriot 2008; Kent 1999; Klorman 1990; Kollins 2006 (PATS); Kollins 2021; Konrad 2005; Kritchman 2019; Leddy 2009; Lehmkuhl 2002; Lin 2014; McCracken 2016; Murray 2011; Musten 1997; NCT02039908; Newcorn 2008; Overtoom 2003; Palumbo 2008; Pearson 2013; Schachar 2008; Schwartz 2004; Shiels 2009; Stein 1996; Stein 2011; Taylor 1987; Tourette's Syndrome Study Group 2002; Van der Meere 1999a; Waxmonsky 2008; Wigal 2004; Wigal 2011; Zeiner 1999; Zeni 2009
History or diagnosis of and/or family history of: major depression or depressive disorder or bipolar disorder or affective disorder or mood disorder	45	Abikoff 2009; Barkley 1989b; Blum 2011; Carlson 1995c; Carlson 2007; Childress 2020b; Döpfner 2004; Findling 2007; Gonzalez-Heydrich 2010; Gorman 2006; Horn 1991; Ialongo 1994; Kent 1995; Kollins 2006 (PATS); Kollins 2021; Kritchman 2019; Lehmkuhl 2002; Lin 2014; Martins 2004; McCracken 2016; Murray 2011; NCT02293655; Newcorn 2008; Oesterheld 1998; Palumbo 2008; Pearson 2013; Pliszka 1990; Pliszka 2000; Riggs 2011; Schachar 1997a; Solanto 2009; Stein 2003; Stein 2011; Sumner 2010; Swanson 2002a; Szobot 2004; Tourette's Syndrome Study Group 2002; Tucker 2009; Waxmonsky 2008; Wigal 2003; Wigal 2004; Wigal 2011; Wilens 2006b; Wilens 2010; Zeiner 1999
History or diagnosis of eating disorder	9	Childress 2020b; Kritchman 2019; Murray 2011; Palumbo 2008; Tourette's Syndrome Study Group 2002; Waxmonsky 2008; Wigal 2004; Wigal 2011; Wilens 2006b
Diagnosis of post-traumatic stress disorder	1	Abikoff 2009
History or diagnosis of obsessive-compulsive disorder	8	Abikoff 2009; Blum 2011; Childress 2009; Jensen 1999 (MTA); Kollins 2021; Murray 2011; Wigal 2004; Wigal 2011
Diagnosis of panic disorder, or severe anxiety disorder, or in the investigator's evaluation very anx-	23	Abikoff 2009; Barkley 1989b; Childress 2020b; Döpfner 2004; Horn 1991; Huang 2021; Ialongo 1994; Kent 1995; Kritchman 2019; Lehmkuhl 2002; Lin 2014; McCracken 2016; Murray 2011; Newcorn 2008; Schachar 1997a; Sum-

Table 3. Key inclusion and exclusion criteria *(Continued)*

ious, tense or agitated, or separation anxiety disorder		ner 2010; Sunohara 1999; Swanson 2002a; Tannock 1995a; Tucker 2009; Wigal 2003; Wigal 2011; Wilens 2006b
History or diagnosis of CD/ behaviour disorder	11	Childress 2020b; Coghill 2013; Kollins 2021; Murray 2011; Sunohara 1999; Swanson 2002a; Tannock 1989; Tannock 1992; Wigal 2003; Wigal 2011; Wilens 2008
History or diagnosis of ODD	2	Swanson 2002a; Wigal 2003
Lifetime history of psychosis or thought disturbance or thought disorder or schizoid, schizotypal or frank psychotic features	66	Abikoff 2009; Barkley 1989b; Bedard 2008; Bhat 2020; Blum 2011; Brown 1985; Brown 1991; Childress 2009; Childress 2020b; Cook 1993; Döpfner 2004; Douglas 1986; DuPaul 1996; Findling 2007; Firestone 1981; Froehlich 2018; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Gonzalez-Heydrich 2010; Gorman 2006; Gruber 2007; Hawk 2018; Heriot 2008; Horn 1991; Huang 2021; Ialongo 1994; Kaplan 1990; Kelly 1989; Kent 1995; Klorman 1990; Kollins 2006 (PATS); Kollins 2021; Kritchman 2019; Leddy 2009; Lehmkuhl 2002; Lin 2014; McCracken 2016; Murray 2011; NCT02293655; Newcorn 2008; Palumbo 2008; Pliszka 1990; Pliszka 2000; Ramtvedt 2013; Riggs 2011; Schachar 2008; Schrantee 2016; Schwartz 2004; Shiels 2009; Smithee 1998; Solanto 2009; Stein 2011; Sumner 2010; Tannock 1993; Tourette's Syndrome Study Group 2002; Tucker 2009; Waxmonsky 2008; Wigal 2003; Wigal 2004; Wigal 2011; Wilens 2006b; Wolraich 2001; Zeiner 1999; Zeni 2009
Lifetime history or diagnosis of mania or hypomania	7	Abikoff 2009; Findling 2007; Froehlich 2011; Froehlich 2018; Gonzalez-Heydrich 2010; NCT02293655; Pliszka 2000
History or diagnosis of sleep disorder	5	Corkum 2008; Corkum 2020; Murray 2011; Wigal 2004; Wigal 2011
Significant suicidality or dangerous to self or others	23	Abikoff 2009; Blum 2011; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Findling 2007; Findling 2010; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Jensen 1999 (MTA); Kollins 2006 (PATS); Kollins 2021; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Pliszka 2017; Riggs 2011; Schrantee 2016; Waxmonsky 2008; Weiss 2021; Zeni 2009
Has a known history of physical, sexual or emotional abuse in the last year, or history of child abuse	5	Childress 2020a; Childress 2020c; Heriot 2008; Jensen 1999 (MTA); Kollins 2006 (PATS)
History or diagnosis of substance abuse or positive drug screening test or suspected drug abuse	41	Abikoff 2009; Arnold 2004; Biederman 2003b; Brams 2008; Brams 2012; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Coghill 2007; Coghill 2013; Cox 2006; Findling 2006; Findling 2007; Findling 2010; Greenhill 2006; Huang 2021; Kollins 2021; Kritchman 2019; Lopez 2003; Martins 2004; Muniz 2008; Murray 2011; NCT02536105; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Pliszka 2007; Pliszka 2017; Schrantee 2016; Silva 2005a; Silva 2006; Silva 2008; Stein 2011; Sumner 2010; Swanson 2004b; Szobot 2004; Tucker 2009; Weiss 2021; Wigal 2004; Wigal 2011; Zeni 2009
Living with a person with a current or earlier substance abuse disorder or family history of drug abuse	12	Biederman 2003b; Childress 2009; Childress 2017; Childress 2020a; Childress 2020c; Findling 2006; Greenhill 2002; Huang 2021; Jensen 1999 (MTA); Kollins 2006 (PATS); Swanson 2004b; Wigal 2003

Table 3. Key inclusion and exclusion criteria *(Continued)*

Inability to take/swallow or tolerate methylphenidate/ingredients in the medication or history of adverse reactions/adverse events	54	Arnold 2004; Barkley 1991; Barkley 2000; Biederman 2003b; Blum 2011; Brams 2008; Brams 2012; Carlson 2007; Childress 2017; Childress 2020b; Childress 2020c; Coghill 2013; Cox 2006; CRIT124US02; Fabiano 2007; Findling 2007; NCT02039908; Gonzalez-Heydrich 2010; Greenhill 2002; Greenhill 2006; Gruber 2007; Huang 2021; Jensen 1999 (MTA); Kent 1995; Kollins 2006 (PATS); Kollins 2021; Murray 2011; NCT02536105; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Palumbo 2008; Pearson 2013; Pelham 2005; Pelham 2014; Pliszka 2017; Quinn 2004; Schachar 2008; Schwartz 2004; Silva 2005a; Stein 2011; Sumner 2010; Swanson 2004b; Tannock 2018; Waxmonsky 2008; Weiss 2021; Wigal 2003; Wigal 2004; Wigal 2011; Wigal 2015; Wilens 2006b; Wilens 2010; Wolraich 2001; Zeni 2009
History of failed/poor response/being non-responsive to methylphenidate (unless naive to stimulants), or past treatment failure on a methylphenidate trial	27	Brams 2012; Childress 2020b; Childress 2020c; Coghill 2013; Fabiano 2007; Findling 2006; Findling 2010; Greenhill 2006; Kollins 2021; McGough 2006; Murray 2011; NCT02039908; Newcorn 2008; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Pearson 2013; Schachar 2008; Schulz 2010; Silva 2006; Silva 2008; Stein 2011; Tannock 2018; Wigal 2003; Wigal 2011; Wilens 2006b; Wilens 2008; Wilens 2010
Satisfied with current pharmacological treatment (if not stimulant-naive) or having effective control of symptoms with acceptable tolerability on current ADHD medication	10	Childress 2020a; Coghill 2013; NCT02536105; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Nikles 2006; Weiss 2021; Wigal 2013; Wigal 2014; Wigal 2015
Had been receiving methylphenidate > 6 months, or daily dose was above dose specified in the research protocol	1	Musten 1997
Previous pharmacological treatment for ADHD	23	Barragán 2017; Buitelaar 1995; Coghill 2007; Cook 1993; Corkum 2008; Corkum 2020; Flapper 2008; Froehlich 2018; Kollins 2006 (PATS); Konrad 2004; Oesterheld 1998; Perez-Alvarez 2009; Ramtvedt 2013; Schachar 1997a; Szobot 2008; Taylor 1987; Tirosh 1993a; Tirosh 1993b; Tucker 2009; Urman 1995; Van der Meere 1999a; Wallander 1987; Zeiner 1999
Any medical/physical disease	10	Castellanos 1997; Flapper 2008; Perez-Alvarez 2009; Pliszka 1990; Pliszka 2000; Quinn 2004; Swanson 1998; Swanson 2002a; Wilkison 1995; Zeiner 1999
Any ongoing chronic condition, or poor physical health, or somatic disorder/medical condition that could contraindicate treatment or confound efficacy or safety, or physical disability, or their medical condition affecting cognitive or neuropsychological performance	92	Barragán 2017; Bedard 2008; Biederman 2003b; Borcherding 1990; Brams 2008; Brams 2012; Brown 1985; Carlson 2007; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Connor 2000; Cox 2006; CRIT124US02; Douglas 1995; Fabiano 2007; Findling 2006; Findling 2007; Findling 2008; Gadow 1990; Gadow 1995; Gadow 2007; Gadow 2011; Gonzalez-Heydrich 2010; Gorman 2006; Greenhill 2002; Greenhill 2006; Hale 2011; Hawk 2018; Heriot 2008; Horn 1991; Huang 2021; Ialongo 1994; Jacobi-Polishook 2009; Jensen 1999 (MTA); Kelly 1989; Kollins 2006 (PATS); Kollins 2021; Lin 2014; Lopez 2003; Lufi 1997; Martins 2004; Matthijssen 2019; McCracken 2016; Musten 1997; NCT00409708; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Oesterheld 1998; Pearson 2013; Pelham 2001a; Pelham 2011; Pelham 2014; Pliszka 2017; Riggs 2011; Schachar 1997a; Schachar 2008; Schulz 2010; Sharp 1999; Shiels 2009; Silva 2005a; Silva 2006; Silva 2008; Smithee 1998; Solanto 2009; Stein 2003; Stein

