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Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents (Review)

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[Intervention Review]

Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents

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ABSTRACT

Background

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric conditions affecting children and adolescents. Amphetamines are among the most commonly prescribed medications to manage ADHD. There are three main classes of amphetamines: dexamphetamine, lisdexamphetamine and mixed amphetamine salts, which can be further broken down into short- and long-acting formulations. A systematic review assessing their efficacy and safety in this population has never been conducted.

Objectives

To assess the efficacy and safety of amphetamines for ADHD in children and adolescents.

Search methods

In August 2015 we searched CENTRAL, Ovid MEDLINE, Embase, PsycINFO, ProQuest Dissertation and Theses, and the Networked Digital Library of Theses and Dissertations. We also searched ClinicalTrials.gov, and checked the reference lists of relevant studies and reviews identified by the searches. No language or date restrictions were applied.

Selection criteria

Parallel-group and cross-over randomized controlled trials (RCTs) comparing amphetamine derivatives against placebo in a pediatric population (< 18 years) with ADHD.

Data collection and analysis

Two authors independently extracted data on participants, settings, interventions, methodology, and outcomes for each included study. For continuous outcomes, we calculated the standardized mean difference (SMD) and for dichotomous outcomes we calculated the risk ratio (RR). Where possible, we conducted meta-analyses using a random-effects model. We also performed a meta-analysis of the most commonly reported adverse events in the primary studies.

Main results

We included 23 trials (8 parallel-group and 15 cross-over trials), with 2675 children aged three years to 17 years. All studies compared amphetamines to placebo. Study durations ranged from 14 days to 365 days, with the majority lasting less than six months. Most studies

were conducted in the United States; three studies were conducted across Europe. We judged 11 included studies to be at a high risk of bias due to insufficient blinding methods, failing to account for dropouts and exclusions from the analysis, and failing to report on all outcomes defined a priori. We judged the remaining 12 studies to be at unclear risk of bias due to inadequate reporting.

Amphetamines improved total ADHD core symptom severity according to parent ratings (SMD -0.57; 95% confidence interval (CI) -0.86 to -0.27; 7 studies; 1247 children/adolescents; very low quality evidence), teacher ratings (SMD -0.55; 95% CI -0.83 to -0.27; 5 studies; 745 children/adolescents; low quality evidence), and clinician ratings (SMD -0.84; 95% CI -1.32 to -0.36; 3 studies; 813 children/adolescents; very low quality evidence). In addition, the proportion of responders as rated by the Clinical Global Impression - Improvement (CGI-I) scale was higher when children were taking amphetamines (RR 3.36; 95% CI 2.48 to 4.55; 9 studies; 2207 children/adolescents; very low quality evidence).

The most commonly reported adverse events included decreased appetite, insomnia/trouble sleeping, abdominal pain, nausea/vomiting, headaches, and anxiety. Amphetamines were associated with a higher proportion of participants experiencing decreased appetite (RR 6.31; 95% CI 2.58 to 15.46; 11 studies; 2467 children/adolescents), insomnia (RR 3.80; 95% CI 2.12 to 6.83; 10 studies; 2429 children/adolescents), and abdominal pain (RR 1.44; 95% CI 1.03 to 2.00; 10 studies; 2155 children/adolescents). In addition, the proportion of children who experienced at least one adverse event was higher in the amphetamine group (RR 1.30; 95% CI 1.18 to 1.44; 6 studies; 1742 children/adolescents; low quality evidence).

We performed subgroup analyses for amphetamine preparation (dexamphetamine, lisdexamphetamine, mixed amphetamine salts), amphetamine release formulation (long acting versus short acting), and funding source (industry versus non industry). Between-group differences were observed for proportion of participants experiencing decreased appetite in both the amphetamine preparation (P < 0.00001) and amphetamine release formulation (P value = 0.008) subgroups, as well as for retention in the amphetamine release formulation subgroup (P value = 0.03).

Authors' conclusions

Most of the included studies were at high risk of bias and the overall quality of the evidence ranged from low to very low on most outcomes. Although amphetamines seem efficacious at reducing the core symptoms of ADHD in the short term, they were associated with a number of adverse events. This review found no evidence that supports any one amphetamine derivative over another, and does not reveal any differences between long-acting and short-acting amphetamine preparations. Future trials should be longer in duration (i.e. more than 12 months), include more psychosocial outcomes (e.g. quality of life and parent stress), and be transparently reported.

PLAIN LANGUAGE SUMMARY

Amphetamines for attention deficit hyperactivity disorder in children and adolescents

Background
Attention deficit hyperactivity disorder (ADHD) is a common problem affecting children and adolescents. ADHD is characterized by inattention (being easily distracted, unable to focus on one task), impulsivity (fidgety; constantly moving), and hyperactivity (impatient; acts without thinking). One of the most common treatments for managing ADHD is the drug class of amphetamines, which are a class of stimulant medications. They are thought to reduce the severity of symptoms associated with ADHD.

Review question

Do children and adolescents (under 18 years of age) diagnosed with ADHD benefit from treatment with amphetamines to reduce the core symptoms of ADHD, compared to other children and adolescents who receive no drug or a fake drug (placebo)?

Study characteristics
As of August 2015, we identified 23 randomized controlled trials (RCTs: a type of scientific experiment in which people are randomly assigned to one of two or more treatments), which included 2675 children and adolescents between three years and 17 years of age. These studies compared amphetamines to placebo. Three different kinds of amphetamines were investigated: dexamphetamine, lisdexamphetamine and mixed amphetamine salts. The duration of the included studies ranged from 14 days to 365 days. The RCTs were conducted in the United States and Europe.

Key results
We found that amphetamines were effective at improving the core symptoms of ADHD in the short term, but that they were also linked to a higher risk of experiencing adverse events such as sleep problems, decreased appetite, and stomach pain. We found no evidence that one kind of amphetamine was better than another, and found no difference between amphetamines that act for longer periods of time versus those that act for shorter periods of time.

Quality of the evidence

The quality of the included studies was low to very low because of problems in their design and large differences between the studies. Well-designed and clearly reported RCTs that are longer in duration are needed, so we may better understand the long-term effects (both positive and negative) of amphetamines.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Amphetamines compared with placebo for attention deficit hyperactivity disorder in children and adolescents

Patient or population: children or adolescents with ADHD

Settings: Beligum, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Spain, Sweden, United Kingdom, United States

Intervention: amphetamines (i.e. dexamphetamine, lisdexamphetamine, mixed amphetamine salts)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Amphetamine				
Total ADHD symptom score - parent ratings (ADHD Rating Scale, Fourth Version; Conners' Rating Scale; Conners' Global Index; Conners' Abbreviated Symptom Questionnaire) Follow-up: 7 to 49 days	-	The mean total score in the intervention groups was **0.57 standard deviations lower** (-0.86 to -0.27)	**SMD** -0.57 (-0.86 to -0.27)	1247 (7)	⊕⊖⊖⊖ **Very low** [1,2,3]	Moderate effect**
Total ADHD symptom score - teacher ratings (ADHD Rating Scale, Fourth Version; Conners' Rating Scale; Conners' Global Index; Conners' Abbreviated Symptom Questionnaire) Follow-up: 7 to 35 days	-	The mean total score in the intervention groups was **0.55 standard deviations lower** (-0.83 to -0.27)	**SMD** -0.55 (-0.83 to -0.27)	745 (5)	⊕⊕⊖⊖ **Low** [1,2]	Moderate effect**
Total ADHD symptom score - clinician ratings (ADHD Rating Scale, Fourth Version) Follow-up: 7 to 28 days	-	The mean total score in the intervention groups was **0.84 standard deviations lower** (-1.32 to -0.36)	**SMD** -0.84 (-1.32 to -0.36)	813 (3)	⊕⊖⊖⊖ **Very low** [1,2,3]	Large effect**
Proportion of responders (Clinical Global Impressions - Improvement (CGI-I) scale)	**187 per 1000**	**605 per 1000**	**RR 3.36** (2.48 to 4.55)	2207 (9)	⊖⊖⊖⊖ **Very low** [1,2,3,4]	-

Academic performance (Permanent Product Measure of Performance; Wechsler Intelligence Scale for Children - Revised; Barnell Lot, Ltd Math Test; Wide Range Achievement Test) Follow-up: 7 to 21 days	-	The mean score in the intervention groups was **0.51 standard deviations higher** (0.31 to 0.70)	**SMD** 0.56 (0.39 to 0.73)	826 (8)	⊕⊕⊖⊖ **Low** [1,2]	Moderate effect**
Retention: proportion of participants who completed the trial	**825 per 1000**	**864 per 1000**	**RR 1.03** (0.97 to 1.10)	2381 (11)	⊕⊖⊖⊖ **Very low** [1,2,3]	-
Proportion of participants who experienced at least 1 adverse event	**366 per 1000**	**582 per 1000**	**RR 1.30** (1.18 to 1.44)	1742 (6)	⊕⊕⊖⊖ **Low** [1,2]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in the footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Magnitude of effect sizes have been defined according to Cohen 1988 (< 0.2 = small, 0.5 to 0.8 = moderate, > 0.8 = large)

ADHD: Attention deficit hyperactivity disorder; **CI:** Confidence interval; **GRADE:** Grades of recommendation, assessment, development and evaluation; **RR:** Risk ratio; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to the majority of studies included in this outcome having a high risk of bias.
[2] Downgraded one level due to this outcome including comparisons of different amphetamine derivatives and release formulations.
[3]Downgraded one level due to presence of significant statistical heterogeneity (I^2 > 50%).
[4]Downgraded one level due to wide 95% CI indicating that the intervention effect for this outcome is highly variable.

BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) is one of the most common pediatric psychiatric conditions, affecting around 5% of children worldwide (Polanczyk 2007). ADHD is characterized by three core symptoms: inattention, impulsivity and hyperactivity, which are more frequently displayed than would be typical in children of the same age (APA 2000). The core symptoms are often presented to various degrees in different children, breaking ADHD down into three subtypes: the predominantly inattentive type, the predominantly hyperactive-impulsive type, and the combined type (i.e. children displaying both inattention and hyperactivity) (APA 2000). The condition is often diagnosed at a young age, usually between the ages of three and six years (NIMH 2009). The potential for comorbidity is extremely high in this population and comorbidities are present in almost two-thirds of pediatric ADHD cases, with the most common being oppositional defiant disorder (50%), conduct disorder (35%), anxiety disorder (33%), and depression (33%) (AHRQ 1999; Mayes 2009).

The symptoms of ADHD have been shown to permeate a child's performance across multiple settings, having long-term effects on their academic performance and social development. Studies have also shown that children with ADHD are more likely to be irritable, impatient, and aggressive (NIH 2000). In addition, families who have children with ADHD often experience higher levels of parental stress and frustration, marital disruption, and social isolation (Edwards 1995). It has been estimated that 50% of childhood ADHD cases will persist into adolescence and adulthood (Biederman 1993), making it a chronic lifetime condition for many.

Description of the intervention

A wide variety of treatments have been used for the management of ADHD, including psychosocial interventions, dietary management, herbal and homeopathic remedies, and biofeedback. However, for the past few decades, the psychostimulant, methylphenidate, has been the first line of treatment (APA 2000), and has been found to be effective in 70% to 90% of school-aged children (NIH 2000; Wigal 1999). Amphetamines are the second most frequently prescribed psychostimulant for pediatric ADHD, and are becoming an increasingly popular alternative for children who fail to respond to methylphenidate (Buck 2002). There are currently three different amphetamine preparations available, including: dexamphetamine (dextroamphetamine or d-amphetamine sulfate), which comes in both short-acting and long-acting formulations; lisdexamphetamine, which is available as a long-acting formulation (Vyvanase); and mixed amphetamine salts, which also comes in both short-acting as well as long-acting preparations (Buck 2002; The Medical Letter 2007).

How the intervention might work

Although the pathophysiology of ADHD is poorly understood, evidence has suggested that ADHD may be the result of insufficient production of norepinephrine and dopamine in the prefrontal cortex (Arnsten 2006). As such, the executive functions carried out by the prefrontal cortex are impaired, resulting in forgetfulness, distractibility, impulsivity, and inappropriate social behaviours (Anderson 1999). Others believe that the limbic system plays a major role in the pathophysiology of ADHD, and it is thought that hyperactivity and impulsivity result from abnormally low tonic dopamine activity within this region of the brain (Moore 2011). In either case, as a psychostimulant, amphetamines are thought to both promote marked neurotransmitter release into the synaptic cleft as well as disrupt normal reuptake of neurotransmitters, thereby increasing levels of norepinephrine and dopamine in these regions of the brain and affecting executive functioning (Arnsten 2006; Swanson 2007). A Cochrane Review of amphetamines for ADHD in adults found they improved short-term symptom severity (Castells 2011).

Why it is important to do this review

Despite being one of the most thoroughly researched disorders in medicine, one of the major controversies regarding ADHD is the use of psychostimulants as a treatment option. While current evidence suggests that amphetamines may be beneficial for improving the core symptoms of ADHD, their effects on academic and social domains remain inconsistent and unclear (NIH 2000). Wide variations in the use and prescription of amphetamines across communities suggest that there is a lack of consensus among practitioners regarding which people with ADHD should be treated with amphetamines. Charach 2011 and Miller 1999 have conducted reviews assessing amphetamines for pediatric ADHD; however, the former focused only on long-term effectiveness of amphetamines (i.e. > 12 months), while the latter is not only out of date, but also focused solely on the dexamphetamine preparation. It is imperative for healthcare providers, parents, and those diagnosed with ADHD to be aware of the most suitable treatment options available, and how they differ in terms of their efficacy and safety profiles. Our synthesis of all available, randomized controlled trials assessing the efficacy and safety of amphetamines for pediatric ADHD will provide evidence to better inform clinical practice and further research relating to ADHD management. While assessing amphetamines against other ADHD treatments, such as methylphenidate, psychotherapy and antidepressants is important, establishing whether amphetamines are superior to placebo is a necessary first step. Thus, this review will focus only on the amphetamine versus placebo comparison.

OBJECTIVES

To assess the efficacy and safety of amphetamines for ADHD in children and adolescents.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel-group and cross-over randomized controlled trials (RCTs).

Types of participants

Children and adolescents under 18 years of age and diagnosed with ADHD using specified diagnostic criteria such as the *Diagnostic and Statistical Manual of Mental Disorders Third Edition* (DSM-III) (APA 1987), *Fourth Edition* (DSM-IV) (APA 2000), or equivalent (note: since the fifth edition (DSM-5) was released during the conduct of this review, studies utilizing this criteria are not included). We included trials that involved children/adolescents with some comorbid conditions (oppositional defiant disorder, conduct disorder, and anxiety). We excluded trials whose inclusion criteria included children/adolescents with psychiatric comorbidity that require

highly specialized treatment programs (for example, autism, bipolar disorder, and psychosis).

Types of interventions

Intervention

Any oral form of amphetamine (i.e. amphetamine, dexamphetamine, lisdexamphetamine and mixed amphetamine salts), at any dose.

Control

Placebo.

Types of outcome measures

Primary outcomes

1. Change in core ADHD symptoms* (inattention, hyperactivity, impulsivity), as measured by a validated scale rated by children, parents, teachers, clinicians, or investigators such as Conners' Parent Rating Scale - Revised (CPRS-R) (Conners 1998a), Conners' Teacher Rating Scale - Revised (CTRS-R) (Conners 1998b), or the ADHD Rating Scale, Fourth Version (ADHD-RS-IV) (DuPaul 1998).

Secondary outcomes

1. Clinical improvement*, as measured by, for example, the Clinical Global Impression - Improvement scale (CGI-I) (Guy 1976).
2. Clinical severity, as measured by, for example, the Clinical Global Impression - Severity scale (CGI-S) (Guy 1976).
3. Academic performance*, as measured by any validated tool that purports to assess academic performance such as the Wechsler Intelligence Scale for Children (WISC) (Wechsler 1991).
4. Quality of life, as measured by a validated scale such as the Pediatric Quality of Life Inventory - 32 (PedsQL-32) (Varni 1998).
5. Retention: proportion of randomized participants who completed the trial*.
6. Adverse events (such as nausea, insomnia/sleep problems, and decreased appetite).
   a. Proportion of adverse events.
   b. Proportion of participants who experienced at least one adverse event*, as reported in the trials.
   c. Proportion of participants who withdrew due to any adverse event.

Outcomes marked with an asterisk (*) were used to populate Summary of findings for the main comparison.

Time frames were denoted as short term (up to six months), medium term (between six and 12 months), and long term (over 12 months).

See Table 1 for further information.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases in May 2013, July 2014, and again on 12 August 2015.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2015 Issue 7; Ovid), which includes the Specialised Register of the Cochrane Developmental, Psychosocial and Learning Problems Group.
2. Ovid MEDLINE (1948 to Week 1, August 2015).
3. Embase (1974 to Week 1, August 2015; Ovid).
4. PsycINFO (1806 to Week 1, August 2015; Ovid).
5. ProQuest Dissertations and Theses (all available years).
6. Networked Digital Library of Theses and Dissertations (ndltd.org; all available years).
7. ClinicalTrials.gov (clinicaltrials.gov; all available years).

No language or date restrictions were applied.

Please see Appendix 1 to Appendix 7 for our search strategies.

Searching other resources

We inspected the reference lists of identified RCTs and review articles to identify additional publications.

Data collection and analysis

Selection of studies

Two review authors (SP and LS) independently screened all titles and abstracts retrieved from the search to identify those that appeared to meet the inclusion criteria. The same authors then obtained the full-text articles of those studies and assessed their eligibility. Disagreements were resolved by SV.