Table 3. Key inclusion and exclusion criteria *(Continued)*

		2011; Sumner 2010; Swanson 2004b; Tannock 1989; Tannock 1992; Tannock 1993; Tannock 1995a; Tannock 1995b; Tannock 2018; Tirosh 1993a; Tirosh 1993b; Tourette's Syndrome Study Group 2002; Van der Meere 1999a; Weiss 2021; Wigal 2003; Wigal 2013; Wigal 2014; Wigal 2015; Wigal 2017; Wilens 2008; Wilens 2010; Wolraich 2001; Zeni 2009
Cardiac abnormalities or cardiac surgery, or clinically significant abnormalities in ECG results, or family history of sudden death or long-QT syndrome, or ventricular arrhythmia, or hypertension, or hypotension, or bradycardia, or syncope	50	Arnold 2004; Barkley 1989b; Barkley 1991; Barkley 2000; Blum 2011; Brams 2012; Buitelaar 1995; Carlson 1995; Childress 2009; Childress 2017; Childress 2020a; Childress 2020b; Childress 2020c; Coghill 2013; Döpfner 2004; DuPaul 1996; Duric 2012; Findling 2008; Findling 2010; Froehlich 2018; Lin 2014; McCracken 2016; NCT02293655; NCT02536105; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Overtoom 2003; Palumbo 2008; Pelham 2001a; Pelham 2011; Quinn 2004; Riggs 2011; Schrantee 2016; Stein 2011; Sumner 2010; Swanson 1998; Swanson 2002a; Swanson 2004b; Tannock 1989; Tourette's Syndrome Study Group 2002; Tucker 2009; Weiss 2021; Wigal 2003; Wigal 2004; Wigal 2011; Wigal 2013; Wigal 2014; Wigal 2015; Wilens 2006b; Wilens 2010
History or evidence of renal disease or impaired renal function	6	Arnold 2004; Childress 2020c; Palumbo 2008; Quinn 2004; Tourette's Syndrome Study Group 2002; Wigal 2004
History or evidence of hepatic disease	2	Childress 2020c; Döpfner 2004
History or evidence of respiratory (other than asthma/allergy) disease	5	Arnold 2004; Buitelaar 1995; Childress 2020c; Quinn 2004; Wigal 2004
History or evidence of endocrine disease (e.g. hyperthyroidism) or insulin dependent diabetes or any metabolic disease	16	Arnold 2004; Barkley 2000; Buitelaar 1995; Childress 2020a; Childress 2020c; Corkum 2008; Corkum 2020; Greenhill 2002; NCT00409708; NCT02536105; Schrantee 2016; Swanson 2004b; Weiss 2021; Wigal 2003; Wigal 2004; Wigal 2015
History or evidence of immune disease	3	Arnold 2004; Childress 2020c; Wigal 2004
Gastrointestinal narrowing, or significant gastrointestinal problems	7	Childress 2020c; Coghill 2013; Huang 2021; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Wigal 2011; Wilens 2006b
Glaucoma	19	Blum 2011; Childress 2020a; Childress 2020c; Coghill 2013; Greenhill 2002; Huang 2021; Kent 1995; NCT02536105; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Schrantee 2016; Swanson 2004b; Weiss 2021; Wigal 2003; Wigal 2011; Wigal 2013; Wigal 2015; Wilens 2006b; Wolraich 2001
Not within 30% of normal body weight, or outside 18/22-59/75 kg at trial entry, or underweight or overweight or weighs less than 9 kg or 79.5 lb, or weight < 3rd percentile for age	16	Arnold 2004; Carlson 2007; Childress 2020a; Childress 2020b; Coghill 2013; Döpfner 2004; Findling 2008; Gonzalez-Heydrich 2010; Lin 2014; Murray 2011; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Oesterheld 1998; Pearson 2013; Pliszka 2017; Wigal 2004
Pregnant or lactating or inadequate form of birth	41	Barkley 2000; Biederman 2003b; Brams 2008; Brams 2012; Childress 2009; Childress 2020a; Childress 2020b; Coghill 2013; CRIT124US02; Findling 2006; Findling 2007; Findling 2008; Findling 2010; Gonzalez-Heydrich 2010;

Table 3. Key inclusion and exclusion criteria *(Continued)*

control or female who had undergone menarche		Greenhill 2002; Greenhill 2006; McCracken 2016; Muniz 2008; NCT02293655; NCT02536105; Newcorn 2017a (flexible dose); Newcorn 2017b (forced dose); Oesterheld 1998; Palumbo 2008; Pelham 2001a; Pliszka 2017; Riggs 2011; Silva 2005a; Silva 2006; Silva 2008; Stein 2011; Sumner 2010; Swanson 2004b; Tourette's Syndrome Study Group 2002; Weiss 2021; Wigal 2003; Wigal 2004; Wigal 2015; Wilens 2010; Wolraich 2001; Zeni 2009
Abnormal laboratory parameters and/or vital signs and/or physical examination	15	Brams 2012; Findling 2008; Greenhill 2002; Greenhill 2006; McGough 2006; NCT02536105; Oesterheld 1998; Overtoom 2003; Pelham 2011; Pliszka 2017; Swanson 1998; Tucker 2009; Weiss 2021; Wigal 2015; Wigal 2017

ADHD: Attention deficit hyperactivity disorder; **CD:** conduct disorder; **CNS:** central nervous system; **ECG:** electrocardiogram; **IQ:** Intelligence quotient; **ODD:** oppositional defiant disorder

[a]Severe learning disability (defined by special education enrolment).
[b]Exceptions: obsessive-compulsive disorder, conduct or oppositional disorder, overanxious disorder and specific developmental disorders.
[c]Only bipolar disorder, not major depressive disorder.

Table 4. ADHD symptoms rating scales

Name of scale	Abbreviation	Reference
Abbreviated Conners' Rating Scales, Parent (ACPRS) and Teacher (ACTRS), including Abbreviated Parent Rating Scale (APRS) and Teacher Rating Scale, Hyperkinesis Index and ADHD and Emotional Lability subscales	ACRS	Conners 1997a
Abbreviated Symptom Questionnaire, including ASQ Teacher and ASQ Parent	ASQ	Conners 1995
Academic Performance Rating Scale	APRS	DuPaul 1991a
The ADD/H Comprehensive Teacher Rating Scale	ACTeRS	Ullmann 1984
ADHD/ODD Rating Scale, Parent- and Teacher-Rated	ADHD-RS	Barkley 1998
ADHD Rating Scale, including ADHD Rating Scale Parent and Teacher Ratings	ADHD-RS	DuPaul 1991a
ADHD Rating Scale-IV, including ADHD Rating Scale-IV Parent and Teacher Versions	ADHD-RS-IV	DuPaul 1991a
Brief Psychiatric Rating Scale for Children	BPRS	Gale 1986
Child Attention Problems Rating Scale	CAP	Achenbach 1986
Child Attention Profile	CAP	Barkley 1988b
Child Behavior Rating Form	NCBHF	Aman 1996
Child Symptom Inventory	CSI	Gadow 1994
Children's Psychiatric Rating Scale	CPRS	Pfefferbaum-Levine 1983
Conners' Abbreviated Hyperactivity Questionnaire	C-HI	Conners 1997a

Table 4. ADHD symptoms rating scales *(Continued)*

Conners' Abbreviated Questionnaire	ASQ	Conners 1995
Conners' Abbreviated Parent Teacher Questionnaire	APTQ	Rowe 1997
Conners' Abbreviated Rating Scale	ABRS	Conners 1997a
Conners' Abbreviated Symptom Questionnaire	ASQ	Conners 1995
Conners Abbreviated Symptom Questionnaire for Parents	ASQ-Parent	Conners 1995
Conners' Abbreviated Symptom Questionnaire for Teachers	ASQ-Teacher	Conners 1997a
Conners' Abbreviated Teacher Rating Scale	ABTRS	Conners 2001
Conners' ADHD/DSM-IV Scales Adolescent	CADS-A	Conners 1997b
Conners' ADHD/DSM-IV Scales Parent	CADS–P, CADS-P DSM-IV	Conners 1997a
Conners' ADHD/DSM-IV Scale Teacher, including Inattentive and Hyperactive-Impulsive subscales	CADS-T, CADS-T DSM-IV	Conners 1997a
Conners' Rating Scale - Revised, Parent and Teacher: Hyperactivity and Conduct Factors score	CPRS-R and CTRS-R	Goyette 1978
Conners' Hyperactivity Index, Parent and Teacher, including abbreviated versions	CPRS/CTRS-Hyperactivity index	Conners 1997a
Conners' Hyperkinesis Index	-	Milich 1980
Conners, Loney and Milich Scale	CLAM	Milich 1980
Conners' Parent and Teacher Rating Scale - Revised, Short Form	CRS-R:S	Conners 1997a
Conners' Parent Rating Scale, including abbreviated versions	CPRS	Conners 1998b
Conners' Parent Rating Scale - Revised	CPRS-R	Conners 1997a
Conners' Parent Rating Scale - Revised, Short Form	CPRS-R:S	Conners 1997a
Conners' Parent Rating Scale - Revised, Long Version	CPRS-R:L	Conners 1997a
Conners' Rating Scale - Revised	CRS-R	Conners 1997a
Conners' Short Form Rating Scale, Parent and Teacher	-	Conners 1997a
Conners' Teacher Rating Scale	CTRS	Conners 1998a
Conners' Teacher Rating Scale - Revised, Long Version	CTRS-R:L	Conners 1998a
Diagnostic and Statistical Manual of Mental Disorders Total	DSM-IV	APA 1994
Diagnostiksystem für Psychische Störungen im Kindes - und Jugendalter nach ICD-10 und DSM-IV	DISYPS	Döpfner 2000
Parental Questionnaire of ADHD symptoms		

Table 4. ADHD symptoms rating scales *(Continued)*

Fremdbeurteilungsbogen für Hyperkinetische Störungen	FBB-HKS	Döpfner 2008
German Teacher's report on ADHD symptoms	FBB-HKS of the DISYPS	Döpfner 2000
Hyperactivity Index of the Revised Conners Parent and Teacher Rating Scales	-	Goyette 1978
IOWA Conners Parent Rating Scale, including abbreviated versions	IOWA CPRS	Loney 1982
IOWA Conners Teacher Rating Scale, including abbreviated versions	IOWA CTRS	Loney 1982
IOWA Conners Teacher Rating Scale, Inattention/Overactivity (I/O) and Oppositional/Defiant (O/D) subscales	IOWA-I/O and O/D subscales	Loney 1982
IOWA Inattention/Overactivity and Aggression/Noncompliance scales - Parent and Teacher rating	IOWA	Loney 1982
Lehrer-Fragenbogen von Steinhausen	LF	Steinhausen 1993
Loney's Time on Task Scale, Hyperactivity, Attention and Aggression subscales	TOTS	Fitzpatrick 1992b
Modified Conner Scale Parent and Teacher	ACR	Conners 1997a
Mothers' Objective Method for Subgrouping	MOMS	Loney 1984
Parent Symptom Checklist	PSC ADHD	Döpfner 2000
Parental Account of Children's Symptoms	PACS	Chen 2006
Restricted Academic Situation Scale	RASS	Fischer 1998
Schedule for Affective Disorders and Schizophrenia	K-SADS/ K-SADS-E for diagnosis	Chambers 1985
Swanson, Nolan, and Pelham - IV SNAP-ADHD Rating scale	SNAP-ADHD	Swanson 1992
Swanson, Nolan, and Pelham - IV SNAP-IV (Brazilian Version)	SNAP-IV	Clark 1993; Clark 1996
Swanson, Kotkin, Atkins, M-Flynn, Pelham Scale (SKAMP combined, SKAMP attention, and SKAMP deportment)	SKAMP (SKAMP combined, SKAMP attention, and SKAMP deportment)	Wigal 1998; Murray 2009
Teacher Self-control Rating Scale	SCRS	Kendall 1979
Turgay - DSM-IV Scale, Parent	T-DSM-IV Scale, Parent	Turgay 1994; Ercan 2001
Turgay - DSM-IV Scale, Teacher	T-DSM-IV Scale, Teacher	Turgay 1994; Ercan 2001
Teacher Hyperactivity Index	THI	Achenbach 1991b
Teacher Symptom Checklist	TSC	Döpfner 2000
Vanderbilt ADHD Rating Scale	VADP(T)RS	Wolraich 2003

Table 4. ADHD symptoms rating scales *(Continued)*

Wender Utah Rating Scale	WURS	Ward 1993
Wide Range Achievement Test	WRAT-4	Wilkinson 2006
Wide Range Achievement Test Revised	WRAT-R	Woodcock 2001

ADD/H: Attention deficit disorder/with hyperactivity; **ADHD:** Attention deficit hyperactivity disorder; **DSM-IV:***Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; **ICD-10:***International Classification of Diseases, Tenth Edition*; **ODD:** ODD

Table 5. General behaviour rating scales

Name of scale	Abbreviation	Reference
Achenbach Child Behaviour Checklist	CBCL	Achenbach 1991a
Achenbach's Teacher Report	ATRF	Achenbach 1991b; Achenbach 2001
ADHD Rating Scale	ADHD-RS	DuPaul 1991a
ADHD School Observation Code	ADHD-SOC	Gadow 1996
Barkley Scales, Disruptive Behavior Disorders Rating Scale	-	Barkley 1991a
Before School Functioning Questionnaire	BSFQ	Faraone 2018
Behavior Rating Inventory of Executive Function	BRIEF	Gioia 2000
Child Attention Problems Scale	CAP	Barkley 1991
Child Attention Profile	CAP	Barkley 1988b
Child Behavior Checklist	CBCL	Achenbach 1991a
Child Health Questionnaire	CHQ	Landgraf 1998
Child and Adolescent Psychiatric Assessment, selected items	CAPA	Angold 1995
Children's Psychiatric Rating Scale	CPRS	Fish 1985
Classroom Observation Code (Abikoff Classroom Observational System)	COC	Abikoff 1980
Code for Observing Social Activity	COSA	Sprafkin 1986
Conners' Child Behavior Scale	UC-CCBS	Ladd 1996
Conners Early Childhood Behavior—Parent Short Response scale	-	Conners 2009
Conners' Global Index Scale	CGI-S	Conners 1998a
Conners' Global Index - Parent	CGI-P	Conners 1997a
Conners' Global Index - Teacher	CGI-T	Conners 1998a

Table 5. General behaviour rating scales *(Continued)*

Conners', Loney and Milich Scale	CLAM	Milich 1980
Conners' Parent Questionnaire	CPQ	Conners 1995
Conners' Parent Rating Scale	CPRS	Conners 1998b
Conners' Teacher Rating Scale	CTRS	Conners 1998a
Conners' Teacher Rating Conduct Problems	-	Miller 1997
Disruptive Behavior Disorders Rating Scale, Parent- and Teacher-Rated	DBS	Mendelsohn 1978
Disruptive Behavior Disorders Rating Scale	DBD	Silva 2005b
Groninger Behaviour Observation Scale	GOO and GBO	Van der Meere 1999b
Groninger Behaviour Checklists, Parent and Teacher Versions of the abbreviated Groninger	GGGS and GGBS	Van der Meere 1999b
Hillside Behavior Rating Scale	HBRS	Gittleman-Klein 1976
Home Situations Questionnaire	HSQ	Barkley 1987
Home Situations Questionnaire - Revised	HSQ-R	DuPaul 1992
Humphrey's Teacher Self-Control Rating Scale	TSCRS	Humphrey 1982
Hyperactivity Index from the Conners Revised Teacher Rating Scale	CTRS-R-Hyperactivity Index	Goyette 1978
Impairment Rating Scale	IRS	Fabiano 2006
Inpatient Global Rating Scale, Revised	IGRS	Conners 1985
Inpatient Global Rating Scale, Somatic factor	IGRS-S	Conners 1985
IOWA Conners' Rating Scale, Oppositional/Defiant (O/D) subscales	IOWA-O/D subscales	Loney 1982
Nisonger Child Behavior Rating Form	NCBRF	Aman 1996
Paired Associates Learning	PAL	Wechsler 1945
Parent Global Assessment for Improvement	PGA	McGough 2006a
Parent Rating of Evening and Morning Behavior-Revised, Morning	PREMP-R AM	Sutton 2003
Parent Rating of Evening and Morning Behavior-Revised, Evening	PREMP-R PM	Sutton 2003
Peer Conflict Scale	PCS	Marsee 2007
Personality Inventory for Children	PIC	Lachar 1986
School Situations Questionnaire	SSQ	Barkley 1987
School Situations Questionnaire - Revised	SSQ-R	DuPaul 1992

Table 5. General behaviour rating scales *(Continued)*

Retrospective Modified Overt Aggression Scale	R-MOAS	Bladder 2009
Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale, Parent and Teacher	SWAN	Swanson 2006; Polderman 2007
Subjective Treatment Emergent Symptom Scale	STESS-R	Guy 1976
Swanson, Nolan and Pelham, Fourth Edition	SNAP-IV	Bussing 2008
Teachers Report Form	TRF	Achenbach 1991b
Telephone Interview Probe (Parent and Teacher)	TIP	Corkum 2007
Vanderbilt ADHD rating scales: Vanderbilt ADHD Diagnostic Parent Rating Scale and Vanderbilt ADHD Diagnostic Teacher Rating Scale	VADPRS and VADTRS	Wolraich 2003
Wahler, House and Stambaugh's Ecobehavioral Assessment System	ECO	Wahler 1976
The Weekly Parent Ratings of Evening and Morning Behaviour	WREMB-R	Kelsey 2004
Werry-Weiss-Peters Activity Rating Scale	WWP	Routh 1978
Woodcock-Johnson Achievement Battery	WJ-III Ach	Woodcock 2001

ADHD: attention deficit hyperactivity disorder

Table 6. Quality of life ratings scales

Name of scale	Abbreviation	Reference
ADHD Impact Module-Child	AIM-C	AIM-C 2013
Child Impact Scale and Home Impact Scale	CIS/HIS	Landgraf 2002
Child Health and Illness Profile, Child Edition: Parent Report Form	CHIP-CE:PRF	Riley 2004
Child Health Questionnaire	CHQ-P	Landgraf 1998
Children's Global Assessment Scale	CGAS	Shaffer 1983
Comprehensive Psychopathological Rating Scale	CPRS	Aasberg 1978
Health Utilities Index - 2	HUI-2	Torrance 1982
The parent- and child-rated Revised questionnaire for Children and adolescents to record health-related quality of life	KINDL-R	Ravens-Sieberer 1998

ADHD: attention deficit hyperactivity disorder

APPENDICES

Appendix 1. Search strategies

Database	Search strategy
Cochrane Central Register of Controlled Trials (CENTRAL; Cochrane Library)	#1 MeSH descriptor: [Methylphenidate] explode all trees #2 (methylphenidate):ti,ab,kw #3 adaphen or adhansia or addwize or aptensio or artige or attenta or biphentin or calocain or centredrin or concerta or cotempla #4 daytrana or dexmethylphenidat* or difumenil or elmifiten or equasym or focalin or foquest or inspiral or jornay or matoride or medikid or medikinet* #5 meridil or metadate or methyl phenidat* or methyl phenidylacetat* or methylfenid* or methylin or methylofenidan or methylphenid* or methyl phenid* #6 methyl phenidyl acetat* or methypatch or metidate or metilfenidat* or motiron* or MPH or omzin or penid* or phenid* or phenidyl hydrochlorid* or phenidylat* or plimasin #7 PMS-methylphenid* or prohiper or quasym* or quilli* or relexxii or Richter Works or riphenidat* or ritalin* or rubifen or stimdat* or tifinidat or tradea or tranquilyn or tsentedrin #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Child] explode all trees #10 MeSH descriptor: [Adolescent] explode all trees #11 MeSH descriptor: [Infant] explode all trees #12 (child* OR boy* OR girl* OR adolescen* OR teen* OR preschool OR pre school OR infant* OR baby OR babies OR toddler* OR school child* or youth*) #13 #9 or #10 or #11 #12 #14 #8 and #13 #15 MeSH descriptor: [Attention Deficit and Disruptive Behavior Disorders] explode all trees #16 adhd or addh or adhs or add #17 (((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))):ti,ab,kw (Word variations have been searched) #18 ((impulsiv* or inattentiv* or inattention*)):ti,ab,kw (Word variations have been searched) #19 MeSH descriptor: [Hyperkinesis] explode all trees #20 (hyperkine*):ti,ab,kw (Word variations have been searched) #21 ((minimal near/3 brain near/3 (disorder* or dysfunct* or damage*))):ti,ab,kw (Word variations have been searched) #22 ((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw (Word variations have been searched) #23 (hyperactiv*):ti,ab,kw #24 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 #25 #14 and #24