Data extraction and management

Two review authors (SP and LS) independently extracted data related to study methods, participant characteristics, and outcomes by using a pre-designed data collection form. Disagreements were resolved through discussion. SP entered all relevant data into Review Manager (RevMan 2014).

We emailed study authors up to three times (minimum one month wait between contact) to obtain missing or unclear data.

Assessment of risk of bias in included studies

Using the Cochrane 'Risk of bias' tool (Higgins 2011a), two review authors (SP and LS) independently assessed each included study as being at low risk, high risk, or unclear (uncertain) risk of bias for each of the seven domains explained in Appendix 8. Disagreements were resolved through discussion.

Measures of treatment effect

Dichotomous outcome data

We calculated the risk ratio (RR) and 95% confidence intervals (CIs) for dichotomous outcomes.

Continuous outcome data

For continuous outcomes, we used the Hedges' method to calculate standardized mean differences (SMDs) with individual study weights calculated as the inverse of the variance, presented with 95% CIs (Hedges 1994). To ensure that all scales were pointing in the same direction, we multiplied the mean value of one set by -1 (Deeks 2011). We combined change scores and endpoint scores, however when both types of scores were available in the same study, priority was given to change scores since they adjust for any imbalances in baseline characteristics.

See Table 1 for further methods archived for future updates of this review.

Unit of analysis issues

Cross-over trials

Since we calculated SMDs for all our continuous outcomes, we treated cross-over studies as if they were parallel and computed a pooled standard deviation. Although this method does not account for the correlation in cross-over studies, it prevented any overestimation of effect sizes, which is desirable when computing SMDs. Carry-over was not reported in any of the cross-over studies.

See Table 1 for further methods archived for future updates of this review.

Studies with multiple comparisons

For studies with more than two independent comparisons, such as amphetamine versus placebo versus psychotherapy, we excluded the psychotherapy arm. We handled studies with multiple and correlated interventions, for example, lisdexamphetamine versus mixed amphetamine salts versus placebo, or 10 mg dexamphetamine versus 20 mg of dexamphetamine versus placebo in the following way. For continuous outcomes of parallel-group studies, we calculated means using the formulae described in Table 7.7.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). For dichotomous outcomes of parallel-group studies, we summed the number of events across intervention arms. For continuous outcomes of cross-over studies, we averaged both the means and the standard deviations of the relevant intervention arms across the groups. For dichotomous outcomes of cross-over studies, we randomly dropped one arm and used the other in the meta-analysis.

Studies with multiple time points

We analysed studies separately according to their time frame. Time frames were denoted as short term (up to six months), medium term (between six and 12 months), and long term (over 12 months). All but one study (Gillberg 1997) were considered short term. Since Gillberg 1997 was the only medium-term study, it was excluded from the meta-analysis.

See Table 1 for further analyses archived for future updates of this review.

Dealing with missing data

We emailed study authors up to three times (with at least one month between contacts) to obtain missing data. For those studies that did not report outcomes using intention-to-treat analysis and for which missing data were unobtainable, we used the number of randomized participants as the denominator for dichotomous variables. For continuous outcomes, we used the sample size to calculate the mean and standard deviations in the study. For studies that did not report standard deviations, we calculated it from P values, CIs, or standard errors (as described in section 7.7.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b)). We did not use any imputations to deal with missing data.

Assessment of heterogeneity

We assessed statistical heterogeneity by examining the I^2 statistic (Higgins 2003), which quantifies the degree of heterogeneity in a meta-analysis, and Chi^2 statistic (P value less than 0.10 as evidence of heterogeneity). We also reported Tau^2 estimates for each random-effects meta-analysis (Deeks 2011).

We explored heterogeneity by conducting a series of subgroup analyses (Subgroup analysis and investigation of heterogeneity), which were selected a priori and based on preliminary evidence from other studies (Castells 2011; Lundh 2012).

Assessment of reporting biases

See Table 1 for methods archived for future updates of this review.

Data synthesis

We synthesized the results in a meta-analysis using the random-effects model since studies were fairly heterogeneous in terms of their study design (inclusion of parallel-group and cross-over trials), intervention protocols, and study duration. We used the inverse variance method for continuous outcomes, and the Mantel-Haenszel method for dichotomous outcomes.

Summary of findings

In Summary of findings for the main comparison, we present data on the following outcomes: total ADHD symptom score - parent ratings, total ADHD symptom score - teacher ratings, total ADHD symptom score - clinician ratings, proportion of responders, academic performance, proportion of participants who completed the trial, and proportion of participants who experienced at least one adverse event. We presented continuous outcomes as SMDs and 95% CIs, and dichotomous outcomes as RRs and 95% CIs. Data regarding number of participants and studies were presented for each outcome. We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE Working Group 2004) to determine the quality of the evidence, where evidence was downgraded if (1) the majority (> 50%) of included studies had a high risk of bias; (2) the outcome included comparisons of different amphetamine derivatives and release formulations; (3) the outcome had significant statistical heterogeneity (I^2 > 50%); and (4) the outcome had wide 95% CIs indicating that the intervention effect was highly variable.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses.

1. Type of amphetamine: dextroamphetamine, lisdexamphetamine, or mixed amphetamine salts.
2. Type of amphetamine release formulation: long acting (extended release) or short acting (immediate release).
3. Funding source: with or without pharmaceutical industry funding. Since some studies failed to report their funding source, we grouped studies as 'industry funded', 'publicly funded', or 'not reported'.

We conducted subgroup analyses on the following outcomes, which had a sufficient number of studies (more than five), regardless of the degree of statistical heterogeneity present in the main analysis:

1. total score on core symptom ADHD scale - parent ratings;
2. proportion of responders according to CGI-I (Guy 1976);
3. academic performance;
4. retention: proportion of participants who completed the trial;
5. proportion of participants who dropped out/withdrew due to an adverse event;
   a. proportion of participants experiencing decreased appetite;
   b. proportion of participants experiencing insomnia;
   c. proportion of participants experiencing abdominal pain; and
   d. proportion of participants experiencing headaches.

We calculated a pooled effect size for each subgroup.

We were unable to conduct a subgroup analysis when all of the studies in a particular meta-analysis belonged to only one strata of any subgroup.

See Table 1 for further analyses archived for future updates of this review.

Sensitivity analysis

We repeated our meta-analyses using a fixed-effect model.

See Table 1 for further analyses archived for future updates of this review.

RESULTS

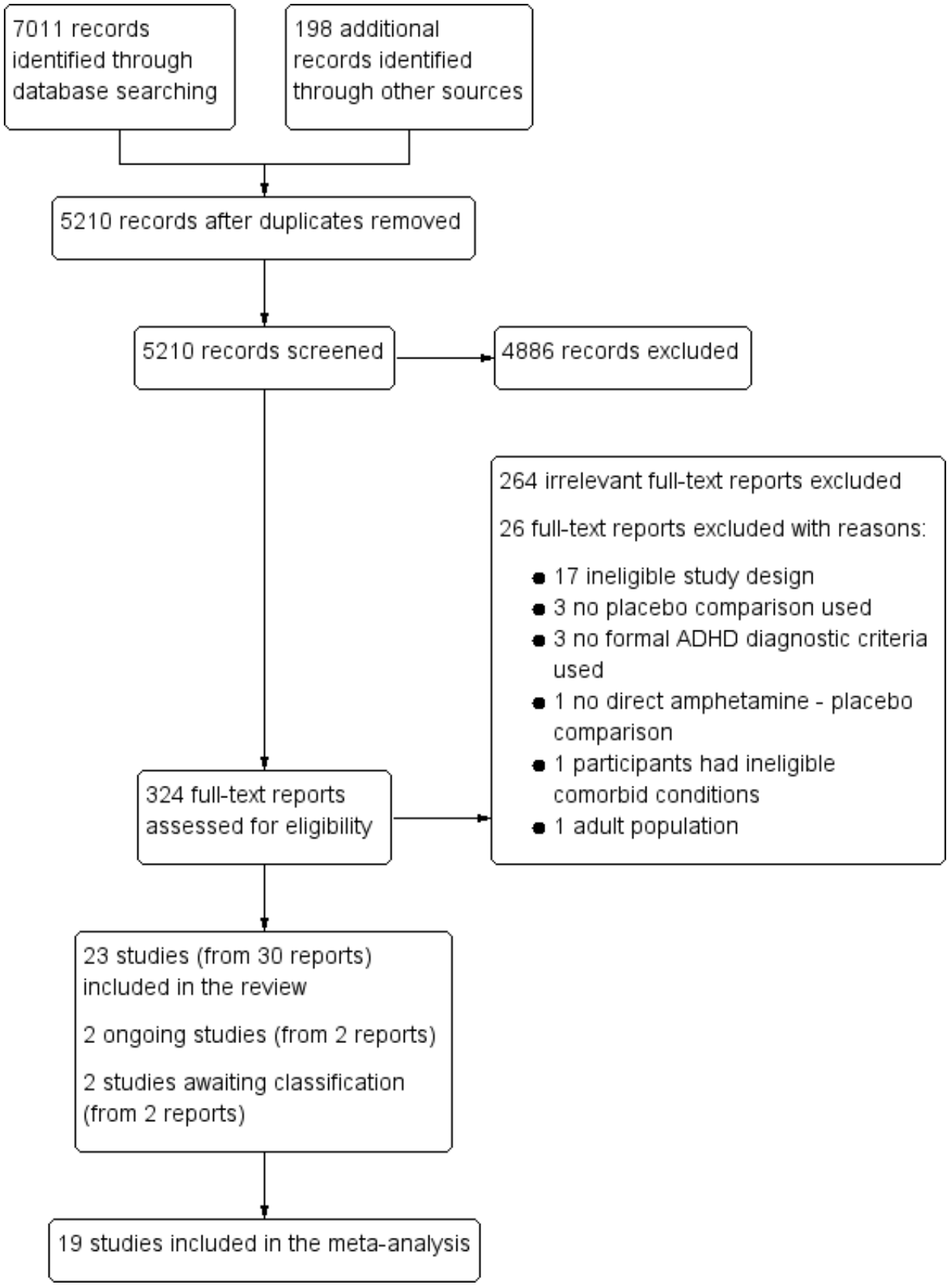
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

Figure 1 summarizes the flow of studies through the screening process. The electronic databases retrieved 7011 records while other sources yielded 198 records. After removing duplicates, we identified 5210 records for further consideration. After screening titles and available abstracts, we examined the full texts of 324 records, 34 met our inclusion criteria. From these, we identified 23 studies, four of which had multiple reports. These were: Borcherding 1990 (four reports), Coghill 2013 (three reports), Donnelly 1989 (two reports; one of which was the pilot, and the other was the full study), and Ramtvedt 2013 (two reports). In addition, we identified two ongoing clinical trials (Fanton 2009; NCT01711021); although recruitment has ended for both of these trials, none of the results have been published. We contacted the authors of both studies three times yielding no response. One non-English language study is awaiting classification until we can ascertain if it was randomized and whether participants had a formal diagnosis of ADHD (Glos 1973). This information is unobtainable given our inability to contact the author. Another study also awaits classification as only the abstract has been published (Itil 1974). Information on whether treatments were randomized and whether participants had a formal diagnosis is needed. We contacted the authors three times yielding no response.

Figure 1. Study flow diagram



Included studies

Twenty-three studies met the inclusion criteria: 15 studies were cross-over trials (Barkley 2000; Biederman 2007a; Borcherding 1990; Childress 2015; Donnelly 1989; James 2001; Manos 1999; McCracken 2003; Nemzer 1986; Ramtvedt 2013; Sharp 1999; Shekim 1986; Short 2004; Swanson 1998a; Wigal 2009a), while eight studies were parallel-group trials (Biederman 2002; Biederman 2007b; Coghill 2013; Findling 2011; Giblin 2011; Gillberg 1997; Pliszka 2000; Spencer 2006a).

Ten studies included a single comparison of an amphetamine derivative versus placebo (Borcherding 1990; Childress 2015; Coghill 2013; Donnelly 1989; Gillberg 1997; Nemzer 1986; Pliszka 2000; Ramtvedt 2013; Sharp 1999; Shekim 1986), and 11 studies compared more than one dose of an amphetamine derivative with placebo (Barkley 2000; Biederman 2002; Biederman 2007b; Findling 2011; Giblin 2011; Manos 1999; McCracken 2003; Short 2004; Spencer 2006a; Swanson 1998a; Wigal 2009a); two studies compared more than one amphetamine derivative, each at various doses, versus placebo (Biederman 2007a; James 2001).

Participants

In total, the 23 included studies recruited 2675 children and adolescents aged between three years and 17 years, 72% (n = 1925) of whom were boys; one study did not report the number of included boys and girls (Pliszka 2000).

Twenty-two studies used various versions of the DSM criteria to confirm ADHD diagnosis in their participants, including criteria from the Third Edition (DSM-III; four trials; n = 102; Borcherding 1990; Donnelly 1989; Nemzer 1986; Shekim 1986); Third Edition Revised (DSM-III-R; one trial; n = 62; Gillberg 1997); Fourth Edition (DSM-IV; eight trials; n = 899; Barkley 2000; Biederman 2002; James 2001; Manos 1999; McCracken 2003; Sharp 1999; Short 2004; Swanson 1998a), and Fourth Edition, Text Revision (DSM-IV-TR; nine trials; n = 1553; Biederman 2007a; Biederman 2007b; Childress 2015; Coghill 2013; Findling 2011; Giblin 2011; Ramtvedt 2013; Spencer 2006a; Wigal 2009a). Pliszka 2000 (n = 59) diagnosed ADHD using the Diagnostic Interview Schedule for Children (Costello 1985).

Interventions

Twelve studies assessed mixed amphetamine salts (Barkley 2000; Biederman 2002; Biederman 2007a; Childress 2015; Gillberg 1997; James 2001; Manos 1999; McCracken 2003; Pliszka 2000; Short 2004; Spencer 2006a; Swanson 1998a); seven studies used dextroamphetamine (Borcherding 1990; Donnelly 1989; James 2001; Nemzer 1986; Ramtvedt 2013; Sharp 1999; Shekim 1986); and six studies looked at lisdexamphetamine (Biederman 2007a; Biederman 2007b; Coghill 2013; Findling 2011; Giblin 2011; Wigal 2009a). Two studies assessed two amphetamine derivatives (Biederman 2007a; James 2001).

Twelve studies randomized children and adolescents to set doses or dosing schedules (Barkley 2000; Biederman 2002; Biederman 2007b; Coghill 2013; Findling 2011; Giblin 2011; Manos 1999; McCracken 2003; Ramtvedt 2013; Short 2004; Spencer 2006a; Swanson 1998a). Seven studies used weight-based dosing (Borcherding 1990; Donnelly 1989; James 2001; Nemzer 1986; Pliszka 2000; Sharp 1999; Shekim 1986), while six studies titrated children and adolescents to their optimal dose (Biederman 2007a; Childress 2015; Gillberg 1997; Pliszka 2000; Shekim 1986; Wigal 2009a). Two studies used both weight-based dosing and titration (Pliszka 2000; Shekim 1986). The mean (range) doses investigated in the included studies were 34.22 mg/day (7.8 mg/day to 90 mg/day) for dextroamphetamine, 50.24 mg/day (30 mg/day to 70 mg/day) for lisdexamphetamine, and 19.86 mg/day (5 mg/day to 120 mg/day) for mixed amphetamine salts.

Duration

Study intervention length ranged from 14 days to 365 days, with a median of 28 days. Only one study was longer than 63 days (Gillberg 1997).

Location

Twenty studies were conducted in the United States (Barkley 2000; Biederman 2002; Biederman 2007a; Biederman 2007b; Borcherding 1990; Childress 2015; Donnelly 1989; Findling 2011; Giblin 2011; James 2001; Manos 1999; McCracken 2003; Nemzer 1986; Pliszka 2000; Sharp 1999; Shekim 1986; Short 2004; Spencer 2006a; Swanson 1998a; Wigal 2009a). One multicenter trial was conducted in 48 centers across 10 countries: Belgium, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden, and the United Kingdom (Coghill 2013). The two remaining studies were conducted in Sweden (Gillberg 1997) and Norway (Ramtvedt 2013).

Outcomes

Details of all ADHD core symptom outcome measures used by study can be found in the Characteristics of included studies and Table 2. The most commonly used outcome tool for the primary outcome included the Conners' Rating Scales (Conners 1998a; Conners 1998b) and the ADHD-RS-IV (DuPaul 1998).