(Continued)

#26 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE, drug effects - DE, chemically induced - CI]

#27 ((safe or safety or adverse or tolerability or toxicity or toxic or adrs or adr or tolerance or tolerate or harm or harms or harmful or complication* or risk or risks)):ti,ab,kw (Word variations have been searched)

#28 (side next effect*):ti,ab,kw

#29 (undesirable next effect*):ti,ab,kw (Word variations have been searched)

#30 (treatment next emergent):ti,ab,kw (Word variations have been searched)

#31 (unintended next event):ti,ab,kw (Word variations have been searched)

#32 (unintended next effect):ti,ab,kw (Word variations have been searched)

#33 #26 or #27 or #28 or #29 or #30 or #31 or #32 827410

#34 MeSH descriptor: [Mood Disorders] explode all trees

#35 (depression or depressive):ti,ab,kw (Word variations have been searched)

#36 MeSH descriptor: [Psychotic Disorders] explode all trees

#37 (psychosis or (psychotic near/4 symptom*)):ti,ab,kw (Word variations have been searched)

#38 MeSH descriptor: [Body Weight] explode all trees

#39 MeSH descriptor: [Anorexia] explode all trees

#40 ((loss or lose or losing or decreas* or reduc*) near/3 (weight or appetite)):ti,ab,kw (Word variations have been searched)

#41 ((reduc* or retard* or inhibit* or deficit*) near/4 growth):ti,ab,kw (Word variations have been searched) 5140

#42 MeSH descriptor: [Hypertension] explode all trees

#43 MeSH descriptor: [Heart Rate] explode all trees

#44 MeSH descriptor: [Tachycardia] explode all trees

#45 MeSH descriptor: [Death] explode all trees

#46 (death):ti,ab,kw (Word variations have been searched)

#47 MeSH descriptor: [Infertility] explode all trees

#48 MeSH descriptor: [Carcinogens] explode all trees

#49 ((increas* near/4 (heart rate or pulse or blood pressure))):ti,ab,kw (Word variations have been searched)

#50 ((((loss or reduc*) near/4 fertility) or infertility)):ti,ab,kw (Word variations have been searched)

#51 MeSH descriptor: [Neoplasms] explode all trees

#52 (((risk near/2 cancer) or (cytogenetic near/2 effect*))):ti,ab,kw (Word variations have been searched)

#53 #33 or #34 or #35 or #36 or #37 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52

#54 #8 and #13 and #24

#55 #8 and #13 and #53

(Continued)

	#56 #54 or #55 with Publication Year from 2015 to 2021, in Trials
Ovid MEDLINE	1 exp "Attention Deficit and Disruptive Behavior Disorders"/
	2 adhd.mp.
	3 addh.mp.
	4 adhs.mp.
	5 "add".mp.
	6 (ad adj hd).mp. (
	7 ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).mp.
	8 ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).mp.
	9 (impulsiv* or inattentiv* or inattention*).mp.
	10 hyperactiv*.mp.
	11 hyperkinesis*.mp.
	12 exp Hyperkinesis/
	13 (minimal adj brain adj3 disorder*).mp.
	14 (minimal adj brain adj3 dysfunction*).mp.
	15 (minimal adj brain adj3 damage*).mp.
	16 or/1-15
	17 randomized controlled trial.pt.
	18 controlled clinical trial.pt.
	19 randomized controlled trials.mp.
	20 exp Randomized Controlled Trial/
	21 random allocation.mp. or Random Allocation/
	22 double blind method.mp.
	23 single blind method.mp.
	24 clinical trial.pt.
	25 (clin* adj25 trial*).ab,ti.
	26 ((singl* or doubl* or tripl* or trebl*) adj25 (blind* or mask* or dumm*)).mp.
	27 exp Clinical Trial/
	28 placebos.mp.
	29 "placebo*".ab,ti.
	30 "random*".ab,ti.
	31 comparative study.mp.
	32 comparative trial.mp.

(Continued)

33 Evaluation Studies as Topic/

34 exp Clinical Trials as Topic/

35 follow up studies.mp.

36 prospective studies.mp.

37 (control* or prospectiv* or volunteer*).ab,ti.

38 or/17-37

39 methylphenidate.mp. or exp Methylphenidate/

40 adaphen.mp.

41 adhansia.mp.

42 addwize.mp.

43 aptensio.mp.

44 artige.mp.

45 attenta.mp.

46 biphentin.mp.

47 calocain.mp.

48 centedrin*.mp.

49 concerta*.mp.

50 cotempla.mp.

51 daytrana.mp.

52 dexmethylphenidat*.mp.

53 difumenil.mp.

54 elmifiten.mp.

55 equasym*.mp.

56 elmifiten*.mp.

57 focalin.mp.

58 focalin*.mp.

59 foquest.mp.

60 inspiral.mp.

61 jornay.mp.

62 matoride.mp.

63 medikid.mp.

64 medikinet*.mp.

65 meridil.mp.

66 metadate*.mp.

(Continued)

67 methyl phenidat*.mp.

68 methyl phenid*.mp.

69 methyl phenidylacetat*.mp.

70 methylfenid*.mp.

71 methylin*.mp.

72 methylofenid*.mp.

73 methylphenid*.mp.

74 methyl phenid*.mp.

75 methypatch.mp.

76 metidate.mp.

77 metilfenidat*.mp.

78 motiron*.mp.

79 MPH.mp.

80 omozin*.mp.

81 penid*.mp.

82 phenida.mp.

83 phenidyl hydrochlorid*.mp.

84 phenidylat*.mp.

85 phenidyl*.mp.

86 plimasin*.mp.

87 PMS-methylphenid*.mp.

88 prohiper.mp.

89 quazym*.mp.

90 quilli*.mp.

91 relexxii.mp.

92 Richter Works.mp.

93 riphenidat*.mp.

94 ritalin*.mp.

95 rubifen*.mp.

96 stimdat*.mp.

97 tifinidat*.mp.

98 tradea.mp.

99 tranquilyn.mp.

100 tsentedrin*.mp.

(Continued)

101 or/39-100

102 exp Child/

103 exp Adolescent/

104 exp Infant/

105 (child* or boy* or girl* or adolescen* or teen* or preschool* or pre school or infant* or baby or babies or

toddler* or school child* or youth* or young).mp.

106 or/102-105

107 16 and 38 and 101 and 106

108 (ae or co or de).fs.

109 (((safe or safety or (side adj1 effect*) or undesirable) adj1 effect*) or (treatment adj1 emergent) or

tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*)).mp. or (un-intendend adj1 effect*).ab,ti.

110 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ab,ti.

111 Methylphenidate/ae, po, to

112 exp Mood Disorders/

113 (depression or depressive).ab,ti.

114 exp Psychotic Disorders/

115 (psychosis or (psychotic adj4 symptom*)).ab,ti.

116 exp body weight/ or anorexia/

117 ((loss or lose or losing or reduc*) adj3 (weight or appetite)).ab,ti.

118 ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ab,ti.

119 exp Hypertension/

120 Heart Rate/

121 Tachycardia/

122 (increas* adj4 (heart rate or pulse or blood pressure)).ab,ti.

123 exp Death, Sudden/

124 death.ab,ti.

125 exp Infertility/

126 (((loss or reduc*) adj4 fertility) or infertility).ab,ti.

127 exp Carcinogens/

128 exp Neoplasms/

129 ((risk adj2 cancer) or (cytogenic adj2 effect*)).ab,ti.

130 or/108-129

(Continued)

	131 38 and 101 and 106 and 130
	132 107 or 131
	133 101 and 106 and 130
	134 16 and 101 and 106 and 38
	135 131 or 134
	136 limit 135 to yr="2015 -Current"
Embase (Ovid)	1 exp attention deficit disorder/
	2 adhd.ti,ab.
	3 addh.ti,ab.
	4 ADHS.ti,ab.
	5 (ad adj HD).ti,ab.
	6 "(ADD)".mp.
	7 ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).ti,ab.
	8 ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).ti,ab.
	9 (impulsiv* or inattentiv* or inattention*).ti,ab.
	10 exp hyperactivity/
	11 hyperkinesia/
	12 "hyperactiv*".ti,ab.
	13 "hyperkinesis*".ti,ab.
	14 (minimal adj brain adj3 disorder*).ti,ab.
	15 (minimal adj brain adj3 dysfunction*).ti,ab.
	16 (minimal adj brain adj3 damage*).ti,ab.
	17 or/1-16
	18 exp methylphenidate/ or methylphenidate.mp.
	19 adaphen.mp.
	20 adhansia.mp.
	21 addwize.mp.
	22 aptensio.mp.
	23 artige.mp.
	24 attenta.mp.
	25 biphentin*.mp.
	26 calocain.mp.
	27 centedrin*.mp.

(Continued)

28 concerta*.mp.

29 cotempla.mp.

30 daytrana.mp.

31 dexmethylphenidat*.mp.

32 difumenil*.mp.

33 elmifiten*.mp.

34 equasym.mp.

35 focalin*.mp.

36 foquest.mp.

37 inspiral.mp.

38 jornay.mp.

39 matoride.mp.

40 medikid.mp.

41 medikinet*.mp.

42 meridil.mp.

43 metadate.mp.

44 methyl phenidat*.mp.

45 methyl phenidylacetat*.mp.

46 methylfenid*.mp.

47 methylin*.mp.

48 methylofenid*.mp.

49 methylphenid*.mp.

50 methyl phenidyl acetat*.mp.

51 methypatch.mp.

52 metidate.mp.

53 metilfenidat*.mp.

54 motiron.mp.

55 MPH.mp.

56 omozin*.mp.

57 penid*.mp.

58 phenidyl hydrochlorid.mp.

59 phenidyl hydrochlorid*.mp.

60 phenidyl*.mp.

61 plimasin*.mp.

(Continued)

62 PMS-methylphenid*.mp.

63 quasym.mp.

64 quilli*.mp.

65 relexxii.mp.

66 Richter Works.mp.

67 riphenidat*.mp.

68 ritalin*.mp.

69 rubifen*.mp.

70 stimdat*.mp.

71 tifinidat*.mp.

72 tradea.mp.

73 tranquilyn.mp.

74 tsentedrin*.mp.