For secondary outcomes, the most commonly utilized outcome tool for academic performance was the Permanent Product Measure of Performance (PERMP; Swanson 1998b). Only one study assessed quality of life (Findling 2011), and used the Youth Quality of Life - Research Version questionnaire (YQOL-R; Salum 2012)

Excluded studies

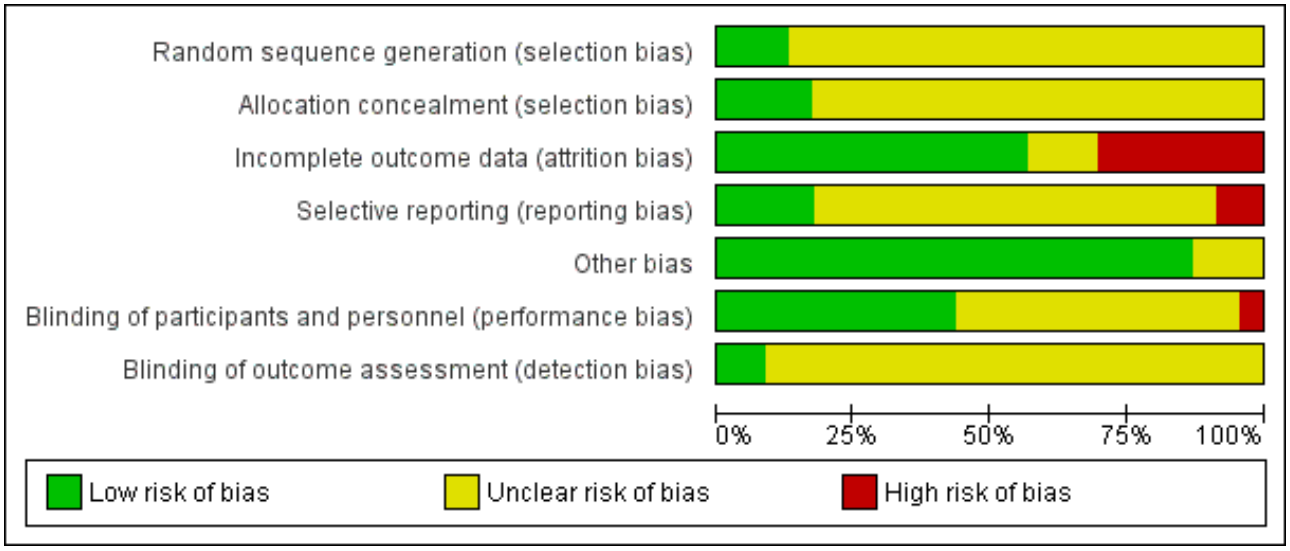
We excluded a total of 290 studies. We excluded 264 clearly irrelevant reports and formally excluded 26 studies for the following reasons: 17 studies because they were not RCTs or used multiple cross-over designs (this review only included single cross-over RCTs); three studies because there was no placebo comparison, three studies because they did not use formal ADHD diagnostic criteria; one study because it had no direct amphetamine - placebo comparison; one study because participants had ineligible comorbid conditions; and one study because it included adults.

See also Characteristics of excluded studies tables.

Risk of bias in included studies

A more in depth risk of bias assessment for each study can be found in Characteristics of included studies. In addition, Figure 2 provides a summary of this assessment.

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



Allocation

Random sequence generation

Only three studies reported on how the random sequence was generated and were assessed as being at 'low' risk of bias on this domain (Biederman 2007b; Childress 2015; Findling 2011). We rated the other 20 studies as 'unclear' risk of bias as they did not adequately describe their methods of randomization.

Allocation concealment

Four studies described the methods used to conceal the allocation sequence and were rated as being at 'low' risk of bias on this domain (Biederman 2007a; Coghill 2013; Findling 2011; Manos 1999). The rest of the studies we assessed as 'unclear' risk of bias, as they did not sufficiently describe their methods of allocation concealment.

Blinding

Performance bias

Although blinding was intended in all of the studies, we assessed risk of bias by how authors described their amphetamine and placebo capsules and rated 10 studies as being at 'low' risk of bias on this domain (Biederman 2007b; Coghill 2013; James 2001; Manos 1999; Nemzer 1986; Pliszka 2000; Sharp 1999; Short 2004; Swanson 1998a; Wigal 2009a). We rated one study as being at 'high' risk of bias on this domain since they described their intervention and placebo as not being identical (Ramtvedt 2013). The other 12 studies we marked as being at 'unclear' risk of bias since they were not explicit about the similarities between the two interventions.

Detection bias

Only two studies explicitly stated that outcome assessors were blinded to interventions and therefore we judged them to be at 'low' risk of bias (Manos 1999; Short 2004). The other 21 studies we rated as 'unclear' risk of bias since they were not explicit about which parties were blinded to the intervention assignment.

Incomplete outcome data

We rated thirteen studies that adequately addressed dropouts and used appropriate statistical methods to compensate for dropouts as having a 'low' risk of bias on this domain (Biederman 2002; Biederman 2007a; Biederman 2007b; Childress 2015; Donnelly 1989; Findling 2011; Gillberg 1997; James 2001; McCracken 2003; Pliszka 2000; Sharp 1999; Spencer 2006a; Wigal 2009a). Seven studies failed to provide reasons for dropouts and failed to address any exclusions from their analyses, and therefore we rated them as having a 'high' risk of bias (Barkley 2000; Borcherding 1990; Coghill 2013; Ramtvedt 2013; Shekim 1986; Short 2004; Swanson 1998a). The three remaining studies did not discuss dropouts in their reports and we rated them as being at 'unclear' risk of bias (Giblin 2011; Manos 1999; Nemzer 1986).

Selective reporting

We assessed 17 studies as having 'unclear' risk of bias on this domain as the study protocols for most of them were not available, so we could not assess reporting bias (Barkley 2000; Biederman 2002; Biederman 2007b; Borcherding 1990; Donnelly 1989; Giblin 2011; Gillberg 1997; James 2001; Manos 1999; McCracken 2003; Nemzer 1986; Pliszka 2000; Sharp 1999; Shekim 1986; Short 2004; Swanson 1998a; Wigal 2009a). We rated four studies as having a 'low' risk of bias, as they appropriately reported on all outcomes defined in their protocols (Biederman 2007a; Childress 2015; Findling 2011; Spencer 2006a). Two studies we assessed as having a 'high' risk of bias since they failed to report on all outcomes mentioned in their registered protocols (Coghill 2013; Ramtvedt 2013).

Other potential sources of bias

We rated three studies as being at 'unclear' risk of bias on this domain since the validity of their primary outcome tools were not described (Borcherding 1990; Donnelly 1989; Ramtvedt 2013). The other 20 studies appeared to be free of other potential sources of bias and therefore we rated them as being at 'low' risk of bias on this domain.

Effects of interventions

See: **Summary of findings for the main comparison**

We included 19 studies in meta-analyses, however, two of those studies had measured other outcomes that were relevant to this review, but were not reported in their results (Borcherding 1990; Swanson 1998a). Biederman 2007b had reported some of their results as bar graphs, which, when extracted using graphic digitizer software, gave implausible results and therefore was excluded from the meta-analysis on those outcomes. Four studies were excluded from all meta-analyses: Giblin 2011 had not reported data on any of the relevant outcomes in this review; Gillberg 1997 was the only medium-term study and therefore could not be combined with the other short-term studies; Ramtvedt 2013 had aggregated their parent- and teacher-rated ADHD scores; and Short 2004 assessed amphetamines versus methylphenidate versus placebo and pooled the amphetamine and methylphenidate data in their results; we were unable to isolate the amphetamine versus placebo comparison.

Primary outcome

Change in core ADHD symptoms

We conducted a series of meta-analyses for the primary outcome, change in core ADHD symptoms (inattention, hyperactivity, impulsivity), as measured by a validated scale rated by children, parents, teachers, clinicians, or investigators (Analysis 1.1 to Analysis 1.11).

For all 11 outcomes, amphetamines were superior to placebo for reducing the core symptoms of ADHD.

1. Total ADHD symptom score - parent ratings (SMD -0.57; 95% CI -0.86 to -0.27; Tau^2 = 0.10; I^2 = 77%; 7 studies; 1247 children/adolescents; Analysis 1.1).
2. Hyperactivity/impulsivity - parent ratings (SMD -0.54; 95% CI -0.89 to -0.19; Tau^2 = 0.00; I^2 = 0%; 2 studies; 132 children/adolescents; Analysis 1.2).
3. Total ADHD symptom score - teacher ratings (SMD -0.55; 95% CI -0.83 to -0.27; Tau^2 = 0.04; I^2 = 41%; 5 studies; 745 children/adolescents; Analysis 1.3).
4. Hyperactivity/impulsivity - teacher ratings (SMD -1.13; 95% CI -1.63 to -0.62; 1 study; 70 children/adolescents; Analysis 1.4).
5. Inattention - teacher ratings (SMD -1.43; 95% CI -2.35 to -0.52; 1 study; 24 children/adolescents; Analysis 1.5).
6. Total ADHD symptom score - clinician ratings (SMD -0.84; 95% CI -1.32 to -0.36; Tau^2 = 0.16; I^2 = 88%; 3 studies; 813 children/adolescents; Analysis 1.6).
7. Hyperactivity/impulsivity - clinician ratings (SMD -0.75; 95% CI -1.28 to -0.23; Tau^2 = 0.20; I^2 = 90%; 3 studies; 813 children/adolescents; Analysis 1.7).
8. Inattention - clinician ratings (SMD -0.78; 95% CI -1.26 to -0.30; Tau^2 = 0.16; I^2 = 88%; 3 studies; 813 children/adolescents; Analysis 1.8).
9. Total ADHD symptom score - investigator/research personnel ratings (SMD -1.15; 95% CI -1.87 to -0.44; Tau^2 = 0.37; I^2 = 94%; 3 studies; 630 children/adolescents; Analysis 1.9).
10. Hyperactivity/impulsivity - investigator/research personnel ratings (SMD -1.46; 95% CI - 1.83 to -1.08; Tau^2 = 0.03; I^2 = 41%; 2 studies; 280 children/adolescents; Analysis 1.10).
11. Inattention - investigator/research personnel ratings (SMD -0.73; 95% CI -1.42 to -0.04; Tau^2 = 0.46; I^2 = 94%; 4 studies; 634 children/adolescents; Analysis 1.11).

It is important to note, however, that the majority of these meta-analyses included between one and three studies, and that Analysis 1.1, Analysis 1.6, Analysis 1.7, Analysis 1.8, Analysis 1.9, and Analysis 1.11 had considerable heterogeneity present with I^2 ranging from 77% to 94%. Only three outcomes included more than three studies: total ADHD symptom score - parent ratings (seven studies; Analysis 1.1; Figure 3), total ADHD symptom score - teacher ratings (five studies; Analysis 1.3; Figure 4), and total ADHD symptom score - investigator/research personnel ratings (four studies; Analysis 1.11).

Figure 3. Forest plot of comparison: 1 Amphetamines versus placebo, outcome: 1.1 Total ADHD symptom score - parent ratings.

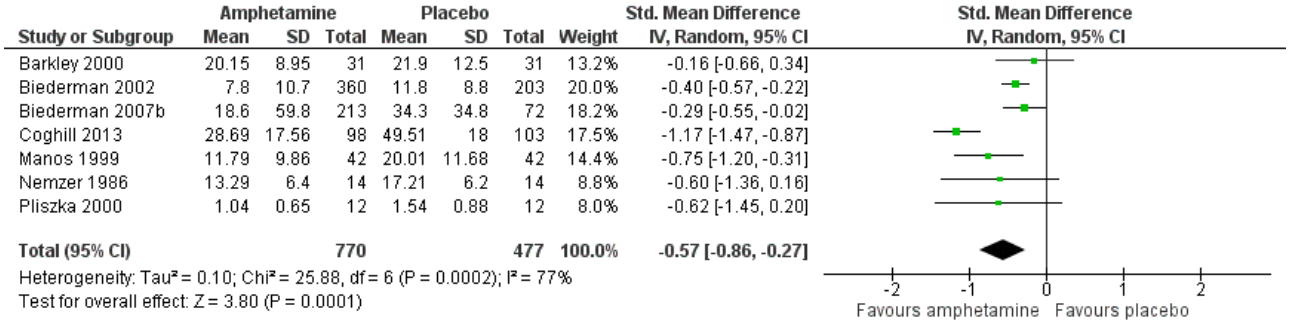
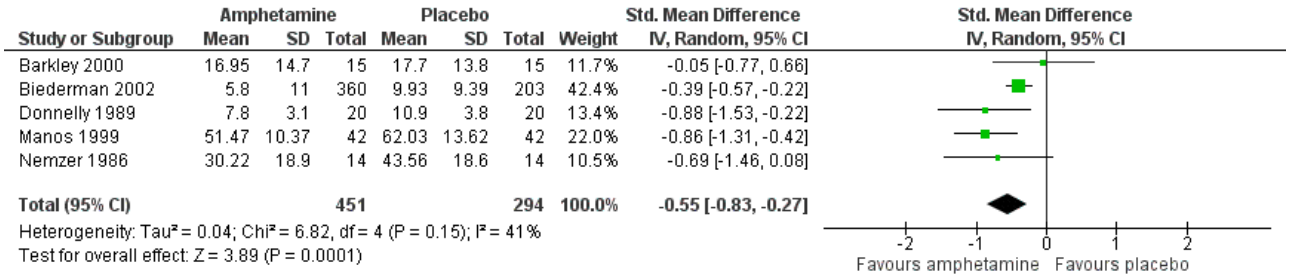


Figure 4. Forest plot of comparison: 1 Amphetamines versus placebo, outcome: 1.3 Total ADHD symptom score - teacher ratings.



Secondary outcomes

We conducted meta-analyses that compared amphetamines versus placebo on five of our six secondary outcomes (see Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16).

Clinical improvement

The proportion of responders was higher in the amphetamine group (RR 3.36; 95% CI 2.48 to 4.55; $Tau^2 = 0.14$; $I^2 = 72\%$; 9 studies; 2207 children/adolescents; Analysis 1.12)

Clinical severity

We found evidence of a significant difference between the two groups on the CGI-S (Guy 1976), in favour of amphetamine (SMD -0.86; 95% CI -1.72 to -0.01; $Tau^2 = 0.25$; $I^2 = 64\%$; 2 studies; 86 children/adolescents; Analysis 1.13).

Academic performance

We found evidence that amphetamines may improve academic performance as compared to placebo (SMD 0.56; 95% CI 0.39 to 0.73; $Tau^2 = 0.02$; $I^2 = 28\%$; 8 studies; 826 children/adolescents; Analysis 1.14).

Quality of life

As shown in the illustrative forest plot, the one study that provided data on quality of life (Findling 2011), found no difference between the two groups (SMD -0.01; 95% CI -0.27 to 0.25; 309 children/adolescents; see Analysis 1.15).

Retention

There was no difference between those given amphetamine and those given placebo for retention (RR 1.03; 95% CI 0.97 to 1.10; $Tau^2 = 0.01$; $I^2 = 83\%$; 11 studies; 2381 children/adolescents; Analysis 1.16).

Adverse events

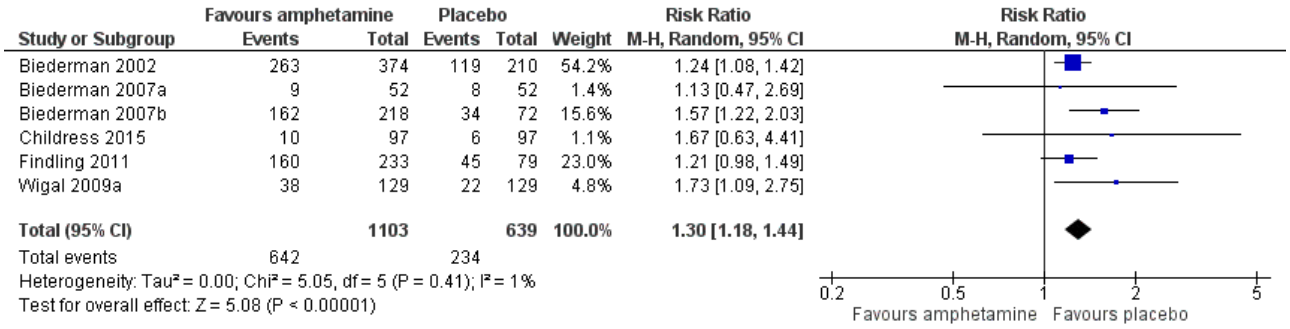
Proportion of adverse events

We performed a series of meta-analyses of the most commonly reported adverse events. A higher proportion of children and adolescents in the amphetamine group as compared to placebo group experienced decreased appetite (RR 6.31; 95% CI 2.58 to 15.46; $Tau^2 = 1.59$; $I^2 = 85\%$; 11 studies; 2467 children/adolescents; Analysis 1.17); insomnia/trouble sleeping (RR 3.80; 95% CI 2.12 to 6.83; $Tau^2 = 0.42$; $I^2 = 59\%$; 10 studies; 2429 children/adolescents; Analysis 1.18); abdominal pain (RR 1.44; 95% CI 1.03 to 2.00; $Tau^2 = 0.04$; $I^2 = 13\%$; 10 studies; 2155 children/adolescents; Analysis 1.19); and nausea/vomiting (RR 1.63; 95% CI 1.04 to 2.56; $Tau^2 = 0.08$; $I^2 = 26\%$; 6 studies; 1579 children/adolescents; Analysis 1.20). There were no differences between the amphetamine and placebo groups in the proportion of children and adolescents who experienced headaches (RR 0.93; 95% CI 0.75 to 1.16; $Tau^2 = 0.00$; $I^2 = 0\%$; 9 studies; 2091 children/adolescents; Analysis 1.21) and anxiety/nervousness (RR 1.22; 95% CI 0.78 to 1.93; $Tau^2 = 0.09$; $I^2 = 32\%$; 5 studies; 1088 children/adolescents; Analysis 1.22).

Proportion of participants who experienced at least one adverse event

The proportion of children and adolescents who experienced at least one adverse event was higher in the amphetamine group as compared to the placebo group (RR 1.30; 95% CI 1.18 to 1.44; $Tau^2 = 0.00$; $I^2 = 1\%$; 6 studies; 1742 children/adolescents; see Analysis 1.23; Figure 5).

Figure 5. Forest plot of comparison: 1 Amphetamines versus placebo, outcome: 1.23 Proportion of participants who experienced at least one adverse event.



Proportion of participants who withdrew due to any adverse event

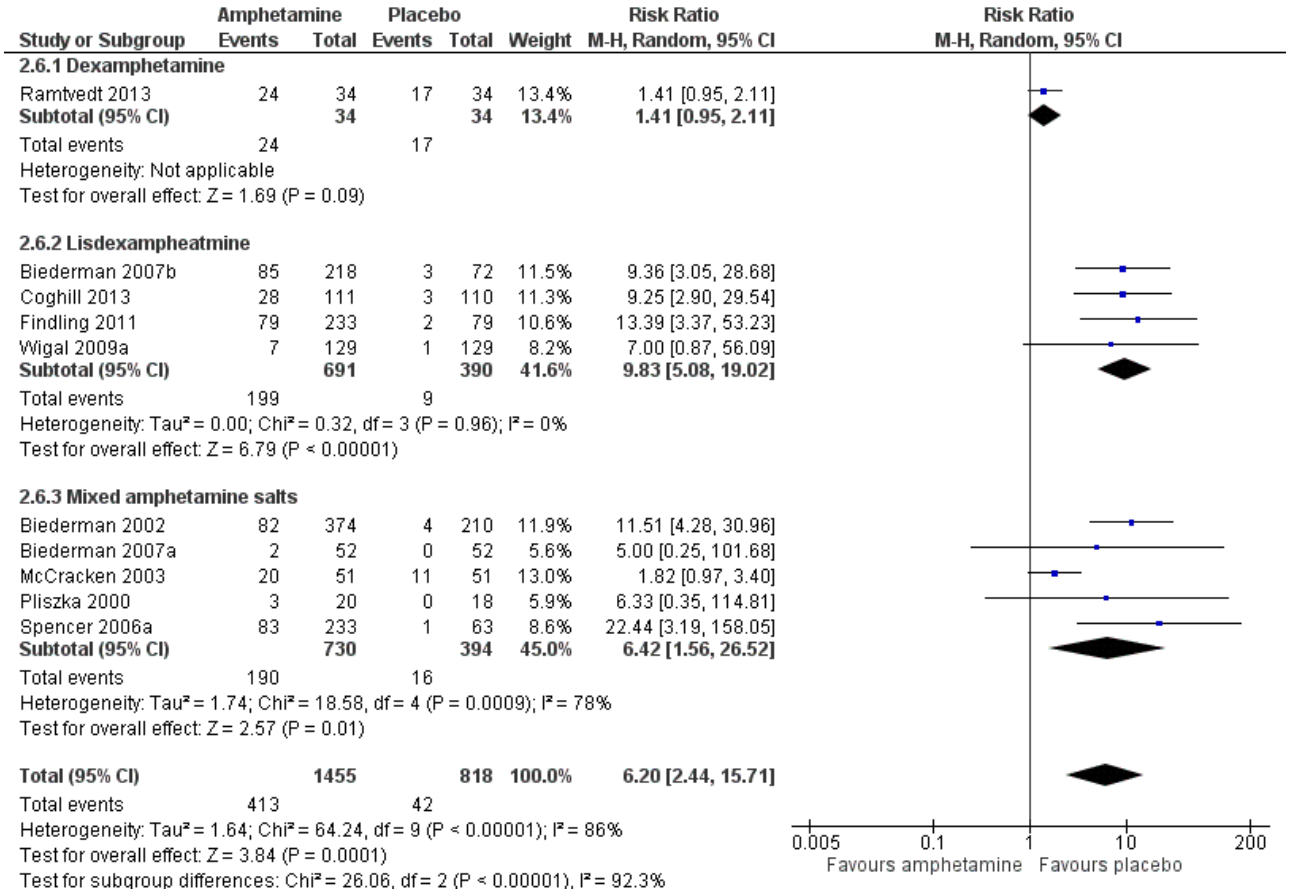
There was no difference between the amphetamine and placebo groups in the proportion of children and adolescents who withdrew due to an adverse event (RR 1.60; 95% CI 0.86 to 2.98; $Tau^2 = 0.00$; $I^2 = 0\%$; 9 studies; 2160 children/adolescents; Analysis 1.24).

Subgroup analyses

Type of amphetamine

We conducted a series of subgroup analyses according to type of amphetamine (dexamphetamine, lisdexamphetamine, and mixed amphetamine salts). Mixed amphetamine salts were associated with improved parent ratings of total ADHD symptoms as compared to dexamphetamine and lisdexamphetamine, however, there appeared to be no between-group differences ($Chi^2 = 0.55$, P value = 0.76; Analysis 2.1). Only one subgroup yielded between-group differences ($Chi^2 = 26.06$, P < 0.00001; Analysis 2.6; Figure 6). There were no between-group differences for any of the other outcomes.

Figure 6. Forest plot of comparison: 2 Subgroup analysis 1: Type of amphetamine, outcome: 2.6 Proportion of participants experiencing decreased appetite.



Type of amphetamine release formulation

We conducted a subgroup analysis to explore the influence of long-acting versus short-acting amphetamine release formulations (Analysis 3.1 to Analysis 3.6). Both rentention: proportion of participants who completed the trial (Chi^2 = 4.50, P value = 0.03; Analysis 3.4) and proportion of participants experiencing decreased appetite (Chi^2 = 6.93, P value = 0.008; Analysis 3.5) yielded between-group differences.

Funding source

We wanted to explore the influence of industry-funded versus publicly-funded sources (Analysis 4.1 to Analysis 4.3). Since five studies did not report their source of funding, we introduced another subgroup, 'not reported'. No between-group differences were found.

Sensitivity analysis

We repeated the analyses by changing the statistical model from a random-effects model to a fixed-effect model. The results were similar (see Analysis 5.1 to Analysis 5.24).

DISCUSSION

Summary of main results

We included 23 studies in this review, 19 of which we included in meta-analyses. Overall, this review found that amphetamines were more efficacious than placebo for reducing ADHD core symptom severity in the short-term, however, they did not influence retention in the trial and were associated with a number of adverse events. According to conventional cut-offs (Cohen 1988), the largest effect sizes observed (i.e. an SMD > 0.8) were teacher ratings of hyperactivity/impulsivity, teacher ratings of inattention, and clinician ratings of total ADHD symptoms. The meta-analyses with the most available data included parent and teacher ratings of total ADHD symptoms, both of which yielded low to moderate effect sizes.

The median study duration was only 28 days, therefore it was not possible to assess the long-term efficacy and safety of amphetamines for pediatric ADHD. This is particularly problematic in a condition such as ADHD, which may require treatment for years.

There was a lot of variation in the amphetamine derivatives and release formulations utilized in the included studies. As such, we conducted subgroup analyses to explore their differences. Minimal between-group differences were found, however, conclusions should not be drawn from these analyses as they are based on observational and not randomized comparisons. Furthermore, given that the majority of studies assessed mixed amphetamine salts and long-acting release formulations, the subgroups assessing other amphetamine derivatives (i.e. lisdexamphetamine, dexamphetamine), and short-acting release formulations, may not have been adequately powered to detect a true difference.

We performed a meta-analysis of the most commonly reported adverse events in the primary studies. These included decreased appetite, insomnia/trouble sleeping, abdominal pain, nausea/vomiting, headaches and anxiety. Meta-analysis revealed that most adverse events occurred more often in the amphetamine groups than in the placebo groups.

Overall completeness and applicability of evidence

This review focused only on the amphetamine versus placebo comparison. While it is important to assess amphetamines versus other active therapies, such as other stimulants, psychotherapy or antidepressants, we believe it is important to first establish whether or not amphetamines are superior to placebo. We were unable to assess the long-term efficacy of amphetamines (i.e. beyond 12 months of use). The average duration of included studies was five weeks long, excluding one long-term study that was 12 months long (Gillberg 1997). Short-term trials are particularly problematic for chronic conditions, such as ADHD, as children will likely be on stimulant medications for much longer periods than have been studied. As mentioned earlier, adverse events occurred more frequently when children and adolescents were treated with amphetamines than when they were treated with placebo, however, it is important to point out the poor reporting around adverse events in the included studies. Some studies only reported on adverse events that were experienced by a certain percentage of children and adolescents, thereby potentially ignoring additional adverse events experienced at less than that fraction. Futhermore, many studies were unclear regarding their methods of collecting adverse events and whether they assessed the causality of these adverse events as it related to the interventions. Heterogeneity of terms used to describe adverse events was also a major hurdle when conducting this review, and limited our ability to appropriately synthesize the data. Finally, as with efficacy data, we were unable to assess the long-term safety profile of amphetamines given the lack of long-term trials.

Only one study explored the impact of amphetamines on children and adolescents' quality of life (Findling 2011). It found no effect, although this may be because the study was underpowered. This is a significant gap in the available evidence on the effects of amphetamines, and studies should include a focus on psychosocial factors such as parental stress or quality of life.

The external validity of our results was also limited by the inclusion/exclusion criteria of the included studies. Since we excluded studies that included children and adolescents with comorbidity other than conduct disorder, oppositional defiant disorder and anxiety, we cannot extrapolate the results of our review to patients with other commonly occurring comorbidity such as depression, and tic disorder.

Few trials reported on the ADHD subtype of their included children and adolescents. Therefore, we were unable to make any conclusions as regards the potential heterogeneity of effect of different formulations of amphetamines across different ADHD subtypes. Furthermore, since primary studies did not subgroup their results according to important prognostic factors, such as age and gender, we were unable to subgroup our meta-analyses, which would have been particularly relevant for clinicians.

Although our review did assess the proportion of children and adolescents who dropped out due to an adverse event and found no differences between amphetamine and placebo groups (Analysis 1.24), it is worth noting that many studies in the meta-analysis had zero events in the placebo group, resulting in potentially invalid results that overestimate variance. The high number of zero events may be attributable to a lack of power to detect these events given the much smaller sample sizes of the

placebo groups (n = 900) as compared to the amphetamine groups (n = 1532).

Finally, it was difficult for us to accurately assess our results in a clinically meaningful way, since interpretation of scores is both sex- and age-dependent.

Quality of the evidence

The overall quality of the evidence ranged from low to very low as assessed by the GRADE approach, indicating that there is room for improvement amongst the current evidence about the efficacy of amphetamines in managing ADHD in children and adolescents. The studies appear to have a multitude of methodological issues making it difficult to draw strong clinical conclusions. Moreover, most studies failed to report on how the random sequence was generated (90%), how allocation was concealed (85%), the methods used to blind participants and personnel (55%), and the methods used to blind outcome assessors (90%). As such, we were unable to determine whether it was a reporting problem or a methodological problem.

Potential biases in the review process

Limitations of our review include not being able to account for correlation in cross-over studies given the formula for calculating SMDs, thereby yielding less precise effect sizes, which may result in overlooking any potential statistical heterogeneity between the studies. Furthermore, caution is warranted in the interpretation of our meta-analyses of adverse events that contain rare events. Most methods of meta-analysis, including the chosen Mantel-Haenszel approach, perform poorly with rare events; they can yield misleading results, have very wide CIs or the statistical power can be too low to detect a difference.

Given the small number of studies included in the primary meta-analyses (maximum of seven studies), we felt that a funnel plot would not provide meaningful information about potential publication bias, which may have led to an overestimation of treatment effects. Furthermore, the exclusion of one potentially eligible non-English study may have also biased our findings. Egger 1997 found that non-English studies tend to be negative, and so excluding them may have yielded an overestimation of treatment effects. On the other hand, other researchers have found that excluding trials reported in languages other than English do not significantly affect the results of a meta-analysis (Moher 2003).

Another limitation arises from the subgroup comparisons. It must be noted that these analyses are based on observational and not randomized comparisons, and therefore should not be interpreted as conclusive evidence.

Another potential bias of our review is that one of the authors, Dr. Catherine J Nikles, has published a study on amphetamines for ADHD; however, two independent authors assessed the eligibility of this study, which was subsequently excluded due to the nature of the design (Nikles 2006).

Agreements and disagreements with other studies or reviews

We identified two previously conducted systematic reviews prior to conducting ours (Charach 2011; Miller 1999). Charach 2011 only assessed the long-term (i.e. more than 12 months) efficacy and safety of amphetamines for pediatric ADHD, and included only one RCT that assessed amphetamines versus placebo, which was also included in our systematic review (Gillberg 1997). Miller 1999 also systematically assessed amphetamines for pediatric ADHD, however, reviewers only included studies that assessed the dexamphetamine derivative of amphetamines. Furthermore, this review was published in 1999, making it over 14 years old. As such, Miller 1999 included only three relevant RCTs in their review, which were also included in this review (Borcherding 1990; Donnelly 1989; Gillberg 1997). The majority of meta-analyses conducted in the Miller 1999 review included RCTs that assessed any stimulant medication (methylphenidate or amphetamine) versus placebo. The one meta-analysis that was restricted to the amphetamine versus placebo comparison showed that amphetamines improve total ADHD symptoms as rated by the Abbreviated Conners Teacher Rating Scale (ATRS; Conners 1990): MD -4.77; 95% CI -6.43 to -2.99. This is consistent with the results of our review for this outcome, which also showed improvement in this outcome in favour of amphetamine (SMD -0.55; 95% CI -0.83 to -0.27).

AUTHORS' CONCLUSIONS

Implications for practice

Although the results of this review demonstrate that amphetamines improve the core symptoms of ADHD in children and adolescents in the short term, they are also associated with higher risk of experiencing adverse events. Given the lack of available evidence as regards the effects of amphetamines on ADHD-subtypes, long-term effectiveness and safety data, and the effects of amphetamines on psychosocial outcomes, it is difficult to extrapolate the results from this research to the clinical population. As such, when making treatment decisions, clinicians must use their own judgement in weighing the benefits with the safety profile of the intervention, accounting for the patient's responsiveness to other stimulant medications (for example, methylphenidate), and integrating patient/family preferences and values when making treatment decisions.

This review does not provide evidence that supports any one amphetamine derivative over another, and does not reveal any differences between long-acting and short-acting formulations.

Implications for research

Future RCTs should be longer in duration in order to explore the long-term safety and efficacy of amphetamines. It would also be beneficial for future studies to subgroup their results based on important prognostic factors, such as age and gender, in order to yield more clinically relevant results. Furthermore, while it has been traditionally assumed that improvements in core ADHD symptoms result in improved overall functioning, including academic performance, peer relations and family functioning, there is a lack of data that supports these correlations. Initiatives such as COMET (Core Outcome Measures in Effectiveness Trials), which aims to develop standardized sets of research outcomes for various health conditions, will be pivotal to areas like ADHD in ensuring that future studies not only focus on symptom management as an outcome, but also on more global outcomes that focus on a child's overall functioning (Williamson 2012).

While there is evidence that shows industry funding has been associated with exaggerated treatment effects (Lundh 2012), the

debate remains unresolved (Bero 2013; Sterne 2013). Future research should assess to what extent funding source, and author affiliation with the funding source, impact treatment effects, and recommendations on whether these factors should be included in the risk of bias assessment may be helpful.

Researchers should consult the Consolidated Standards of Reporting Trials (CONSORT) statement when designing their study and reporting their methods and results so that an appropriate risk of bias assessment can be made allowing for a more robust interpretation (Schulz 2010).

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REFERENCES

References to studies included in this review

Barkley 2000 *{published data only}*

Barkley RA, Connor DF, Kwasnik D. Challenges to determining adolescent medication response in an outpatient clinical setting: comparing Adderall and methylphenidate for ADHD. *Journal of Attention Disorders* 2000;**4**(2):102-13. [DOI: 10.1177/108705470000400204]

Biederman 2002 *{published data only}*

Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2002;**110**(2):258-66.

Biederman 2007a *{published data only}*

Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analogue classroom study. *Biological Psychiatry* 2007;**62**(9):970-6. [PUBMED: 17631866]

Biederman 2007b *{published data only (unpublished sought but not used)}*

Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clinical Therapeutics* 2007;**29**(3):450-63. [PUBMED: 17577466]

Borcherding 1990 *{published data only (unpublished sought but not used)}*

* Borcherding BG, Keysor CS, Rapoport JL, Elia J, Amass J. Motor/vocal tics and compulsive behaviors on stimulant drugs: is there a common vulnerability?. *Psychiatry Research* 1990;**33**(1):83-94. [PUBMED: 2217661]

Elia J, Borcherding BG, Potter WZ, Mefford IN, Rapoport JL, Keysor CS. Stimulant drug treatment of hyperactivity: biochemical correlates. *Clinical Pharmacaology and Therapeutics* 1990;**48**(1):57-66. [DOI: 10.1038/clpt.1990.118]

Elia J, Borcherding BG, Rapoport JL, Keysor CS. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders?. *Psychiatry Research* 1991;**36**(2):141-55. [PUBMED: 2017529]

Elia J, Welsh PA, Gullotta CS, Rapoport JL. Classroom academic performance: improvement with both methylphenidate and dextroamphetamine in ADHD boys. *Journal of Child Psychology and Psychiatry* 1993;**34**(5):785-804. [DOI: 10.1111/j.1469-7610.1993.tb01071.x]

Childress 2015 *{published data only}*

Childress AC, Brams M, Culter AJ, Kollins SH, Northcutt J, Padilla A, et al. The efficacy and safety of evekeo, racemic amphetamine sulfate, for treatment of attention-deficit/hyperactivity disorder symptoms: a multicenter, dose-optimized, double-blind, randomized, placebo-controlled crossover laboratory classroom study. *Journal of Child and Adolescent Psychopharmacology* 2015;**25**(5):402-14. [DOI: 10.1089/cap.2014.0176]

Coghill 2013 *{published data only}*

Banachewski T, Soutullo C, Lecendreux M, Johnson M, Zuddas A, Hodgkins P, et al. Health-related quality of life and functional outcomes from a randomized, controlled study of lisdexamfetamine dimesylate in children and adolescents with attention deficit hyperactivity disorder. *CNS Drugs* 2013;**27**(10):829-40. [DOI: 10.1007/s40263-013-0095-5]

* Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, et al. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. *European Neuropsychopharmacology* 2013;**23**(10):1208-18. [DOI: 10.1016/j.euroneuro.2012.11.012]

Coghill DR, Banaschewski T, Lecendreux M, Zuddas A, Dittmann RW, Otero IH, et al. Efficacy of lisdexamfetamine dimesylate throughout the day in children and adolescents with attention-deficit/hyperactivity disorder: results from a randomized, controlled trial. *European Child and Adolescent Psychiatry* 2014;**23**(2):61-8. [PUBMED: 23708466]

Donnelly 1989 *{published data only (unpublished sought but not used)}*

Donnelly M, Rapoport JL, Ismond DR. Fenfluramine treatment of childhood attention deficit disorder with hyperactivity: a preliminary report. *Psychopharmacology Bulletin* 1986;**22**(1):152-4.