75 or/18-62

76 exp child/

77 exp adolescent/

78 exp juvenile/

79 exp infant/

80 (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or young or youth*).mp.

81 76 or 77 or 78 or 79 or 80

82 clinical trial/

83 randomized controlled trial/

84 randomization/

85 single blind procedure/

86 double blind procedure/

87 crossover procedure/

88 placebo/

89 prospective study/

90 (randomi?ed controlled adj1 trial*).ti,tw.

91 rct.ti,tw.

92 randomly allocated.ti,tw.

93 allocated randomly.ti,tw.

94 random allocation.ti,tw.

95 (allocated adj2 random).ti,tw.

(Continued)

96 (single adj1 blind*).ti,tw.

97 (double adj1 blind*).ti,tw.

98 ((treble or triple) adj1 blind*).ti,tw.

99 "placebo*".ti,tw.

100 or/82-99

101 17 and 75 and 81 and 100

102 (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or

tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (un-intended adj1 effect*)).ab,ti.

103 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ab,ti.

104 exp adverse drug reaction/

105 exp side effect/

106 methylphenidate/ae, to [Adverse Drug Reaction, Drug Toxicity]

107 exp mood disorder/si [Side Effect]

108 (depression or depressive).ab,ti.

109 exp psychosis/si [Side Effect]

110 (psychosis or (psychotic adj4 symptom*)).ab,ti.

111 growth retardation/

112 growth inhibition/

113 ((loss or lose or losing or reduc*) adj3 (weight or appetite)).ab,ti.

114 ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ab,ti.

115 hypertension/si [Side Effect]

116 heart rate/

117 cardiovascular effect/

118 tachycardia/si [Side Effect]

119 (increas* adj4 (heart rate or pulse or blood pressure)).ab,ti. (68994)

120 sudden death/

121 death.ab,ti.

122 infertility/si [Side Effect]

123 (((loss or reduc*) adj4 fertility) or infertility).ab,ti.

124 cancer risk/

125 drug carcinogenicity/ or carcinogenicity/

126 chromosome aberration/si [Side Effect]

127 childhood cancer/si [Side Effect]

(Continued)

	128 ((risk adj2 cancer) or (cytogenic adj2 effect*)).ab,ti. 129 or/102-128 130 75 and 81 and 100 and 129 131 101 or 130 132 limit 131 to yr="2015 -Current"
CINAHL (Cumulative Index to Nursing and Allied Health Literature; EBSCOhost)	S1 (MH "Methylphenidate") S2 AB methylphenidate S3 TI methylphenidate S4 S2 OR S3 S5 TI (adaphen or adhansia or addwize or aptensio or artige or attenta or biphentin) OR AB (adaphen or adhansia or addwize or aptensio or artige or attenta or biphentin) S6 TI (calocain or centedrin or concerta or cotempla or daytrana or dexmethylphenidat* or difumenil or elmifiten or equasym or focalin or foquest or inspiral or jornay or motoride ord medikid or medikinet*) OR AB (calocain or centedrin or concerta or cotempla or daytrana or dexmethylphenidat* or difumenil or elmifiten or equasym or focalin or foquest or inspiral or jornay or motoride ord medikid or medikinet*) S7 TI (meridil or metadate or methyl phenidat or methyl phenidylacetat* or methylphenid* or methylfenid* or methylin or methylofenidan or methylphenid* or methyl phenid*) OR AB (meridil or metadate or methyl phenidat or methyl phenidylacetat* or methylphenid* or methylfenid* or methylin or methylofenidan or methylphenid* or methyl phenid*) S8 TI (methylphenidyl acetat* or methypatch or metidate or metilfenidat* or motiron* or MPH or omzin* or penid* or phenid* or phenidyl hydrochlorid* or phenidylat* or plimasin*) OR AB (methylphenidyl acetat* or methypatch or metidate or metilfenidat* or motiron* or MPH or omzin* or penid* or phenid* or phenidyl hydrochlorid* or phenidylat* or plimasin*) S9 TI (PMS-methylphenid* or prohiper or quasym* or quilli* or relexxii or Richter Works or riphenidat* or ritalin* or rubifen or stimdat* or tifinidat or tradea or tranquilyn or tsentedrin) OR AB (PMS-methylphenid* or prohiper or quasym* or quilli* or relexxii or Richter Works or riphenidat* or ritalin* or rubifen or stimdat* or tifinidat or tradea or tranquilyn or tsentedrin) S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 S11 (MH "Child+") OR (MH "Infant+") OR (MH "Adolescence+") S12 TI ((child* OR boy* OR girl* OR adolescen* OR teen* OR preschool OR pre school OR infant* OR baby OR babies OR toddler* OR school child* or youth*)) OR AB ((child* OR boy* OR girl* OR adolescen* OR teen* OR preschool OR pre school OR infant* OR baby OR babies OR toddler* OR school child* or youth*)) S13 S11 OR S12 S14 S10 AND S13 S15 (MH "Randomized Controlled Trials+") OR (MH "Double-Blind Studies") OR (MH "Single-Blind Studies") OR (MH "Random Assignment") OR (MH "Pretest-Posttest Design+") OR (MH "Cluster Sample+") S16 TI randomised or randomized S17 AB random* S18 TI trial

(Continued)

	S19 (MH "Sample Size") AND AB (assigned or allocated or control)
	S20 (MH "Placebos")
	S21 PT Randomized Controlled Trials
	S22 PT randomized controlled trial
	S23 AB control W5 group
	S24 (MH "Crossover Design") OR (MH "Comparative Studies+")
	S25 AB cluster W3 RCT
	S26 (MH "Animals+")
	S27 (MH "Animal Studies")
	S28 TI animal model*
	S29 S26 OR S27 OR S28
	S30 (MH "Human")
	S31 S29 NOT S30
	S32 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
	S33 S32 NOT S31
	S34 S14 AND S33
	S35 S14 AND S33
PsycINFO (Ovid)	1 exp Attention Deficit Disorder/
	2 adhd.ab,ti.
	3 addh.ab,ti.
	4 ADHS.ab,ti.
	5 (AD adj HD).ab,ti.
	6 "ADD".ab,ti.
	7 ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).ab,ti.
	8 ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).ab,ti.
	9 (impulsiv* or inattentiv* or inattention*).ab,ti.
	10 "hyperactiv*".ab,ti.
	11 hyperkinesis.ab,ti.
	12 exp HYPERKINESIS/
	13 (minimal adj brain adj3 disorder*).ab,ti.
	14 (minimal adj brain adj3 dysfunction*).ab,ti.
	15 (minimal adj brain adj3 damage*).ab,ti.
	16 or/1-15

(Continued)

17 exp Treatment Effectiveness Evaluation/

18 exp "Treatment outcomes"/

19 Placebo/

20 Followup Studies/

21 placebo*.ab,ti.

22 random*.ab,ti.

23 comparative stud*.ab,ti.

24 (clinical adj3 trial*).ab,ti.

25 (research adj3 design).ab,ti.

26 (evaluat* adj3 stud*).ab,ti.

27 (prospectiv* adj3 stud*).ab,ti.

28 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ab,ti.

29 or/17-28

30 methylphenidate.mp. or exp METHYLPHENIDATE/

31 adaphen.mp.

32 adhansia.mp.

33 addwize.mp.

34 aptensio.mp.

35 artige.mp.

36 attenta.mp.

37 biphentin.mp.

38 calocain.mp.

39 centedrin.mp.

40 concerta.mp.

41 cotempla.mp.

42 daytrana.mp.

43 dexmethylphenidat*.mp.

44 difumenil.mp.

45 elmifiten.mp.

46 equasym*.mp.

47 focalin*.mp.

48 foquest.mp.

49 inspiral.mp.

50 jornay.mp.

(Continued)

51 matoride.mp.

52 medikid.mp.

53 medikinet*.mp.

54 meridil.mp.

55 metadate*.mp.

56 methyl phenidat*.mp.

57 methyl phenidylacetat*.mp.

58 methylfenid*.mp.

59 methylin.mp.

60 methylofenidan.mp.

61 methylphenid*.mp.

62 methyl phenid*.mp.

63 methyl phenidyl acetat*.mp.

64 methypatch.mp.

65 metidate.mp.

66 metilfenidat*.mp.

67 motiron*.mp.

68 MPH.mp.

69 omozin.mp.

70 penid*.mp.

71 phenid*.mp.

72 phenidyl hydrochlorid*.mp.

73 phenidylat*.mp.

74 plimasin*.mp.

75 PMS-methylphenid*.mp.

76 prohiper.mp.

77 quasym*.mp.

78 quilli*.mp.

79 relexxii.mp.

80 Richter works.mp.

81 riphenidat*.mp.

82 ritalin*.mp.

83 rubifen.mp.

84 stimdat*.mp.

(Continued)

85 tifinidat.mp.

86 tradea.mp.

87 tranquilyn.mp.

88 tsentedrin*.mp.

89 or/30-88

90 (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or

toddler* or school child* or young or youth*).ab,ti.

91 16 and 29 and 89 and 90

92 exp "Side Effects (Drug)"/

93 (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability

or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (un-intended adj1 effect*)).ab,ti.

94 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ab,ti.

95 92 or 93 or 94

96 exp Major Depression/

97 exp Affective Disorders/

98 (depression or depressive).ab,ti.

99 exp Psychosis/

100 (psychosis or (psychotic adj4 symptom*)).ab,ti.

101 exp Body Weight/

102 exp Appetite Depressing Drugs/

103 exp Appetite/

104 ((loss or lose or losing or reduc*) adj3 (weight or appetite)).mp. [mp=title, abstract, heading word, table of

contents, key concepts, original title, tests & measures, mesh]

105 ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ab,ti.

106 exp Cardiovascular Disorders/

107 exp Heart Rate/

108 exp Heart Rate Affecting Drugs/

109 (increas* adj4 (heart rate or pulse or blood pressure)).ab,ti.

110 exp "Death and Dying"/

111 death.ab,ti.