* Donnelly M, Rapoport JL, Potter WZ, Oliver J, Keysor CS, Murphy DL. Fenfluramine and dextroamphetamine treatment of childhood hyperactivity: clinical and biochemical findings. *Archives of General Psychiatry* 1989;**46**(3):205-12. [DOI: 10.1001/archpsyc.1989.01810030011002]

Findling 2011 *{published data only}*

Findling RL, Childress AC, Cutler AJ, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2011;**50**(4):395-405. [PUBMED: 21421179]

Giblin 2011 *{published data only (unpublished sought but not used)}*

Giblin GM, Strobel AL. Effect of lisdexamphetamine dimesylate on sleep in children with ADHD. *Journal of Attention Disorders* 2011;**15**(6):491-8. [DOI: 10.1177/1087054710371195]

Gillberg 1997 *{published data only}*

Gillberg C, Melander H, Knorring AL, Janols LO, Thernlund G, Hagglof B, et al. Long-term stimulant treatment of children with attention-deficit hyperactivity disorder symptoms: a randomized, double-blind, placebo-controlled trial. *Archives of General Psychiatry* 1997;**54**(9):857-64. [PUBMED: 9294377]

James 2001 *{published data only}*

James RS, Sharp WS, Bastain TM, Lee PP, Walter JM, Czarnolewski M, et al. Double-blind, placebo-controlled study of single-dose amphetamine formulations in ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2001;**40**(11):1268-76. [PUBMED: 11699800]

Manos 1999 *{published data only}*

Manos MJ, Short EJ, Findling RL. Differential effectiveness of methylphenidate and Adderall in school-age youths with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 1999;**38**(7):813-9. [PUBMED: 10405498]

McCracken 2003 *{published data only}*

McCracken JT, Biederman J, Greenhill LL, Swanson JM, McGough JJ, Spencer TJ, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (Adderall XR), in children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;**42**(6):673-83. [PUBMED: 12921475]

Nemzer 1986 *{published data only}*

Nemzer ED, Arnold E, Votolato NA, McConnell H. Amino acid supplementation as therapy for attention deficit disorder. *Journal of the American Academy of Child Psychiatry* 1986;**25**(4):509-13.

Pliszka 2000 *{published data only}*

Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2000;**39**(5):619-26. [DOI: 10.1097/00004583-200005000-00016]

Ramtvedt 2013 *{published data only}*

Ramtvedt BE, Aabech HS, Sundet K. Minimizing adverse events while maintaining clinical improvement in a pediatric attention-deficit/hyperactivity disorder crossover trial with dextroamphetamine and methylphenidate. *Journal of Child and Adolescent Psychopharmacology* 2014;**24**(3):130-9. [DOI: 10.1089/cap.2013.0114]

* Ramtvedt BE, Røinås E, Aabech HS, Sundet KS. Clinical gains from including both dextroamphetamine and methylphenidate in stimulant trials. *Journal of Child and Adolescent Psychopharmacology* 2013;**23**(9):597-604. [DOI: 10.1089/cap.2012.0085]

Sharp 1999 *{published data only (unpublished sought but not used)}*

Sharp WS, Walter JM, Marsh WL, Ritchie GF, Hamburger SD, Castellanos FX. ADHD in girls: clinical comparability of a research sample. *Journal of the American Academy of Child and Adolescent Psychiatry* 1999;**38**(1):40-7. [PUBMED: 9893415]

Shekim 1986 *{published data only}*

Shekim WO, Bylund DB, Alexson J, Glaser RD, Jones SB, Hodges K, et al. Platelet MAO and measures of attention and impulsivity in boys with attention deficit disorder and hyperactivity. *Psychiatry Research* 1986;**18**(2):179-88. [DOI: 10.1016/0165-1781(86)90029-6]

Short 2004 *{published data only}*

Short EJ, Manos MJ, Findling RL, Schubel EA. A prospective study of stimulant response in preschool children: insights from ROC analyses. *Journal of the American Academy of Child and Adolescent Psychiatry* 2004;**43**(3):251-9. [DOI: 10.1097/00004583-200403000-00005]

Spencer 2006a *{published data only}*

Spencer TJ, Wilens TE, Biederman J, Weisler RH, Read SC, Pratt R. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of attention-deficit/hyperactivity disorder in adolescent patients: a 4-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clinical Therapeutics* 2006;**28**(2):266-79. [DOI: 10.1016/j.clinthera.2006.02.011]

Swanson 1998a *{published data only (unpublished sought but not used)}*

Swanson JM, Wigal S, Greenhill LL, Browne R, Waslik B, Lerner M, et al. Analog classroom assessment of Adderall (R) in children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 1998;**37**(5):519-26.

Wigal 2009a *{published data only}*

Wigal SB, Kollins SH, Childress AC, Squires L, for the 311 Study Group. A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *Child and Adolescent Psychiatry and Mental Health* 2009;**3**(1):17. [DOI: 10.1186/1753-2000-3-17]

References to studies excluded from this review

Akhondzadeh 2003 *{published data only}*

Akhondzadeh S, Tavakolian R, Davari-Ashtiani R, Arabgol F, Amini H. Selegiline in the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2003;**27**(5):841-5. [DOI: 10.1016/S0278-5846(03)00117-9]

Alexandris 1968 *{published data only}*

Alexandris A, Lundell FW. Effect of thioridazine, amphetamine and placebo on the hyperkinetic syndrome and cognitive area in mentally deficient children. *Canadian Medical Association Journal* 1968;**98**(2):92-6.

Arnold 2011 *{published data only}*

Arnold LE, Disilvestro RA, Bozzolo D, Bozzolo H, Crowl L, Fernandez S, et al. Zinc for attention-deficit/hyperactivity disorder: placebo-controlled double-blind pilot trial alone and combined with amphetamine. *Journal of Child and Adolescent Psychopharmacology* 2011;**21**(1):1-19. [PUBMED: 21309695]

Biederman 2006 *{published data only}*

Biederman J, Wigal SB, Spencer TJ, McGough JJ, Mays DA. A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in

school-age girls with attention-deficit/hyperactivity disorder. *Clinical Therapeutics* 2006;**28**(2):280-93. [DOI: 10.1016/j.clinthera.2006.02.008]

Biederman 2008 *{published data only}*

Biederman J, Seidman LJ, Petty CR, Fried R, Doyle AE, Cohen DR, et al. Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry* 2008;**69**(7):1150-6.

Boellner 2010 *{published data only}*

Boellner SW, Stark JG, Krishnan S, Zhang Y. Pharmacokinetics of lisdexamfetamine dimesylate and its active metabolite, d-amphetamine, with increasing oral doses of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder: a single-dose, randomized, open-label, crossover study. *Clinical Therapeutics* 2010;**32**(2):252-64. [PUBMED: 20206783]

Brown 2010 *{published data only}*

Brown TE, Landgraf JM. Improvements in executive function correlate with enhanced performance and functioning and health-related quality of life: evidence from 2 large, double-blind, randomized, placebo-controlled trials in ADHD. *Postgraduate Medicine* 2010;**122**(5):42-51. [PUBMED: 20861587]

Denhoff 1971 *{published data only}*

Denhoff E, Davids A, Hawkins R. Effects of dextroamphetamine on hyperkinetic children: a controlled double blind study. *Journal of Learning Disabilities* 1971;**4**(9):491-8. [DOI: 10.1177/002221947100400906]

Donner 2007 *{published data only}*

Donner R, Michaels MA, Ambrosini PJ. Cardiovascular effects of mixed amphetamine salts extended release in the treatment of school-aged children with attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2007;**61**(5):706-12. [DOI: 10.1016/j.biopsych.2006.05.002]

Efron 1997 *{published data only}*

Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997;**100**(4):662-6. [PUBMED: 9310521]

Findling 2009 *{published data only}*

Findling RL, Ginsberg LD, Jain R, Gao J. Effectiveness, safety, and tolerability of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder: an open-label, dose-optimization study. *Journal of Child and Adolescent Psychopharmacology* 2009;**19**(6):649-62. [PUBMED: 20035583]

Greenhill 2003 *{published data only}*

Greenhill LL, Swanson JM, Steinhoff K, Fried J, Posner K, Lerner M, et al. A pharmacokinetic/pharmacodynamic study comparing a single morning dose of Adderall to twice-daily dosing in children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;**42**(10):1234-41. [PUBMED: 14560174]

Kamien 1998 *{published data only}*

Kamien M. The use of an N-of-1 randomised clinical trial in resolving therapeutic doubt. The case of a patient with an 'attention disorder'. *Australian Family Physician* 1998;**27 Suppl 2**:S103-5.

Lopez 2008 *{published data only}*

Lopez FA, Ginsberg LD, Arnold V. Effect of lisdexamfetamine dimesylate on parent-rated measures in children aged 6 to 12 years with attention-deficit/hyperactivity disorder: a secondary analysis. *Postgraduate Medicine* 2008;**120**(3):89-102. [DOI: 10.3810/pgm.2008.09.1910]

McGough 2005 *{published data only}*

McGough JJ, Biederman J, Wigal SB, Lopez FA, McCracken JT, Spencer T, et al. Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR) in children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;**44**(6):530-8. [DOI: 10.1097/01.chi.0000157550.94702.a2]

Najib 2009 *{published data only}*

Najib J. The efficacy and safety profile of lisdexamfetamine dimesylate, a prodrug of d-amphetamine, for the treatment of attention-deficit/hyperactivity disorder in children and adults. *Clinical Therapeutics* 2009;**31**(1):142-76. [DOI: 10.1016/j.clinthera.2009.01.015]

Nikles 2006 *{published data only}*

Nikles CJ, Mitchell GK, Del Mar CB, Clavarino A, McNairn N. An n-of-1 trial service in clinical practice: testing the effectiveness of stimulants for attention-deficit/hyperactivity disorder. *Pediatrics* 2006;**117**(6):2040-6.

Quintana 2007 *{published data only}*

Quintana H, Cherlin EA, Duesenberg DA, Bangs ME, Ramsey JL, Feldman PD, et al. Transition from methylphenidate or amphetamine to atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder - a preliminary tolerability and efficacy study. *Clinical Therapeutics* 2007;**29**(6):1168-77. [DOI: 10.1016/j.clinthera.2007.06.017]

Scheffer 2005 *{published data only}*

Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *American Journal of Psychiatry* 2005;**162**(1):58-64. [PUBMED: 15625202]

Sleator 1974 *{published data only}*

Sleator EK, Von Neumann A, Sprague RL. Hyperactive children: a continuous long-term placebo-controlled follow-up. *JAMA* 1974;**229**(3):316-7. [DOI: 10.1001/jama.1974.03230410040022.]

Spencer 2005 *{published data only}*

Spencer TJ, Biederman J, Wilens TE. Efficacy and tolerability of long-term, open-label, mixed amphetamine salts extended release in adolescents with ADHD. *CNS Spectrums* 2005;**10 Suppl 15**:14-21. [DOI: 10.1017/S1092852900014103]

Spencer 2006b *{published data only}*

Spencer TJ, Abikoff HB, Connor DF, Biederman J, Pliszka SR, Boellner S, et al. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of oppositional defiant disorder with or without comorbid attention-deficit/hyperactivity disorder in school-aged children and adolescents: a 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study. *Clinical Therapeutics* 2006;**28**(3):402-18. [DOI: 10.1016/j.clinthera.2006.03.006]

Turgay 2010 *{published data only}*

Turgay A, Ginsberg L, Sarkis E, Jain R, Adeyi B, Gao J, et al. Executive function deficits in children with attention-deficit/hyperactivity disorder and improvement with lisdexamfetamine dimesylate in an open-label study. *Journal of Child and Adolescent Psychopharmacology* 2010;**20**(6):503-11. [DOI: 10.1089/cap.2009.0110]

Wigal 2009b *{published data only}*

Wigal SB, Kollins SH, Childress AC, Squires L, for the 311 Study Group. A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *Child and Adolescent Psychiatry and Mental Health* 2009;**3**(1):17. [DOI: 10.1186/1753-2000-3-17]

Wigal 2010a *{published data only}*

Wigal SB, Kollins SH, Childress AC, Adeyi B. Efficacy and tolerability of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder: sex and age effects and effect size across the day. *Child and Adolescent Psychiatry and Mental Health* 2010;**4**:32. [DOI: 10.1186/1753-2000-4-32]

Wigal 2010b *{published data only}*

Wigal T, Brams M, Gasior M, Gao J, Squires L, Giblin J, et al. Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using a simulated adult workplace environment design. *Behavioral and Brain Functions* 2010;**6**:34. [DOI: 10.1186/1744-9081-6-34]

References to studies awaiting assessment

Glos 1973 *{published data only}*

Glos J. Amphetamines in the treatment of hyperactive and unstable children. *Ceskoslovenska Pediatrie* 1973;**28**(10):559-60.

Itil 1974 *{published data only}*

Itil TM, Simeon J. Proceedings: computerized EEG in the prediction of outcome of drug treatment in hyperactive childhood behavior disorders. *Psychopharmacology Bulletin* 1974;**10**(4):36. [PUBMED: 4610619]

References to ongoing studies

Fanton 2009 *{published data only}*

Fanton J, Waslick B, Harvey E. The 49th Annual National Institute of Mental Health (NIMH) New Clinical Drug Evaluation Unit (NCDEU) meeting Hollywood, Florida, June 29-July 2, 2009: posters most relevant to child and adolescent psychopharmacology. Journal of Child and Adolescent Psychopharmacology 2009; Vol. 19, issue 6:786.

NCT01711021 *{published data only}*

NCT01711021. A randomized, double-blind, placebo-controlled, crossover, laboratory classroom study to evaluate the safety and efficacy of d-amphetamine transdermal drug delivery system (d-ATS) compared to placebo in children and adolescents with ADHD. http://clinicaltrials.gov/ct2/show/record/NCT01711021 (accessed 11 February 2014).

Additional references

AHRQ 1999

Agency for Health Care Policy and Research. Diagnosis of attention-deficit/hyperactivity disorder. Summary: technical review: number 3. www.ahrq.gov/clinic/epcsums/adhdsutr.htm (accessed 1 May 2012).

Anderson 1999

Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Natural Neuroscience* 1999;**2**(11):1032-7.

APA 1987

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

APA 2000

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). 4th Edition. Washington, DC: American Psychiatric Association, 2000.

Arnsten 2006

Arnsten AFT. Stimulants: therapeutic actions in ADHD. *Neuropsychopharmacology* 2006;**31**(11):2376-83.

Bero 2013

Bero LA. Why the Cochrane risk of bias tool should include funding source as a standard item [editorial]. Cochrane Database of Systematic Reviews 2013, issue 12:1. [DOI: 10.1002/14651858.ED000075]

Biederman 1993

Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry* 1993;**150**(12):1792-8.

Buck 2002

Buck ML. Amphetamines in the treatment of attention-deficit/hyperactivity disorder. *Pediatric Pharmacotherapy* 2002;**8**(3):1-3.

Castells 2011

Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: 10.1002/14651858.CD007813.pub2]

Charach 2011

Charach A, Dashti B, Carson P, Booker L, Lim CG, Lillie E, et al. Attention deficit hyperactivity disorder: effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Agency for Healthcare Research and Quality 2011.

Cohen 1988

Cohen J. Statistical Power Analysis in Behavioral Sciences. 2nd Edition. Hillsdale, NJ: Lawrence Erlbaum Associates Inc, 1988.

Conners 1990

Conners CK. Conners' Abbreviated Symptom Questionnaire: Parent Version, Teacher Version Manual. Toronto: Multi-Health Systems, 1990.

Conners 1998a

Conners CK, Sitarenios G, Parker JDA, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology* 1998;**26**(4):257-68.

Conners 1998b

Conners CK, Sitarenios G, Parker JDA, Epstein JN. Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability and criterion validity. *Journal of Abnormal Child Psychology* 1998;**26**(4):279-91.

Costello 1985

Costello EJ, Edelbrock CS, Costello AJ. Validity of the NIMH Diagnostic Interview Schedule for Children: a comparison between psychiatric and pediatric referrals. *Journal of Abnormal Child Psychology* 1985;**13**(4):579-95.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

DuPaul 1998

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale—IV: Checklists, Norms, and Clinical Interpretation. New York: The Guilford Press, 1998:186-201.

Edwards 1995

Edwards L, Salant V, Howard VF, Brougher J, McLaughlin TF. Effectiveness of self-management on attentional behavior and reading comprehension for children with attention deficit disorder. *Child and Family Behavior Therapy* 1995;**17**(2):1-17. [DOI: 10.1300/J019v17n02_01]

Egger 1997

Egger M, Zellwenger- Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomized controlled trials published in English and German. *Lancet* 1997;**350**(9074):329-9. [DOI: 10.1016/S0140-6736(97)02419-7]

Follman 1992

Follman D, Elliott P, Suh II, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology* 1992;**45**(7):769-73. [DOI: 10.1016/0895-4356(92)90054-Q]

GRADE Working Group 2004

GRADE Working Group. Education and debate: grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**:1490-9. [DOI: 10.1136/bmj.328.7454.1490]

Guy 1976

Busner J, Targum SD. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health, 1976.

Hedges 1994

Hedges LV. Statistical considerations. In: Cooper H, Hedges LV (editors). The Handbook of Research Synthesis. New York (NY): Russell Sage Foundation 1994.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [PUBMED: 12958120]

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lundh 2012

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.MR000033.pub2]

Mayes 2009

Mayes SD, Calhoun SL, Bixler EO, Vgontzas AN, Mahr F, Hillwig-Garcia J, et al. ADHD subtypes and comorbid anxiety, depression and oppositional-defiant disorder: differences in sleep problems. *Journal of Pediatric Psychology* 2009;**34**(33):328-37.

Miller 1999

Miller A, Lee S, Raina P, Klassen A, Zupancic J, Olsen L. A review of therapies for attention-deficit/hyperactivity disorder. www.cadth.ca/en/products/health-technology-assessment/publication/20 (accessed 11 February 2014).

Moher 2003

Moher D, Pham B, Lawson ML, Klassen TP. The inclusion of reports of randomized trials published in languages other than English in systematic reviews. *Health Technology Assessment* 2003;**7**(41):1-90.

Moore 2011

Moore EA. Ritalin, Adderall and other treatments for ADHD. The Amphetamine Debate: The Use of Adderall, Ritalin and Related Drugs for Behavior Modification, Neuroenhancement, and Anti-Aging Purposes. Jefferson, North Carolina: McFarland and Company, Inc, 2011:80-107.

NIH 2000

National Institute of Health. National Institutes of Health consensus development conference statement: diagnosis and treatment of attention-deficit/hyperactivity disorder (ADHD). *Journal of the American Academy of Child and Adolescent Psychiatry* 2000;**39**(2):182-97.

NIMH 2009

National Institute for Mental Health. Attention Deficit Hyperactivity Disorder (ADHD). www.nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder/complete-index.shtml (accessed 1 May 2012).

Polanczyk 2007

Polanczyk G, Silva de Lima M, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metagression analysis. *American Journal of Psychiatry* 2007;**164**(6):942-8.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Salum 2012

Salum GA, Patrick DL, Isolan LR, Manfro GG, Fleck MP. Youth Quality of Life Instrument-Research version (YQOL-R): psychometric properties in a community sample [Youth Quality of Life Instrument-Research version (YQOL-R): propriedades psicométricas em uma amostra comunitária]. *Journal of Pediatrics* 2012;**88**(5):443-8. [PUBMED: 22850664]

Schulz 2010

Schulz KF, Altman DG, Moher D, for the CONSORT Group. Research Methods & Reporting: CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. *BMJ* 2010;**340**:c332. [DOI: 10.1136/bmj.c332]

Sterne 2013

Sterne JAC. Why the Cochrane risk of bias tool should not include funding source as a standard item [editorial]. Cochrane Database of Systematic Reviews 2013, issue 12:1. [DOI: 10.1002/14651858.ED000076]

Swanson 1998b

Swanson J, Wigal S, Greenhill L, Browne R, Waslick B, Lerner M, et al. Objective and subjective measures of the pharmacodynamic effects of Adderall in the treatment of children with ADHD in a controlled laboratory classroom setting. *Psychopharmacoly Bulletin* 1998;**34**(1):55-60. [PUBMED: 9564199]

Swanson 2007

Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, et al. Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. *Neuropsychology Reviews* 2007;**17**(1):39-59. [PUBMED: 17318414]

The Medical Letter 2007

The Medical Letter Online. Lisdexamfetamine dimesylate (Vyvanase) for ADHD. *The Medical Letter on Drugs and Therapeutics* 2007;**49**(1265):58-9.

Varni 1998

Varni JW, Katz ER, Seid M, Quiggins DJ, Friedman-Bender A. The Pediatric Quality of Life Inventory-32 (PedsQL-32): reliability and validity. *Cancer* 1998;**82**(6):1184-96. [PUBMED: 9506367]

Wechsler 1991

Wechsler D. Wechsler Intelligence Scale for Children. San Antonio, TX: The Psychological Corporation, 1991.

Wigal 1999

Wigal T, Swanson JM, Regino R, Lerner MA, Soliman I, Steinoff K, et al. Stimulant medications for the treatment of ADHD: efficacy and limitations. *Mental Retardation and Development Disabilities Research Reviews* 1999;**5**(3):215-24.

Williamson 2012

Williamson PR, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: its role in improving Cochrane Reviews [editorial]. Cochrane Database of Systematic Reviews 2012, issue 4. [DOI: 10.1002/14651858.ED000041]

References to other published versions of this review

Punja 2012

Punja S, Shamseer L, Hartling L, Urichuk L, Vandermeer B, Nikles CJ, et al. Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD009996]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Barkley 2000

Methods	Randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** per protocol
Participants	**Sample size:** 46* children/adolescents with an ADHD diagnosis according to the DSM-IV criteria **Dropouts:** NR **Psychiatric comorbid conditions:** NR **Age range:** 12 years to 17 years **Mean age (SD):** 14 (NR) years **Sex:** 30 (86%) males **ADHD subtype:** NR
Interventions	**Five interventions (all 46 children/adolescents participated in each of the five interventions):** 1. Mixed amphetamine salts (short acting), 5 mg, twice a day, (n = 46) 2. Mixed amphetamine salts (short acting), 10 mg, twice a day, (n = 46) 3. Methylphenidate, 5 mg, twice a day, (n = 46) 4. Methylphenidate, 10 mg, twice a day, (n = 46) 5. Placebo (n = 46) **Duration:** 35 days (5 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with ADHD Rating Scale, Fourth Version (parents and teachers) 2. Clinical impression, assessed with Clinical Global Impressions - Improvement scale 3. Adverse events **Other outcomes:** 1. Oppositional defiant disorder symptom severity, assessed with an oppositional defiant disorder rating scale (not specified) 2. Assessment attention and impulsivity, as measured by the Conners' Continuous Performance Test 3. Response inhibition and interference control, assessed with the Stroop Word - Color Association Test
Notes	**ClinicalTrials.gov identifier:** not available **Authors' affiliation:** university **Study funding:** pharmaceutical industry *Clinical characteristics were only reported on children/adolescents who started the trial (n = 35)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described

Barkley 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Only data for completers included in analysis. For one of the primary outcomes, only 37% of randomized children/adolescents included in analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Biederman 2002

Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial **Country:** United States **Number of study sites:** 47 **Statistical methods:** modified ITT (last observation carried forward)
Participants	**Sample size:** 584* children/adolescents with an ADHD diagnosis according to DSM-IV criteria **Dropouts:** 75 **Psychiatric comorbid conditions:** NR **Age range:** 6 years to 12 years **Mean age (SD):** 8.6 (1.7) years **Sex:** 434 (77%) males **ADHD subtype:** 28 (5%) hyperactive - impulsive; 12 (2%) inattentive; 523 (93%) combined
Interventions	**Four interventions (584 children/adolescents participated in one of four interventions):** 1. Mixed amphetamine salts (long acting), 10 mg/day, (n = 129) 2. Mixed amphetamine salts (long acting), 20 mg/day (10 mg/day for week 1 with forced dose escalation to 20 mg/day in weeks 2 to 3), (n = 121) 3. Mixed amphetamine salts (long acting), 30 mg/day (10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3), (n = 124) 4. Placebo (n = 210) **Duration:** 21 days
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners Global Index, teacher- and parent-rated 2. Clinician impression, assessed with Clinical Global Impressions - Improvement scale 3. Retention: proportion of participants who completed the trial 4. Number of participants who experienced at least one adverse event 5. Number of participants who dropped out due to any adverse event 6. Adverse events
Notes	**ClinicalTrials.gov identifier:** not available

Biederman 2002 *(Continued)*

Authors' affiliations: university
Study funding: pharmaceutical industry

*Clinical characteristics are only provided on those children included in the primary efficacy analysis (n = 563)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Moderate attrition (13%). Reasons for attrition reported and 96% of randomized children/adolescents included in primary analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Biederman 2007a

Methods	Multi-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 4 **Statistical methods:** modified ITT (all randomized children/adolescents who had at least one post-randomization score on primary outcome measure)
Participants	**Sample size:** 52 children/adolescents with an ADHD diagnosis according to the DSM-IV-TR criteria **Dropouts:** 2 **Psychiatric comorbid conditions:** NR **Age range:** 6 years to 12 years **Mean age (SD):** 9.1 (1.7) years **Sex:** 33 (64%) males **ADHD subtypes:** 52 (100%) combined
Interventions	**Three interventions (all 52 children/adolescents participated in each of the three interventions):** 1. Mixed amphetamine salts (long acting), either 10 mg/day, 20 mg/day or 30 mg/day (determined by dose optimisation period), (n = 52)* 2. Lisdexamphetamine (long acting), either 30 mg/day, 50 mg/day or 70 mg/day (determined by dose optimisation period), (n = 52) 3. Placebo (n = 52)

Biederman 2007a *(Continued)*

	Duration: 21 days (3 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with the attention subscale (investigator) of the Swanson, Kotkin, Agler, M-Flynn and Pelham scale 2. Academic performance, assessed with Permanent Product Measure of Performance scale 3. Clinical impression, assessed with Clinical Global Impressions - Severity and Clinical Global Impressions - Improvement scales 4. Retention: number of participants who completed the study 5. Adverse events **Other outcomes:** 1. Conduct problems, assessed with deportment subscale of the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) scale 2. Vital signs (blood pressure, pulse)
Notes	**ClinicalTrials.gov identifier:** NCT00557011 **Authors' affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry *Mixed amphetamine salts - extended release was randomly chosen to represent the amphetamine group in this study for binary outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	Method of allocation concealment involved pre-packaged, serially-numbered drug kits, in which the next participant enrolled received the next available drug kit. Drug kits prepared by a third party
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although the primary analysis only included trial completers, attrition was low at 4%
Selective reporting (reporting bias)	Low risk	Data provided on all outcomes listed in the registered protocol. Study appears to be free of selective reporting
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Biederman 2007b

Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial

Biederman 2007b *(Continued)*

	Country: United States **Number of study sites:** 40 **Statistical methods:** modified ITT (children/adolescents who had baseline and at least one post-randomization primary efficacy measure, last observation carried forward)
Participants	**Sample size:** 290 children/adolescents with an ADHD diagnosis according to the DSM-IV-TR criteria **Dropouts:** 60 **Psychiatric comorbid conditions:** NR **Age range:** 6 years to 12 years **Mean age (SD):** 9 (1.8) years **Sex:** 201 (69%) males **ADHD subtype:** 12 (4%) hyperactive - impulsive; 278 (96%) combined
Interventions	**Four interventions (290 children/adolescents participated in one of four interventions):** 1. Lisdexamphetamine (long acting), 30 mg/day, (n = 71) 2. Lisdexamphetamine (long acting), 50 mg/day (30 mg/day for week 1 with forced dose escalation to 50 mg/day for weeks 2 to 4), (n = 74) 3. Lisdexamphetamine (long acting), 70 mg/day (30 mg/day for week 1 with forced dose escalation to 50 mg/day for week 2 and 70 mg/day for weeks 3 to 4), (n = 73) 4. Placebo (n = 72) **Duration:** 28 days
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with ADHD Rating Scale, Fourth Version, and the Conners' Parent Rating Scale-Revised: Short Form 2. Clinical impression, assessed with Clinical Global Impression - Severity and Clinical Global Impressions - Improvement scales 3. Retention: proportion of participants who completed the trial 4. Number of participants who experienced at least one adverse event 5. Number of participants who dropped out due to any adverse event 6. Adverse events
Notes	**ClinicalTrials.gov identifier:** not available **Authors' affiliation:** university **Study funding:** pharmaceutical industry *The authors reported their results of parent ratings of hyperactivity/impulsivity and inattention on the ADHD Rating Scale, Fourth Version, as well as total ADHD symptom scores on the Conners' Parent Rating Scale - Revised as bar graphs. We sought to extract relevant data using graphic digitizer software but this gave implausible results. Consequently, this data could not be included in the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated by a computer program
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Moderate attrition (21%). However, 98% of randomized children/adolescents included in primary analysis. Reasons for dropouts provided

Biederman 2007b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo are described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Borcherding 1990

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** ITT (all randomized children/adolescents are included in the analysis, with any missing data imputed with the group mean value)
Participants	**Sample size:** 46 children/adolescents with an ADHD diagnosis according to DSM-III criteria **Dropouts:** NR **Psychiatric comorbid conditions:** oppositional defiant disorder, conduct disorder, reading developmental disorder, arithmetic disorder, dysthymic disorder **Age range:** 6 years to 12 years **Mean age (SD):** 8.6 (1.7) years **Sex:** 46 (100%) males **ADHD subtype:** NR
Interventions	**Three interventions (all 46 children/adolescents participated in each of the three interventions):** 1. Dextroamphetamine (short acting), weight-based dosing increasing each week (children < 30 kg (66 lbs) received 10, 25, and 40 mg/day, twice a day; children/adolescents > 30 kg (66 lbs) received 15, 30, and 45 mg/day, twice a day), (n = 46) 2. Methylphenidate hydrochloride, weight-based dosing increasing each week (children < 30 kg (66 lbs) received 25, 40, and 70 mg/day, twice a day; children/adolescents > 30 kg (66 lbs) received 30, 50, and 90 mg/day, twice a day), (n = 46) 3. Placebo (n = 46) **Duration:** 63 days (3 x 21-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Teacher Rating Scale - Short Form* and Conners' Parent Rating Scale - Long Form 2. Clinical impression, assessed with Clinical Global Impressions - Improvement scale 3. Academic performance, assessed with: the Barnell Loft, Ltd, *Developing Key Concepts in Math* test 4. Retention: proportion of participants who completed the trial 5. Adverse events **Other outcomes:** 1. Nervous habits/mannerisms, compulsive acts and obsessive thinking assessed with Children's Psychiatric Rating Scale 2. Urine biochemistry

Borcherding 1990 *(Continued)*

	3. Plasma biochemistry 4. Renal clearance 5. Cognitive ratings, assessed with Conners' Continuous Performance Test
Notes	**ClinicalTrials.gov identifier:** not available **Authors' affiliation:** National Institute of Mental Health **Study funding:** NR Outcomes were presented across four publications with varying sample sizes *Unpublished data on the ADHD symptoms as rated by the Conners' Teacher Rating Scale - Short Form were sought on three separate occasions but were not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	High risk	This study has four associated publications, and all reports have varying numbers of participants. Upon communication with the corresponding author of these reports, it was confirmed that the numbers of participants vary in the four publications due to missing data and dropouts. Reasons for missing data not provided
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Unclear risk	No information on the validity of the primary outcome measure provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Childress 2015

Methods	Multi-center, randomized, double-blinded, placebo-controlled, cross-over trial **Countries:** United States **Number of study sites:** 7 **Statistical methods:** modified ITT (all randomized children/adolescents who took at least one dose of the study medication, and had at least one post-randomization score on primary outcome measure)
Participants	**Sample size:** 97 children/adolescents with an ADHD diagnosis according to DSM-IV-TR criteria **Dropouts:** 2 **Psychiatric comorbid conditions:** NR **Age range:** 6 years to 12 years **Mean age (SD):** 9.6 (1.86) years **Sex:** 59 (60.8%) males

Childress 2015 *(Continued)*

	ADHD subtype: 0 (0%) hyperactive - impulsive; 18 (18.6%) inattentive; 79 (81.4%) combined
Interventions	**Two interventions (all 97 children/adolescents participated in both interventions):** 1. Mixed amphetamine salts (short acting), dose determined by dose optimisation period (mean (SD) dose: 23.4 (8.18) mg/day), (n = 97) 2. Placebo (n = 97) **Duration:** 14 days (2 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with the combined (investigator/research personnel) and attention subscales of the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) scale 2. Academic performance, assessed with Permanent Product Measure of Performance 3. Retention: proportion of participants who completed the trial 4. Adverse events
Notes	**ClinicalTrials.gov identifier:** NCT01986062 **Authors' affiliation:** pharmaceutical industry **Study funding:** pharmaceutical industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated using an interactive web-based response system
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very low attrition (2%)
Selective reporting (reporting bias)	Low risk	Data provided on all outcomes listed in the registered protocol. Study appears to be free of selective reporting
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Coghill 2013

Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial **Countries:** Belgium, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden, UK **Number of study sites:** 48 **Statistical methods:** modified ITT (last observation carried forward)

Coghill 2013 *(Continued)*

Participants	**Sample size:** 336* children/adolescents with an ADHD diagnosis according to DSM-IV-TR criteria **Dropouts:** 140 **Psychiatric comorbid conditions:** ODD **Age range:** 6 years to 17 years **Mean age (SD):** 10.9 (2.8) **Sex:** 268 (81%) male **ADHD subtype:** 10 (3%) hyperactive-impulsive; 53 (16%) inattentive; 268 (80.7%) combined; 1 (0.3%) NR
Interventions	**Three interventions (336 children/adolescents participated in one of three interventions):** 1. Lisdexampehtamine (long acting), varying doses at either 30, 50, or 70 mg/day, (n = 113) a. Mean (SD) dose across participants: 53.8 (15.6) mg/day 2. Osmotic release oral system methylphenidate, varying doses at either 18, 36, or 59 mg/day, (n = 112) a. Mean (SD) dose across participants: 45.4 (12.7) mg/day 3. Placebo (n = 111) **Duration:** 49 days
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with ADHD Rating Scale, Fourth Version (investigator), and Conners' Parent Rating Scale - Revised 2. Clinical impression, assessed with Clinical Global Impression - Severity and Clinical Global Impression - Improvement scales 3. Retention: proportion of participants who completed the trial 4. Number of participants who dropped out due to lack of efficacy 5. Number of participants who dropped out due to any adverse event 6. Adverse events
Notes	**ClinicalTrials.gov identifier:** NCT00763971 **Authors' affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry Outcomes were presented across three publications *Clinical characteristics were only reported on those who received at least one dose of the intervention to which they were randomized (n = 332)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	Study utilized an interactive voice/web response system, which automatically generated a unique randomization number for each child/adolescent
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition (58%). 14 (4%) children/adolescents excluded from the efficacy analysis with no reasons provided
Selective reporting (reporting bias)	High risk	Outcomes listed in the registered protocol are not reported in any of the three publications
Other bias	Low risk	Study appears to be free of other biases