112 exp Infertility/

(Continued)

	113 exp Fertility/ 114 (((loss or reduc*) adj4 fertility) or infertility).ab,ti. 115 exp Neoplasms/ 116 exp Carcinogens/ 117 ((risk adj2 cancer) or (cytogenic adj2 effect*)).ab,ti. 118 or/96-117 119 29 and 89 and 90 and 118 120 91 or 119 121 limit 120 to yr="2015 -Current"
Epistemonikos	searched with a simple search: (title:((title:(attention deficit OR adhd OR hyperactivity OR hypekinetic) OR abstract:(attention deficit OR adhd OR hyperactivity OR hypekinetic)) AND (title:(methylphenidate OR ritalin OR MPH) OR abstract:(methylphenidate OR ritalin OR MPH)) AND ((title:children OR child OR young OR youth OR adolescent) OR abstract:(children OR child OR young OR youth OR adolescent))) 2015-2021 Combined with search for ten published reviews where all included studies for each review where downloaded if possible. 1. Catala-Lopez F, Hutton B, Nunez-Beltran A, et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: A systematic review with network meta-analyses of randomised trials. PLOS ONE 2017;12:e0180355. doi: 10.1371/journal.pone.0180355 2. Cerrillo-Urbina AJ, Garcia-Hermoso A, Pardo-Guijarro MJ, et al. The effects of long-acting stimulant and nonstimulant medications in children and adolescents with attention-deficit/hyperactivity disorder: A meta-analysis of randomized controlled trials. J Child Adolesc Psychopharmacol 2018;28:494-507. doi: 10.1089/cap.2017.0151 3. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 2018;5:727-38. doi: 10.1016/s2215-0366(18)30269-4 4. Holmskov M, Storebø OJ, Moreira-Maia CR, et al. Gastrointestinal adverse events during methylphenidate treatment of children and adolescents with attention deficit hyperactivity disorder: A systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. PLOS ONE 2017;12:e0178187. doi: 10.1371/journal.pone.0178187 5. Kemper AR, Maslow GR, Hill S, et al. AHRQ Comparative Effectiveness Reviews Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 [Available from: Available from: https://www.ncbi.nlm.nih.gov/books/NBK487761/. 6. Liu H, Feng W, Zhang D. Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis. Eur Child Adolesc Psychiatry 2019;28:1283-93. doi: 10.1007/s00787-018-1217-x 7. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev 2018;6:Cd007990. doi: 10.1002/14651858.CD007990.pub3

(Continued)

	8. Punja S, Xu D, Schmid CH, et al. N-of-1 trials can be aggregated to generate group mean treatment effects: a systematic review and meta-analysis. J Clin Epidemiol 2016;76:65-75. doi: 10.1016/j.jclinepi.2016.03.026 9. Ramstad E, Storebø OJ, Gerner T, et al. Hallucinations and other psychotic symptoms in response to methylphenidate in children and adolescents with attention-deficit/hyperactivity disorder: a Cochrane systematic review with meta-analysis and trial sequential analysis. Scandinavian Journal of Child and Adolescent Psychiatry and Psychology 2018;6(1):52-71. doi: https://doi.org/10.21307/sjcapp-2018-003 10. Solmi M, Fornaro M, Ostinelli EG, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry 2020;19(2):214-32. doi: https://doi.org/10.1002/wps.20765
CPCI-S (Conference Proceedings Citation Index - Science); CPCI-SSH (Conference Proceedings Citation Index - Social Science & Humanities) (Web of Science)	#2 AND #1 #2 TS=(child* or boy* or girl* or adolescen* or teen* or preschool* or "pre school*" or infant* or baby or babies or toddler* or "school child*" or schoolchild* or youth*) #1 TS=(Methylphenidate or Attenta or Biphentin or Calocain or Centedrin* or Concerta or Daytrana or Dexmethylphenidat* or Elmifiten or Equasym or Focalin or Medikid or Medikinet or Meridil or Metadate or "Methyl phenidat*" or "Methyl phenidylacetat" or Methylfenid or Methylin or Methylofenidan or Methylphenid* or "Methyl phenidyl acetat*" or Methypatch or Metilfenidato or Motiron or MPH or Penid or Omozin or Quazym or "Phenidyl hydrochlorid*" or Phenidylat* or Plimasin* or "PMS-Methylphenid* " or "Richter Works" or Riphenidat* or Ritalin* or Rubifen or Stimdat* or Tifinidat or Tranquilyn or Tsentedrin*)
ClinicalTrials.gov	Advanced search: Methylphenidate OR concerta OR daytrana OR dexmethylphenidate OR equasym OR focalin OR medikinet OR MPH OR Ritalin Studies with results Age group: Child Studies With Results | Methylphenidate OR concerta OR daytrana OR dexmethylphenidate OR equasym OR focalin OR medikinet OR MPH OR Ritalin | Child Applied Filters: With Results Child (birth–17)
WHO ICTRP (World Health Organisation International Clinical Trials Registry Platform; who.int/ictrp/en)	Methylphenidate OR concerta OR daytrana OR dexmethylphenidate OR equasym OR focalin OR medikinet OR MPH OR Ritalin Children
NDLTD (Networked Digital Library of Theses and Dissertations; ndltd.org/)	methylphenidate AND child* AND (attention deficit or hyperactiv*)
DART-Europe E-theses Portal (https://www.dart-europe.org/basic-search.php)	methylphenidate AND child*
Thesis Canada (https://library-archives.canada.ca/eng/services/services-libraries/theses/Pages/theses-canada.aspx)	methylphenidate

(Continued)

Worldcat (https://www.worldcat.org/search?q=methylphenidate)	methylphenidate

Appendix 2. Letter to pharmaceutical companies

Date: September 2021

The Cochrane Methylphenidate Group

Psychiatric Research Unit

Fælledvej 6

4200 Slagelse, Denmark

Ole Jakob Storebø

Email: ojst@regionsjaelland.dk

Phone: +45 24965917

To whom it might concern,

Regarding: Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – a Cochrane systematic review.

On behalf of the Cochrane Methylphenidate Group we address you in order to request your assistance. We are presently updating our systematic review on the effects of methylphenidate for children and adolescents with ADHD, first version published in 2015 [1, 2]. We are entrusted the elaboration of this review by the Cochrane Developmental, Psychosocial and Learning Problems Group, and it has become relevant to update the review with new randomized clinical trials and data.

The Cochrane systematic review intends to include all relevant literature empirically describing both the positive and negative effects of the treatment. We believe the elaboration of this review is in common interest of patients, physicians and manufacturers of methylphenidate. The results from the first version of the review has been cited 202 times (Cochrane version), 129 (BMJ version), and applied into 7 guidelines. By updating the review, it will continue to be applicable to guide authorities, clinicians and researchers when it comes to considering the use of methylphenidate in the treatment for children and adolescents with ADHD.

For the original version of the review, we contacted authors of significant publications, experts in the field and pharmaceutical companies, asking for information on possible relevant clinical trials. We did this because the published literature only provides us with limited and possibly selective knowledge, as it is unlikely that all studies and data are available through these databases. In 2015 we received many additional possible relevant studies for screening. We are now using the same approach for the update of the Cochrane review and are hoping that you will be as forthcoming in assisting us in our work to include published as well as unpublished studies.

We hope you will assist us with providing data that are relevant for our review. As previously noted, we are interested in data regarding both positive and negative effects of methylphenidate from randomized clinical trials, regardless of the year the data was recorded or published.

It is important for us to point out that we are not investigating specific methylphenidate preparations but simply the effect of the active substance, methylphenidate. Thus, we will not refer to or recommend any specific methylphenidate preparation or drug company. However, as we did in 2015 we will state which companies we had been in contact with, and which of these who have assisted us with data.

If possible, we would be very pleased to meet a representative from your company.

Enclosed to this letter are a list of the currently included studies in our review.

We are hoping to hear from you. If you have any questions, please contact us.

With best wishes

On behalf of the study authors

Ole Jakob Storebø, Project coordinator, Ph.D, Research Manager at Center for Evidence Based Psychiatry, Psychiatric Research Unit and senior researcher at Department of Child and Adolescent Psychiatry, Region Zealand. Professor at Department of Psychology, University of Southern Denmark, Odense, Denmark.
Phone: +45 24965917 E-mail: ojst@regionsjaelland.dk

Erik Simonsen, Medical Director, PhD, Dr.h.c. Psychiatric Research Unit, Region Zealand. Professor at Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

Christian Gluud, MD, Dr, Med, Sci, Head of Department, Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital − Rigshospitalet, Denmark. Professor at Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.

1. Storebø, O.J.; Ramstad, E.; Krogh, H.B.; Nilausen, T.D.; Skoog, M.; Holmskov, M.; Rosendal, S.; Groth, C.; Magnusson, F.L.; Moreira-Maia, C.R.; Gilles, D. et al. Methylphenidate for children and adolescents with attention deficit hyperac-tivity disorder (ADHD). Cochrane Database Syst. Rev. 2015, CD009885, doi:10.1002/14651858.cd009885.pub2.

2. Cochrane Central Register of Controlled Trials (CENTRAL) part of the Cochrane Library, MEDLINE, PsycINFO, EMBASE, CINAHL, ISI Conference Proceedings Citation Index (Science, and Social Science and Humanities), Clinical Trials.gov, and International Clinical Trials Registry Platform (ICTRP)

Appendix 3. Data extraction sheet RCTs: parallel-group trials

Version 09.04.2014

Source

Trial ID (e.g. Plizska 2000)
Trial registry with ID *Search* clinicaltrials.gov*(from 2008 -) and* who.int/ictrp/en *(from 2004 -)*
Full citation
Form filled by
Author contact information
Other publications on same trial

ID: identifier.

Eligibility

Confirm eligibility	Yes No Awaiting assessment

Correspondence

Correspondence required

Method

Cluster-randomised	Yes/no Intervention (n (number)) =, control (n) =
Location (e.g. hospital, out-clinic)	-
Summary (method)	Parallel trial with 2 arms: 1. Methylphenidate 2. Control

Participants

Summary (participants)	Number of participants screened
	Number of participants included
	Number of participants randomly assigned to methylphenidate and control
	Number of participants followed up in each arm: methylphenidate and control
	Number of withdrawals in each arm: Methylphenidate and control
	Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) diagnosis of attention deficit hyperactivity disorder (ADHD) (combined (%), hyperactive-impulsive (%), inattentive (%))
	Age (years) (mean, range)
	IQ (mean, range)
	Sex (male, female)
	Methylphenidate naive (%/number)
	Ethnicity (white (%), African American (%), Asian (%), Hispanic (%), other (%))
	Country
	Comorbidity (type %)
	Comedication (no/yes)
	Sociodemographics (e.g. double or single parent family, low, middle or upper class)
	Inclusion criteria
	Exclusion criteria

Interventions

Participants were randomly assigned to type of (e.g. immediate-release (IR), extended-release (ER)) (dex-) methylphenidate or control
Methylphenidate dosage: Mean (standard deviation (SD))
Administration schedule: time points
Duration of intervention
Titration period: none/duration initiated before/after randomisation
Treatment compliance