Coghill 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo are described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is not described

Donnelly 1989

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** ITT
Participants	**Sample size:** 20 children/adolescents with an ADHD diagnosis according to DSM-III criteria **Dropouts:** NR **Psychiatric comorbid conditions:** oppositional defiant disorder, conduct disorder, mental learning disorder, language disorder **Age range:** NR **Mean age (SD):** 8 (2) years **Sex:** 20 (100%) males **ADHD subtype:** NR
Interventions	**Three interventions (all 20 children/adolescents participated in each of the three interventions):** 1. Dextroamphetamine (short acting), weight-based dose, 0.5 mg/kg/day, twice a day, (n = 20) 2. Fenfluramine hydrochloride, weight-based dosing increasing each week (0.6 mg/kg/day, 1.3 mg/kg/day, 2.0 mg/kg/day), twice a day, (n = 20) 3. Placebo (n = 20) **Duration:** 63 days (3 x 21-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Teacher Rating Scale - Short Form 2. Clinical impression, assessed with Clinical Global Impression scale* 3. Adverse events **Other outcomes:** 1. Vigiliance/attention and impulsivity, assessed with Conners' Continuous Performance Test 2. Motor activity, assessed with activity monitor 3. Biochemical and platelet measures (urine and plasma) 4. Measures of prolactin
Notes	**ClinicalTrials identifier:** not available **Authors' affiliation:** university and National Institute of Mental Health **Study funding:** NR Donnelly 1986 is a pilot study of Donnelly 1989 and therefore have overlapping data *Unpublished data on the Clinical Global Impression scale sought on three separate occasions but not obtained

Donnelly 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited children/adolescents included in analyses. Only one dropout, with reasons provided
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Unclear risk	No information on the validity of the primary outcome measure provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Findling 2011

Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial **Country:** United States **Number of study sites:** 45 **Statistical methods:** modified ITT (last observation carried forward)
Participants	**Sample size:** 314 children/adolescents with an ADHD diagnosis according to DSM-IV-TR criteria **Dropouts:** 52 **Psychiatric comorbid conditions:** NR **Age range:** 13 years to 17 years **Mean age (SD):** 14.6 (1.31) years **Sex:** 249 (79%) males **ADHD subtype:** 203 (65%) combined
Interventions	**Four interventions (312 children/adolescents participated in one of four interventions):** 1. Lisdexamphetamine (long acting), 30 mg/day, (n = 78*) 2. Lisdexamphetamine (long acting), 50 mg/day (30 mg/day for week 1 with forced dose escalation to 50 mg/day for weeks 2 to 4), (n = 77*) 3. Lisdexamphetamine, long acting, 70 mg/day (30 mg/day for week 1 with forced dose escalation to 50 mg/day for week 2 and 70 mg/day for weeks 3 to 4), (n = 78*) 4. Placebo (n = 79) **Duration:** 28 days
Outcomes	**Relevant outcomes:**

Findling 2011 *(Continued)*

1. ADHD core symptom severity, assessed with ADHD Rating Scale, Fourth Version (clinician ratings)
2. Clinical impression, assessed with Clinical Global Impression - Severity and Clinical Global Impression - Improvement scales
3. Quality of life, assessed with Youth Quality of Life - Research Version (YQOL-R)
4. Retention: proportion of participants who completed the trial
5. Number of participants who dropped out due to lack of efficacy
6. Number of participants who experienced at least one adverse event
7. Number of participants who dropped out due to any adverse event
8. Adverse events

Notes	**ClinicalTrials.gov identifier:** NCT00735371 **Authors' affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry *Numbers are based on participants included in the safety analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated by a web-based computer system
Allocation concealment (selection bias)	Low risk	Allocation concealment ensured using the web-based computer system and third party, which serially numbered treatment bottles for each participant
Incomplete outcome data (attrition bias) All outcomes	Low risk	Moderate attrition (16%). However, 98% of randomized children/adolescents included in primary efficacy analysis. Reasons for dropouts provided
Selective reporting (reporting bias)	Low risk	Data provided on all outcomes listed in the registered protocol. Study appears to be free of selective reporting
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Giblin 2011

Methods	Single-center, randomized, double-blind, placebo-controlled, parallel-group trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** modified ITT (all randomized children/adolescents who had both a baseline and a post-randomization primary outcome assessment)
Participants	**Sample size:** 24 children/adolescents with an ADHD diagnosis according to DSM-IV-TR criteria **Dropouts:** 0 **Psychiatric comorbid conditions:** NR

Giblin 2011 *(Continued)*

	Age range: 6 years to 12 years **Mean age (SD):** 9.65 (2.2) years **Sex:** 10 (42%) males **ADHD subtype:** NR
Interventions	**Four interventions (24 children/adolescents participated in one of four interventions):** 1. Lisdexamphetamine (long acting), 30 mg/day, (n = 3) 2. Lisdexamphetamine, (long acting), 50 mg/day, (n = 11) 3. Lisdexamphetamine, (long acting), 70 mg/day, (n = 2) 4. Placebo (n = 8) **Duration:** 28 days
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with ADHD Rating Scale, Fourth Version (investigator) and Conners' Parent Rating Scale - Revised: Short Form* 2. Clinical impression, assessed with Clinical Global Impression - Severity scale 3. Adverse events **Other outcomes:** 1. Sleep onset latency, assessed with polysomnography 2. Wake time after sleep onset, assessed with polysomnography and actigraphy 3. Number awakenings after sleep onset, assessed with polysomnography 4. Total sleep time, assessed with polysomnography and actigraphy 5. Sleep efficiency, assessed with actigraphy
Notes	**ClinicalTrials.gov identifier:** not available **Authors' affiliation:** private organization and pharmaceutical industry **Study funding:** pharmaceutical industry *Unpublished data sought on both outcome measures on three separate occasions but not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Incomplete outcome data not addressed; number of completers not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described

Giblin 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Gillberg 1997

Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial **Country:** Sweden **Number of sites:** 4 **Statistical methods:** modified ITT (for inclusion into the analysis at least two measurements had to be available, with the last observation carried forward)
Participants	**Sample size:** 62 children/adolescents with an ADHD diagnosis according to DSM-III-R criteria **Dropouts:** NR **Psychiatric comorbid conditions:** oppositional defiant disorder, conduct disorder, anxiety, autistic disorder, pervasive development disorder, motor tic disorder, Tourette syndrome, mild mental retardation **Age range:** 6 years to 11 years **Mean age (SD):** 9 (1.6) years **Sex:** 52 (84%) males **ADHD subtype:** NR
Interventions	**Two interventions (62 children/adolescents participated in one of two interventions):** 1. Mixed amphetamine salts (short acting), dosage was titrated from 10 mg/day, twice a day, to a maximum of 60 mg/day, twice a day, (n = 32) 2. Placebo (n = 30) **Duration:** 365 days
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Teacher Rating Scale and Conners' Parent Rating Scale 2. Adverse events **Other outcomes:** 1. Depression, assessed with the Birleson Depression Self-Rating Scale 2. Mood, assessed with the McGrath Test
Notes	**ClinicalTrials.gov identifier:** not available **Authors' affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry and public funds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described

Gillberg 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Moderate attrition (14%). However, all dropouts occurred prior to randomization. Reasons for dropout provided. All randomized children/adolescents included in primary analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

James 2001

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** per protocol
Participants	**Sample size:** 35 children/adolescents with an ADHD diagnosis according to DSM-IV criteria **Dropouts:** NR **Psychiatric comorbid conditions:** oppositional defiant disorder, anxiety, enuresis, dysthymic disorder, learning disorder **Age range:** 6.9 years to 12.2 years **Mean age (SD):** 9.1 (1.5) years **Sex:** 21 (60%) males **ADHD subtype:** 35 (100%) combined
Interventions	**4 interventions:*** 1. Dextroamphetamine (short acting)* 2. Dextroamphetamine spansules (long acting)* 3. Mixed amphetamine salts (long acting)* 4. Placebo **Duration:** 56 days (4 x 14-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Teacher Rating Scale and Conners' Parent Rating Scale 2. Academic performance, assessed with a 5-minute timed math task 3. Adverse events **Other outcomes:** 1. Motor activity, assessed with an actometer
Notes	**ClinicalTrial.gov identifier:** not available

James 2001 *(Continued)*

Authors' affiliation: National Insitute of Mental Health
Study funding: NR
*Doses were individualized and based on age, weight, prior medication experience and symptom severity (overall mean dose range: 7.8 mg/day to 12.8 mg/day)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (7%), and reasons provided. All dropouts occurred prior to randomization. All randomized children/adolescents completed the trial and included in primary analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Manos 1999

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** unclear
Participants	**Sample size:** 84 children/adolescents with an ADHD diagnosis according to DSM-IV criteria **Dropouts:** NR **Psychiatric comorbid conditions:** oppositional defiant disorder, anxiety, mood disorder, learning disability **Age range:** 5 years to 17 years **Mean age (SD):** 10.1 (NR) years **Sex:** 66 (79%) males **ADHD subtypes:** 38 (45%) inattentive; 46 (55%) combined
Interventions	**Two conditions (84 children/adolescents participated in one of two conditions):** 1. Mixed amphetamine salts (short acting), (42 children/adolescents participated in each of the following four interventions)**:** a. 5 mg/day, once daily b. 10 mg/day, once daily c. 15 mg/day, once daily

Manos 1999 *(Continued)*

	d. Placebo 2. 2. Methylphenidate (42 children/adolescents participated in each of the following four interventions): a. 5 mg/day, twice a day b. 10 mg/day, twice a day c. 15 mg/day, twice a day d. Placebo Children/adolescents received either the four mixed amphetamine salt OR methylphenidate conditions (determined by his or her physician) in a randomly assigned sequence **Duration:** 28 days (4 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Abbreviated Symptoms Questionnaire - Parent Version and Conners' Abbreviated Symptoms Questionnaire - Teacher Version 2. Adverse events **Other outcomes:** 1. Concentration in school, assessed with School Situations Questionnaire - Revised
Notes	**ClinicalTrial.gov identifier:** not available **Authors' affiliations:** university **Study funding:** public funds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	A third party pharmacist prepared individually sealed bottles dated by week
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study did not describe if any children/adolescents dropped out from the trial
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo are described as identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinician, teacher and parent (outcome assessors) were blinded to treatment order

McCracken 2003

Methods	Multi-center, randomized, double-blind, placebo-controlled, cross-over trial

McCracken 2003 *(Continued)*

	Country: United States **Number of study sites:** 4 **Statistical methods:** modified ITT
Participants	**Sample size:** 51 children/adolescents with an ADHD diagnosis according to DSM-IV criteria **Dropouts:** 4 **Psychiatric comorbid conditions:** NR **Age range:** 6 years to 12 years **Mean age (SD):** 9.5 (1.9) years **Sex:** 44 (86%) males **ADHD subtypes:** 1 (2%) hyperactive - impulsive; 50 (98%) combined
Interventions	**Five interventions (all 51 children/adolescents participated in each of the five interventions):** 1. Mixed amphetamine salts (short acting), 10 mg, once a day, (n = 51) 2. Mixed amphetamine salts (long acting), 10 mg, once a day, (n = 51) 3. Mixed amphetamine salts (long acting), 20 mg, once a day*, (n = 51) 4. Mixed amphetamine salts (long acting), 30 mg, once a day, (n = 51) 5. Placebo (n = 51) **Duration:** 35 days (5 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with the attention subscale (investigator ratings) of the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) scale 2. Academic performance, assessed with Permanent Product Measure of Performance 3. Retention: proportion of participants who completed the trial 4. Number of participants who dropped out due to any adverse event 5. Adverse events **Other outcomes:** 1. Conduct problems, assessed with the deportment subscale of the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) scale
Notes	**ClinicalTrial.gov identifier:** not available **Authors' affiliation:** university **Study funding:** pharmaceutical industry *We randomly chose mixed amphetamine salts (long acting), given at 20 mg/day, to represent the amphetamine group in this study for binary outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (4%) and reasons provided. All randomized children/adolescents included in primary analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed

McCracken 2003 *(Continued)*

Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Nemzer 1986

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** NR
Participants	**Sample size:** 14 children/adolescents with an ADHD diagnosis according to DSM-III criteria **Dropouts:** NR **Psychiatric comorbid conditions:** NR **Age range:** 7 years to 12 years **Mean age (SD):** 9.36 (NR) years **Sex**: 11 (79%) males **ADHD subtype:** NR
Interventions	**Four interventions (all 14 children/adolescents participated in each of the four interventions):** 1. Dextroamphetamine (short acting), weight-based dosing (children < 32 kg (70.5 lbs) received 5 mg/day, twice a day; children/adolescents > 32 kg (70.5 lbs) received 10 mg/day), twice a day, (n = 14) 2. Tyrosine supplement, 140 mg/kg/day, (n = 14) 3. Tryptophan supplement, 100 mg/kg/day, (n = 14) 4. Placebo (n = 14) **Duration:** 28 days (4 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Parent Rating Scale and Conners' Teacher Rating Scale 2. Academic performance, assessed with Wechsler Intelligence Scale for Children - Revised 3. Adverse events **Other outcomes:** 1. Tyrosine serum levels 2. Tryptophan serum levels
Notes	**ClinicalTrials.gov identifier:** not available **Authors' affiliation:** university **Study funding:** NR

Risk of bias

Nemzer 1986 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not discussed
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo are described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Pliszka 2000

Methods	Single-center, randomized, double-blind, placebo-controlled, parallel-group trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** modified ITT (last observation carried forward)
Participants	**Sample size:** 59* children/adolescents with an ADHD diagnosis according to the Diagnostic Interview Schedule for Children **Dropouts:** 5 **Psychiatric comorbid disorders:** oppositional defiant disorder, conduct disorder, anxiety **Age range:** 6 years to 10 years **Mean age (SD):** 8.2 (1.6) years **Sex:** NR **ADHD subtype:** NR
Interventions	**Three interventions (58 children/adolescents participated in one of three interventions):** 1. Mixed amphetamine salts (short acting), weight-based, titrated dosing (maximum dose for children < 27.2 kg (60 lbs) was 15 mg/day; maximum daily dose for children/adolescents > 27.2 kg (60 lbs) was 30 mg/day), (n = 20) 2. Methylpehnidate, weight-based, titrated dosing (maximum dose for children < 27.2 kg (60 lbs) was 25 mg/day; maximum daily dose for children/adolescent > 27.2 kg (60 lbs) was 50 mg/day), (n = 20) 3. Placebo (n = 18) **Duration:** 21 days
Outcomes	**Relevant outcomes:**

Pliszka 2000 *(Continued)*

1. ADHD core symptom severity, assessed with IOWA (inattention/overactivity with aggression) Conners' Teacher Rating Scale and Conners' Parent Global Index
2. Clinical impression, assessed with Clinical Global Impressions - Improvement scale
3. Number of participants who dropped out due to any adverse event
4. Adverse events

Other outcomes:

1. Agression/defiance, assessed with Conners' Teacher Rating Scale

Notes	**ClinicalTrials.gov identifier:** not available **Author's affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry *1 participant dropped out before the end of the study, and was not accounted for in the participant characteristic description (data only provided on 58 participants)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (10%), and reasons provided. All randomized children/adolescents included in primary analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo are described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Ramtvedt 2013

Methods	Multi-center, randomized, placebo-controlled, cross-over trial **Country:** Norway **Number of study sites:** 4 **Statistical methods:** unclear
Participants	**Sample size:** 36* children/adolescents with an ADHD diagnosis according to DMS-IV-TR criteria **Dropouts:** 0 **Psychiatric comorbid disorders:** oppositional defiant disorder, anxiety/depression, learning disability **Age range:** 9 years to 14 years

Ramtvedt 2013 *(Continued)*

	Mean age (SD): 11.4 (1.4) years **Sex:** 29 (81%) males **ADHD subtype:** 10 (28%) inattentive; 1 (3%) hyperactive - impulsive; 25 (69%) combined
Interventions	**Three interventions (all 36 children/adolescents participated in each of the three interventions):** 1. Dextroamphetamine (short acting), 5 mg twice a day in week 1; 10 mg twice a week in week 2, (n = 36) 2. Methylphenidate (short acting): 10 mg three times a day in week 1; 15 mg twice a day, 10 mg once daily in week 2, (n = 36) 3. Placebo (n = 36) **Duration:** 42 days (3 x 14-day treatment periods)
Outcomes	**Relevant outcomes:** 1. Improvement of ADHD symptoms, assessed with a 21-item ADHD questionnaire developed for the study by parents and teachers** 2. Adverse events **Other outcomes:** 1. Inattention, assessed with Conners' Continuous Performance Test 2. Motor activity, assessed with Conners' Continuous Performance Test
Notes	**ClinicalTrials.gov identifier:** NCT01220440 **Authors' affiliation:** university and hospital **Study funding:** public funds Outcomes were presented across two publications *Data only provided on those children/adolescents who completed the trial; no information provided regarding number of children/adolescents randomized **Data is presented as an aggregate score of parent and teacher ratings and therefore could not be incorporated into the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary analysis only included a subset of completers without any reason provided. No information on non-completers provided
Selective reporting (reporting bias)	High risk	Although the registered protocol stated that they would collect adverse events using the Side-Effects Rating Scale, this was not reported in the published manuscript
Other bias	Unclear risk	No information on the validity of the primary outcome measure provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions and placebo were not identical