Outcome listing

(Our outcomes according to our protocol: short, general description)
ADHD symptoms
Measure instrument (e.g. ADHD Rating Scale (ADHD-RS); Swanson, Kotkin, Atkins, M-Flynn and Pelham (SKAMP) Scale), parent-/teacher-/independent assessor-rated, time point
General behaviour
Measure instrument (e.g. Child Behavior Checklist (CBCL)), parent-/teacher-/independent assessor-rated, time point
Quality of life
Measure instrument, parent-/teacher-/independent assessor-rated, time point
Serious adverse events
Type of outcome/adverse event, measure method/instrument, parent-/teacher-/independent assessor-rated, time point
Non-serious adverse events
Type of outcome/adverse event, measure method/instrument, parent-/teacher-/independent assessor-rated, time point

Outcomes (positive effects)

e.g. copy of table from article

Outcomes (adverse events)

e.g. copy of table from article

Outcomes specified	Type of adverse events/ responses	Total numbers	Mean	SD	Time point
Serious adverse events (temporal association, but not necessarily causal relationship)					
Serious adverse reaction (response to the drug)					
Non-serious adverse events (temporal association)					

Risk of bias

Item	Quote	Risk of bias (high, unclear, low)
Random sequence generation/generation of allocation sequence (selection bias)		

(Continued)

Allocation concealment (selection bias)	
Blinding of participants and personnel (performance bias)	
Blinding of outcome assessment (detection bias)	
Incomplete outcome data (intention-to-treat (ITT), imputation method) (attrition bias)	
Selective outcome reporting (according to protocol?)	
Vested interest	
Other sources of bias	Authors' affiliations (e.g. Novartis) Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders)

Notes

Sample calculation
Ethics approval
Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate
Any withdrawals due to adverse events
Comments from trial authors
Key conclusions of trial authors
Comments from review authors
Supplemental information/data received through personal email correspondence with trial authors in *month* 2014

Appendix 4. Data extraction sheet RCTs: cross-over trials

Version 09.04.2014

Source

Trial ID (e.g. Plizska 2000)
Trial registry with ID *Search* clinicaltrials.gov*(from 2008 -) and* who.int/ictrp/en*(from 2004 -)*
Full citation

(Continued)

Form filled by	Date and name
Author contact information	
Other publications on same trial	

ID: identifier

Eligibility

Confirm eligibility	Yes No Awaiting assessment

Correspondence

Correspondence required	Data for each intervention period

Method

Cluster-randomised	Yes/No Intervention (number (n)) =, control (n) =
Location (e.g. hospital, out-clinic)	
Ethics approval	Yes/No/No information
Summary (method)	Cross-over trial with 2 interventions: 1. Methylphenidate 2. Control Phases

Participants

Summary (participants)	Number of participants screened Number of participants included Participants were randomly assigned to 1 of X possible drug condition orders Number of participants followed up Number of withdrawals

(Continued)

	Diagnostic and Statistical Manual of Mental Disorders (DSM) or *International Classification of Diseases* (ICD) diagnosis of attention deficit hyperactivity disorder (ADHD) (combined (%), hyperactive-impulsive (%), inattentive (%))
	Age (years) (mean, range)
	IQ (mean, range)
	Sex (male, female)
	Methylphenidate naive (%/number)
	Ethnicity (white (%), African-american (%), Asian (%), Hispanic (%), other (%))
	Country
	Comorbidity (type %)
	Comedication (no/yes)
	Sociodemographics (e.g. double- or single-parent family, low, middle or upper class)
	Inclusion criteria
	Exclusion criteria

Interventions

Participants were randomly assigned to 1 of X possible drug condition orders of methylphenidate and control
Methylphenidate dosage: mean (standard deviation (SD))
Administration schedule: time points
Duration of each medication condition
Washout before trial initiation
Medication-free period between interventions
Titration period: none/duration initiated before/after randomisation
Treatment compliance

Outcome listing

(Our outcomes according to our protocol: short, general description)
ADHD symptoms
Measure instrument (e.g. ADHD Rating Scale (ADHD-RS), Swanson, Kotkin, Atkins, M-Flynn and Pelham (SKAMP) scale), parent-/teacher-/independent assessor-rated, time point
General behaviour
Measure instrument (e.g. Child Behavior Checklist (CBCL)), parent-/teacher-/independent assessor-rated, time point
Quality of life
Measure instrument, parent-/teacher-/independent assessor-rated, time point
Serious adverse events
Type of outcome/adverse event, measure method/instrument, parent- /teacher-/independent assessor-rated, time point
Non-serious adverse events
Type of outcome/adverse event, measure method/instrument, parent- /teacher-/independent assessor-rated, time point

Outcomes (positive effects)

e.g. copy of table from article

Outcomes (adverse events)

e.g. copy of table from article

Outcomes specified	Types of adverse events/ responses	Total numbers	Mean	SD	Time point
Serious adverse events (temporal association, but not necessarily causal relationship)					
Serious adverse reaction (response to the drug)					
Non-serious adverse events (temporal association)					

Risk of bias

Item	Quote	Risk of bias (high, unclear, low)
Random sequence generation/generation of allocation sequence (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data (intention-to-treat (ITT), imputation method) (attrition bias) Exclusion of placebo responders etc.: methylphenidate non-responders (after randomisation)		
Selective outcome reporting (according to protocol?)		
Vested interest		
Other sources of bias	Authors' affiliations (e.g. Novartis) Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders)	

Notes

Sample calculation
Ethics approval
Comments from trial authors
Key conclusions of trial authors
Comments from review authors
Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate
Any withdrawals due to adverse events
Supplemental information/data received through personal email correspondence with trial authors in *month* 2014

FEEDBACK

Comments on the BMJ version of this review, 29 November 2016

Summary

Fazel M. Methylphenidate for ADHD. BMJ 2015;351:h5875. [DOI: 10.1136/bmj.h5875]. Available from bmj.com/content/351/bmj.h5875.long

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Kremer HJ. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 27 November 2015. Available from bmj.com/content/351/bmj.h5203/rr-0

Chandrasekaran V, Mahadevan S. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 29 November 2015. Available from bmj.com/content/351/bmj.h5203/rr-1

Büchter RB, Thomas S. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 10 December 2015. Available from bmj.com/content/351/bmj.h5203/rr-3

Saripanidis S. Management and treatment of hyperactivity and ADHD, without methylphenidate [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 27 December 2015. Available from bmj.com/content/351/bmj.h5203/rr-5

Banaschewski T, Buitelaar J, Chui CSL, Coghill D, Cortese S, Simonoff E, et al, on behalf of the European ADHD Guidelines Group. Are Methylphenidate Effects in Children with ADHD Really Uncertain? [personal communication]. Response to Storebø OJ, Krogh HB, Ramstad E, Moreira-Maia CR, Holmskov M, Skoog M, et al. 27 July 2016. Available from bmj.com/content/351/bmj.h5203/rr-6

Reply

Storebø OJ, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: E Grant, HJ Kremer, V Chandrasekaran, S Mahadevan. 30 November 2015. Available from bmj.com/content/351/bmj.h5203/rr-2

Storebø OJ, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: RB Büchter, S Thomas. 22 December 2015. Available from bmj.com/content/351/bmj.h5203/rr-4

Storebø OJ, Zwi M, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: T Banaschewski, J Buitelaar, CSL Chui, D Coghill, S Cortese, E Simonoff, et al. 29 July 2016. Available from bmj.com/content/351/bmj.h5203/rr-9

Storebø OJ, Zwi M, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: T Banaschewski, J Buitelaar, CSL Chui, D Coghill, S Cortese, E Simonoff. 29 July 2016. Available from bmj.com/content/351/bmj.h5203/rr-10

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Mental Elf Blog, 29 November 2016

Summary

Hollis C. Methylphenidate for ADHD: have Cochrane got it wrong this time? [personal communication]. Response to: Storebø OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, et al. 10 March 2016. Available from nationalelfservice.net/mental-health/adhd/methylphenidate-for-adhd-have-cochrane-got-it-wrong-this-time

Reply

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Hollis C. Re: Methylphenidate for ADHD: have Cochrane got it wrong this time? [personal communication]. Response to: OJ Storebø, C Gluud. April 2016. Availabe from nationalelfservice.net/mental-health/adhd/methylphenidate-for-adhd-have-cochrane-got-it-wrong-this-time/#comment-1007912

Storebø OJ, Gluud C. Re: Methylphenidate for ADHD: have Cochrane got it wrong this time? [personal communication]. Response to: C Hollis. April 2016. Available from nationalelfservice.net/mental-health/adhd/methylphenidate-for-adhd-have-cochrane-got-it-wrong-this-time/#comment-1008187

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Comments on the JAMA version of this review, 29 November 2016

Summary

Shaw P. Quantifying the benefits and risks of Methylphenidate as treatment for childhood attention-deficit/hyperactivity disorder. JAMA. 2016;315(18):1953-5. [DOI:10.1001/jama.2016.3427]. Available from jamanetwork.com/journals/jama/article-abstract/2520612

Romanos M, Reif A, Banaschewski T. Methylphenidate for attention-deficit/hyperactivity disorder. JAMA. 2016;316(9):994-5. [DOI:10.1001/jama.2016.10279]. Available from jamanetwork.com/journals/jama/article-abstract/2547744

Reply

Storebø OJ, Simonsen E, Gluud C. Methylphenidate for attention-deficit/hyperactivity disorder — Reply. JAMA. 2016;316(9):995. [DOI:10.1001/jama.2016.10300]. Available from jamanetwork.com/journals/jama/article-abstract/2547750

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Author 2: Erik Simonsen, Psychiatric Research Unit, Region Zealand, Denmark.
Author 3: Christian Gluud, Copenhagen Trial Unit, Copenhagen, Denmark.

Other comments on this review published elsewhere, 29 November 2016

Summary

Mulder R, Hazell P, Rucklidge JJ, Malhi GS. Methylphenidate for attention-deficit/hyperactivity disorder: too much of a good thing? Australian & New Zealand Journal of Psychiatry 2016;50(2):113–4. [DOI: 10.1177/0004867415626823] Available from anp.sagepub.com/search/results?fulltext=storebo&x=0&y=0&submit=yes&journal_set=spanp&src=selected&andorexactfulltext=and

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Reply

Storebø OJ, Simonsen E, Gluud C. The evidence base of methylphenidate for children and adolescents with attention-deficit hyperactivity disorder is in fact flawed. European Child & Adolescent Psychiatry 2016;25(9):1037–8. [DOI:10.1007/s00787-016-0855-0]. Available from link.springer.com/article/10.1007/s00787-016-0855-0

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Storebø OJ, Gluud C. Re: Trust, but verify. The errors and misinterpretations in the Cochrane analysis by O. J. Storebo and colleagues on the efficacy and safety of methylphenidate for the treatment of children and adolescents with ADHD [personal communication]. Response to: T Banaschewskl, M Gerlach, K Becker, M Holtmann, M Döpfner, M Romanos. 24 June 2016. Available from ncbi.nlm.nih.gov/pubmed/27270192#cm27270192_16360

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*Typo in article. Author's name should be reported as Groth C.

WHAT'S NEW

Date	Event	Description
27 March 2023	New citation required but conclusions have not changed	Twenty-nine new studies included in the review
27 March 2023	New search has been performed	Updated following a new search in January 2021 and a top-up search in March 2022

HISTORY

Protocol first published: Issue 5, 2012
Review first published: Issue 12, 2015

Date	Event	Description
29 November 2016	Feedback has been incorporated	This review was published in the Cochrane Library on 25 November 2015, with abridged versions appearing in the BMJ on 26 November 2015 and JAMA on 10 May 2016. These abridged reviews have received many comments in editorials, 'letters to the editor', articles, rapid responses, and blogs. Interestingly, however, no comment has been directed to the full review in the Cochrane Library. In order to inform readers of the Cochrane Library, we have provided the links to these comments, as well as review authors' responses, in the Feedback section below.

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OJS has overall responsibility for the review and is a guarantor for the review.

OJS developed the design of the review and was responsible for the co-ordination of the review.

CG, ES and MZ updated the background sections of the review.

OJS, HEC, JPS, JPR, MROS, PDR, and CMLH selected the studies.

MROS, CMLH, JPR, JPS, MS, and OJS extracted data and evaluated risk of bias.

OJS and HEC assessed the certainty of the body of evidence.

OJS, CGl and HEC interpreted the data.

OJS and CGl developed the analytical strategy.

MS, HEC, JPR, JPS, MROS, and OJS entered data into Review Manager 5.

OJS, MS, RK, HEC, JPR, and MROS conducted the statistical analysis.

All review authors participated in discussion and writing of the final review.

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Morris Zwi (MZ) is a Child and Adolescent Psychiatrist working part time in private practice; previously, he worked exclusively for the NHS for 32 years, before retiring. He is a former Editor for CDPLP and occasionally is consulted by the group for his expertise; however, he was not involved in the editorial process for this review and it has been over one year since he did any editorial work. MZ declares a payment from the Paediatric Medicines Expert Advisory Board of the Medicines and Healthcare Products Regulatory Agency for his attendance at their monthly/bimonthly (i.e. every two months) meetings.

Richard Kirubakaran: has declared that he has no conflicts of interest.

Erik Simonsen: has declared that he has no conflicts of interest.

Christian Gluud: is the Co-ordinating Editor of the Cochrane Hepato-Biliary Group. He has declared that he has no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Psychiatric Research Unit, Region Zealand Psychiatry, Roskilde, Denmark

  Ole Jakob Storebø, Johanne Pereira Ribeiro, Julie Schaug, Maja Rosenberg Overby Storm, and Erik Simonsen worked on this review during office hours
- Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Denmark

Christian Gluud worked on this review during office hours

External sources

- None, Other

N/A

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods

Criteria for considering studies for this review

Types of studies

We split the review into two systematic reviews to make the review more manageable. The Storebø 2015a review deals with benefits and harms of methylphenidate as reported by RCTs. Storebø 2018b assessed the risk of harms based on the findings of non-randomised studies.

Types of participants

We decided to include trials in which at least 75% of participants were 18 years of age or younger, and the mean age of the trial population was 18 years of age or younger. We included two trials with such participants. These two trials included a few participants at 19 and 20 years of age and we thought it was better to include these trials than to exclude them. The effects of methylphenidate intervention on any outcome did not change when these two trials were removed from the analysis.

We decided to include trials in which at least 75% of participants had a normal intellectual quotient (IQ > 70). We included four trials with such participants. These four trials included a few participants with IQ below 70 and we thought it was better to include these trials than to exclude them. The effects of methylphenidate intervention on any outcome did not change when these four trials were removed from the analysis.

Types of outcome measures. Duration of studies

We changed the subdivision of duration from short term (≤ 6 months), medium term (6 to 12 months) and long term (> 12 months) to short term (≤ 6 months) and long term (> 6 months) because no trials had a duration of between 6 and 12 months. Only one trial (Jensen 1999 (MTA)), provided data on a duration longer than six months (14 months). We included the change in duration classification in analyses of ADHD symptoms and general behaviour.

Search methods for identification of studies Electronic searches

We did not search OpenGrey as this database closed down in 2020. We did not contact the medical authorities in the European Union for information about beneficial and adverse events. We did not ask for access to security updates and risk management plans of pharmaceutical companies due to lack of time and resources.

Data collection and analysis

Selection of studies and data extraction and management

More review authors than stated in the protocol screened titles and abstracts, extracted data, entered data into Review Manager 5 and conducted statistical analyses in Review Manager 5 (Review Manager 2020). More authors were added to the review as it became a bigger review than we expected at the protocol stage.

Measures of treatment effect. Continuous data

For the primary outcome of teacher-rated attention deficit hyperactivity disorder (ADHD) symptoms, we recalculated the standardised mean difference (SMD) as mean difference (MD) on the ADHD-Rating Scale (DuPaul 1991a), to check whether our result exceeded the minimum clinically important difference (MCID; Zhang 2005), for this specific rating scale. This was not stated in the protocol (Storebø 2012).

For the secondary outcome of quality of life, we recalculated the SMD as MD on the Child Health Questionnaire (Landgraf 1998), to check whether our results exceeded the MCID (Rentz 2005) for this specific rating scale. This was not stated in the protocol (Storebø 2012).

Dealing with missing data

We tried to obtain missing data by contacting the authors of the trials that we included in this review. When we were not able to obtain missing data, we conducted the analyses using the available (incomplete) data. We had intended to assess the impact of missing data by applying intention-to-treat as well as 'best-case scenario' and 'worst-case scenario' analyses. We could not use 'best-case scenario' and 'worst-case scenario' analyses in our assessment of benefits as there were no dichotomous outcomes. We decided not to use 'best-case scenario' and 'worst-case scenario' analyses in our assessment of adverse events, because we evaluated these analyses to be imprecise

due to the high number of trials not reporting adverse events, and due to the high number of dropouts in the trials reporting adverse events. Moreover, we were unable to conduct intention-to-treat analyses for continuous outcomes due to lack of data for imputing means.

Data synthesis. Heterogeneity-adjusted required information size and Trial Sequential Analysis

We performed a Trial Sequential Analysis on the total number of serious adverse events and on the total number of non-serious adverse events only, as they were the only outcomes with dichotomous data with a substantial number of outcomes. Trial Sequential Analysis can be conducted on individual types of adverse events, but for this, the accrued information would represent a minute fraction of the required information size (RIS). We were not able to conduct a Trial Sequential Analysis for teacher-, independent assessor- or parent-rated outcomes, as the programme can be used only for MDs, not for SMDs.

Subgroup analysis and investigation of heterogeneity

We planned few subgroup analyses in our protocol. Due to large methodological and clinical heterogeneity in the included trials, we decided to conduct several post-hoc subgroup analyses.

1. Types of scales (e.g. Conners' Teacher Rating Scale (CTRS; Conners 1998a) compared to Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale (Swanson 2006). We did this subgroup analysis to test the potential differences in effect estimates between the numerous scales measuring comparable content.
2. Dose of methylphenidate (low dose (≤ 20 mg/d or ≤ 0.6 mg/kg/day) compared to moderate/high dose (> 20 mg/day or > 0.6 mg/kg/day)). We did this subgroup analysis to test the potential differences in effect estimates between doses, as this is very relevant for clinicians and patients.
3. Duration of treatment (short-term trials (≤ 6 months) compared to long-term trials (> 6 months)). We did this subgroup analysis to test the potential differences in effect estimates between short- compared to long-term trials.
4. Trial design (parallel-group trials compared to cross-over trials (first period data and endpoint data)). We conducted this subgroup analysis as we pooled first-period data with parallel-group data and we used end-of-period data from cross-over trials without adjusting for unit of analysis error.
5. Medication status before randomisation (medication-naive (> 80% of included participants were medication-naive) compared to not medication-naive (< 20% of included participants were medication-naive)). We did this subgroup analysis to test the potential differences in effect estimates between medication-naïve and not medication-naïve participants, as this is very relevant for clinicians and patients.
6. Risk of bias (trials at low risk of bias compared to trials at high risk of bias). We did this subgroup analysis to test the potential differences in effect estimates between trials at low risk of bias compared to those at high risk of bias.
7. Cohort selection bias (trials with enrichment design compared to trials without enrichment design). We did this subgroup analysis to test the potential differences in effect estimates between the trials that had used the enrichment design to those that did not use this design.
8. Vested interest (trials at high or unclear compared to trials at low risk of vested interests). There is empirical evidence showing that trials funded by industry might overestimate the benefits compared to trials not funded by industry and therefore we wanted to do this subgroup analysis.
9. Type of control group (trials with placebo control group compared to trials with no-intervention control group). We wanted to test the impact of choice of control group on estimated intervention effects.

Differences between this update and the original review

Methods

Search methods for identification of studies. Electronic searches

We updated the search strategy to include additional brand names for methylphenidate. Instead of conducting two separate searches for efficacy and adverse effects, we combined these into a single search. We also added a new source of systematic reviews (Epistemonikos) for reference list checking.

Data collection and analysis. Assessment of risk of bias in included studies. Vested interests

We did not evaluate vested interest as a risk of bias domain in this update as this is not recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Results

Description of studies

During this update, we found that one of the included trials was actually a subpublication of another trial (Bhat 2020). Therefore, the number of trials from the 2015 version is only 184 trials. Furthermore, we excluded one of the studies awaiting classification due to ineligible study design. Two studies that were included in the 2015 review based on reports of preliminary data had their study ID changed to match

the primary reference included in the present version (Bhat 2020; Hawk 2018). One additional trial had its primary reference and study ID changed for naming consistency (Wigal 2011).

Included studies

In the 2015 version of this review (Storebø 2015b), we did not describe the trials that did not contribute to the analyses because they had no usable data. We have now added this information to the Included studies section and also made reference to these trials in the 'Main results' section of the abstract and additional Table 2.

Risk of bias in included studies

We did not assess all trials included in the 2015 review for enrichment (evaluated under the 'Notes' heading in all inclusion tables) and 'Selection bias' (evaluated under incomplete outcome data bias in all bias assessment tables). However, in this update, we reassessed all trials to include both of these assessments consistently throughout the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Attention Deficit Disorder with Hyperactivity [drug therapy]; *Central Nervous System Stimulants [adverse effects]; Cross-Over Studies; *Methylphenidate [adverse effects]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Female; Humans; Male