Ramtvedt 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Sharp 1999

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** ITT (missing data were imputed using group means)
Participants	**Sample size:** 32* children/adolescents with an ADHD diagnosis according to DSM-IV criteria **Dropouts:** 1 **Psychiatric comorbid disorders:** oppositional defiant disorder, conduct disorder, depression, separation anxiety, specific phobias, tic disorder, enuresis, reading disorder **Age range:** 6.2 years to 12.7 years **Mean age (SD):** 8.9 (1.7) years **Sex:** 0 (0%) males **ADHD subtype:** 32 (100%) combined
Interventions	**Three interventions (all 32 children/adolescents participated in each of the three interventions):** 1. Dextroamphetamine (short acting), weight-based dosing and increasing over time (mean doses of 0.23 mg/kg/day, 0.43 mg/kg/day, and 0.64 mg/kg/day, twice a day for weeks 1, 2, and 3 respectively), (n = 32) 2. Methylphenidate, weight-based dosing and increasing over time (mean doses of 0.45 mg/kg/day, 0.85 mg/kg/day, and 1.28 mg/kg/day, once daily for weeks 1, 2, and 3 respectively), (n = 32) 3. Placebo (n = 32) **Duration:** 63 days (3 x 21-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Parent Rating Scale and Conners' Teacher Rating Scale** 2. Clinician impression, assessed with Clinical Global Impressions - Severity and Clinical Global Impressions - Improvement scales 3. Retention: proportion of participants who completed the trial 4. Adverse events
Notes	**ClinicalTrial.gov identifier:** not available **Authors' affiliation:** university and National Institute for Mental Health **Study funding:** NR *Clinical characteristics were presented on 42 children/adolescents, 10 of whom participated in a separate pilot program **Unpublished data on the ADHD core symptoms sought on three separate occasions but not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described

Sharp 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Moderate attrition (14%), with reasons provided
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo are described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Shekim 1986

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** NR
Participants	**Sample size:** 22 children/adolescents with an ADHD diagnosis according to DSM-III criteria **Dropouts:** NR **Psychiatric comorbid disorders:** 0 **Age range:** 6 years to 12 years **Mean age (SD):** 9.75 (2.08) years **Sex:** 22 (100%) males **ADHD subtype:** NR
Interventions	**Two interventions (all 22 children/adolescents participated in both interventions):** 1. Dextroamphetamine (short acting), weight-based at 0.3 mg/kg twice a day, and titrated upwards during trial period, (n = 22) 2. Placebo (n = 22) **Duration:** 28 days (2 x 14-day treatment periods)
Outcomes	**Relevant outcomes:** 1. Academic performance, assessed with Wide Range Achievement Test - math subset **Other outcomes:** 1. Wide Range Achievement Test - spelling and reading subsets 2. Monoamine oxidase activity 3. Attention and impulsivity, assessed with Conners' Contininuous Performance Test
Notes	**ClinicalTrials.gov identifier:** not available

Shekim 1986 *(Continued)*

Authors' affiliation: university
Study funding: public funds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for exclusions from the analysis not provided. Methods of analysis not described. Number of individuals included in the analyses not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Short 2004

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** per protocol
Participants	**Sample size:** 34* children/adolescents with an ADHD diagnosis according to DSM-IV criteria **Dropouts:** NR **Psychiatric comorbid conditions:** NR **Age range:** 3 years to 5.9 years **Mean age (SD):** 5.3 (NR) years **Sex:** 24 (85%) males **ADHD subtype:** 5 (17%) inattentive; 23 (83%) hyperactive - impulsive or combined
Interventions	**Two conditions (28 children/adolescents participated in one of two conditions)*:** 1. Amphetamine: a. Mixed amphetamine salts (short acting), 5 mg/day, once daily b. Mixed amphetamine salts (short acting), 10 mg/day, once daily c. Mixed amphetamine salts (short acting), 15 mg/day, once daily d. Placebo 2. Methylphenidate: a. Methylphenidate, 5 mg/day, twice a day

Short 2004 *(Continued)*

	b. Methylphenidate, 10 mg/day, twice a day c. Methylphenidate, 15 mg/day, twice a day d. Placebo Amphetamine or methylphenidate determined by a physician **Duration:** 28 days (4 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with Conners' Parent Rating Scale-short form and Conners' Teacher Rating Scale-short form** 2. Adverse events
Notes	**ClinicalTrial.gov identifier:** not available **Authors' affiliations:** university **Study funding:** public funds *Clinical characteristics only presented on children/adolescents included in analysis (n = 28) **The authors did not separate the two active interventions (amphetamine and methylphenidate) in their analysis. We contacted the authors on three occasions to obtain the data on amphetamines only, but we received no response, and therefore outcomes could not be included in the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not sufficiently described
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition not described. In addition, six participants were dropped from the analysis, and their last data point was not carried forward
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to order of trial interventions

Spencer 2006a

Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial **Country:** United States **Number of study sites:** NR **Statistical methods:** modified ITT (those with at least one post-baseline primary efficacy assessment)

Spencer 2006a *(Continued)*

Participants	**Sample size:** 287* children/adolescents with an ADHD diagnosis according to DSM-IV-TR criteria **Dropouts:** 52 **Psychiatric comorbid conditions:** NR **Age range:** 13 years to 16 years **Mean age (SD):** 14.2 (1.2) years **Sex:** 182 (66%) males **ADHD subtypes:** 114 (41%) inattentive; 7 (2.5%) hyperactive-impulsive; 157 (56.5%) combined
Interventions	**Five interventions (287 children/adolescents participated in one of five interventions):** 1. Mixed amphetamine salts (long acting), 10 mg/day, once daily, (n = 56) 2. Mixed amphetamine salts (long acting), 20 mg/day, once daily (10 mg/day for week 1 with forced dose escalation to 20 mg/day for weeks 2 to 4), (n = 56) 3. Mixed amphetamine salts (long acting), 30 mg/day, once daily (10 mg/day for week 1, with forced dose escalation to 20 mg/day for week 2, and 30 mg/day for weeks 3 to 4), (n = 58) 4. Mixed amphetamine salts (long-acting), 40 mg/day, once daily (10 mg/day for week 1, with forced dose escalation to 20 mg/day for week 2, 30 mg/day for week 3, and 40 mg/day for week 4), (n = 63) 5. Placebo (n = 54) **Duration:** 28 days (4 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with ADHD Rating Scale, Fourth Version (clinician ratings) 2. Clinical impression, assessed with Clinical Global Impression - Severity and Clinical Global Impression - Improvement scales 3. Retention: proportion of participants who completed the trial 4. Number of participants who dropped out due to any adverse event 5. Adverse events **Other outcomes:** 1. Vital signs 2. Body weight
Notes	**ClinicalTrials.gov Identifier:** NCT00507065 **Authors' affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry *Clinical characteristics only provided on the study's ITT population (n = 278)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (10%), and reasons provided. Only 3% of children/adolescents excluded from analysis due to no post-baseline primary efficacy assessment
Selective reporting (reporting bias)	Low risk	Data provided on all outcomes listed in the registered protocol. Study appears to be free of selective reporting

Spencer 2006a *(Continued)*

Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Swanson 1998a

Methods	Single-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 1 **Statistical methods:** unclear
Participants	**Sample size:** 33 children/adolescents with an ADHD diagnosis according to DSM-IV criteria **Dropouts:** 3 **Psychiatric comorbid conditions:** NR **Age range:** 7 years to 14 years **Mean age (SD):** 10.58 (1.81) years **Sex:** 26 (79%) males **ADHD subtypes:** NR
Interventions	**Six interventions (all 33 children/adolescents participated in each of the six interventions):** 1. Mixed amphetamine salts (short acting), 5 mg/day, once daily, (n = 33) 2. Mixed amphetamine salts (short acting), 10 mg/day, once daily, (n = 33) 3. Mixed amphetamine salts (short acting), 15 mg/day, once daily, (n = 33) 4. Mixed amphetamine salts (short acting), 20 mg/day, once daily, (n = 33) 5. Methylphenidate (dose determined by physician), (n = 33) 6. Placebo (n = 33) **Duration:** 49 days (6 x 7-day treatment periods defined by the six medication conditions above, plus an extra seven-day period to provide an opportunity to make-up any missed weeks)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with the attention subscale (teacher ratings)* of the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) scale 2. Academic performance, assessed with Permanent Product Measure of Performance* 3. Retention: proportion of randomized participants who completed the trial **Other outcomes:** 1. Conduct problems, assessed with the deportment subscale of the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) scale
Notes	**ClinicalTrials identifier:** not available **Authors' affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry *Unpublished data on outcomes sought on three separate occasions but not obtained

Swanson 1998a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Low attrition (8%), but reasons for dropout not provided, and only 88% of children/adolescents contributed to primary analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and the possibility of reporting bias could not be assessed
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

Wigal 2009a

Methods	Multi-center, randomized, double-blind, placebo-controlled, cross-over trial **Country:** United States **Number of study sites:** 7 **Statistical methods:** modified ITT (children/adolescents who received at least one dose of study medication, with at least one post-randomization measurement of the primary efficacy variable - last observation carried forward)
Participants	**Sample size:** 117* children/adolescents with an ADHD diagnosis according to DSM-IV-TR criteria **Dropouts:** 6 **Psychiatric comorbid disorders:** NR **Age range:** 6 years to 12 years **Mean age (SD):** 10.1 (1.5) years **Sex:** 98 (76%) males **ADHD subtypes:** NR
Interventions	**Two interventions (all 117 children/adolescents participated in both interventions):** 1. Lisdexamphetamine (long acting), either 30 mg/day, 50 mg/day or 70 mg/day (determined by dose optimisation period), (n = 117) 2. Placebo (n = 117) **Duration:** 14 days (2 x 7-day treatment periods)
Outcomes	**Relevant outcomes:** 1. ADHD core symptom severity, assessed with ADHD Rating Scale, Fourth Version (clinician ratings) 2. Academic performance, assessed with Permanent Product Measure of Performance

Wigal 2009a *(Continued)*

3. Clinical impression, assessed with Clinical Global Impression - Severity and Clinical Global Impressions - Improvement scales
4. Retention: number of participants who completed the study
5. Number of participants who experienced at least one adverse event
6. Number of participants who dropped out due to an adverse event
7. Adverse events

Notes	**ClinicalTrials.gov Identifier:** NCT00500149 **Authors' affiliation:** university and pharmaceutical industry **Study funding:** pharmaceutical industry *Clinical characteristics provided on 129 children/adolescents first enrolled into an open-label dose-optimisation phase. Of these, 117 children/adolescents randomized to the double-blind phase

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (9%), and reasons provided; 97% of randomized children/adolescents included in primary analysis. Four individuals not included due to no post-baseline efficacy measure
Selective reporting (reporting bias)	Unclear risk	Data provided on all outcomes listed in the registered protocol. However, also reported on additional outcomes not listed in protocol
Other bias	Low risk	Study appears to be free of other biases
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not described

ADHD: attention deficit hyperactivity disorder.
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.*
ITT: intention-to-treat.
NR: not reported.

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

Study	Reason for exclusion
Akhondzadeh 2003	No placebo comparison assessed

Study	Reason for exclusion
Alexandris 1968	ADHD diagnosis not confirmed using formal diagnostic criteria
Arnold 2011	No direct amphetamine - placebo comparison
Biederman 2006	Not a randomized controlled trial
Biederman 2008	Not a randomized controlled trial
Boellner 2010	Not a randomized controlled trial
Brown 2010	Not a randomized controlled trial
Denhoff 1971	ADHD diagnosis not confirmed using formal diagnostic criteria
Donner 2007	Not a randomized controlled trial
Efron 1997	No placebo comparison assessed
Findling 2009	Not a randomized controlled trial
Greenhill 2003	No placebo comparison assessed
Kamien 1998	Study design was a series of multiple, cross-over, randomized controlled trials; our review included only single, cross-over, randomized controlled trials
Lopez 2008	Not a randomized controlled trial
McGough 2005	Not a randomized controlled trial
Najib 2009	Not a randomized controlled trial
Nikles 2006	Study design was a series of multiple, cross-over, randomized controlled trials; our review included only single, cross-over, randomized controlled trials
Quintana 2007	Not a randomized controlled trial
Scheffer 2005	Included children/adolescents who had comorbid bipolar disorder and were treated with mood stabilizers (divalproex sodium)
Sleator 1974	Not a randomized controlled trial
Spencer 2005	Not a randomized controlled trial
Spencer 2006b	ADHD diagnosis not confirmed using formal diagnostic criteria
Turgay 2010	Not a randomized controlled trial
Wigal 2009b	Not a randomized controlled trial
Wigal 2010a	Not a randomized controlled trial
Wigal 2010b	Study participants were adults with ADHD

ADHD: attention deficit hyperactivity disorder.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Glos 1973

Methods	Double-blind, controlled trial*
Participants	**Sample size:** 20 hyperactive children** **Mean age:** 9.4 years
Interventions	Amphetamine and placebo
Outcomes	
Notes	*Information on whether or not the trial was randomized is necessary for inclusion into this review **Information on whether participants were diagnosed with ADHD and according to formal diagnostic criteria is necessary for inclusion into this review. Since we were unable to contact the author due to lack of contact information, we are unable to classify this study as either included or excluded

Itil 1974

Methods	Double-blind, three-way study design
Participants	Children with hyperactivity
Interventions	Thioridazine, dextroamphetamine and placebo
Outcomes	Global behavior evaluation
Notes	Only abstract available. Detailed outcome data not in abstract. Unsure: 1. If treatments were randomized 2. If participants had a formal diagnosis of ADHD 3. Of the ages of the participants included Author has been contacted three times but no response received as yet

ADHD: attention deficit hyperactivity disorder.

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

Fanton 2009

Trial name or title	Effectiveness of an extended-release stimulant medication in treating preschool children with attention deficit hyperactivity disorder
Methods	Six-week, placebo-controlled, cross-over trial
Participants	Children aged 3 years to 6 years with ADHD
Interventions	Mixed amphetamine salts (long acting) and placebo
Outcomes	**Primary** 1. Composite parent and teacher Conners' Rating Scale score 2. Tolerance of extended-release mixed amphetamine salts

Fanton 2009 *(Continued)*

	Secondary 1. Clinical Global Impression - Improvement Scale score
Starting date	June 2008
Contact information	Dr. John Fanton, Baystate Medical Center
Notes	**Clinicaltrials.gov identifier:** NCT00712699. States that recruitment period ended in August 2010. However, no results have been published as yet. Currently, only abstract available

NCT01711021

Trial name or title	A randomized, double-blind, placebo-controlled, cross-over, laboratory, classroom study to evaluate the safety and efficacy of d-amphetamine transdermal drug delivery system (d-ATS) compared to placebo in children and adolescents with ADHD
Methods	Two-week, double-blind, randomized cross-over trial
Participants	Children and adolescents aged 6 years to 17 years with ADHD
Interventions	D-Amphetamine Transdermal System and placebo patch
Outcomes	**Primary** 1. Change in ADHD symptoms using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale
Starting date	October 2012
Contact information	Dr. James Waxmonsky (affiliation not stated)
Notes	**ClinicalTrials.gov identifier:** NCT01711021. States that recruitment period ended in March 2013. However, no results have been published as yet. No abstract available

ADHD: attention deficit hyperactivity disorder.

DATA AND ANALYSES

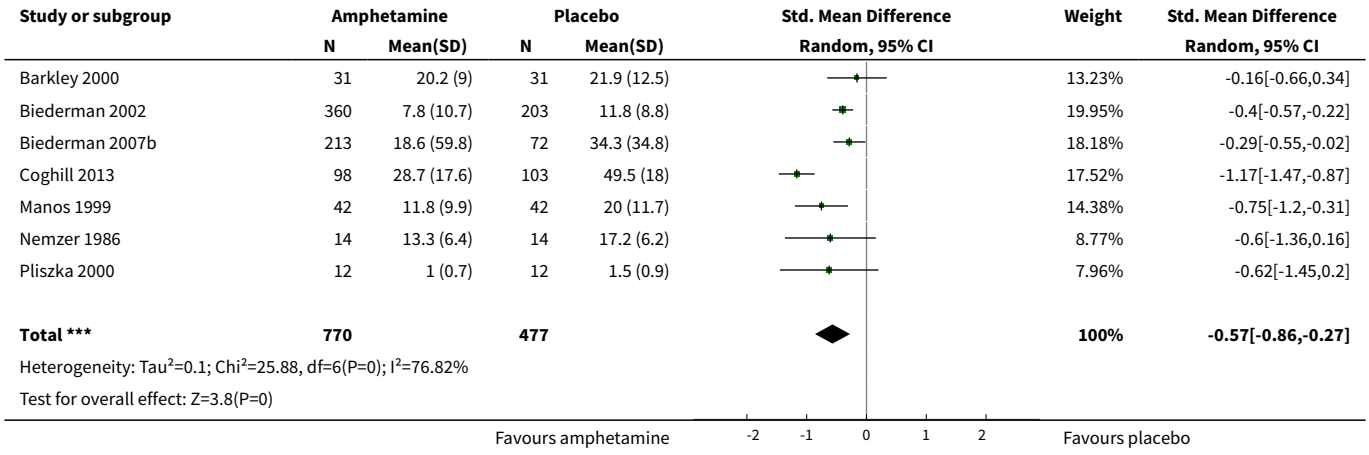
Comparison 1. Amphetamines versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total ADHD symptom score - parent ratings	7	1247	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.86, -0.27]
2 Hyperactivity/impulsivity - parent ratings	2	132	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.89, -0.19]
3 Total ADHD symptom score - teacher ratings	5	745	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-0.83, -0.27]

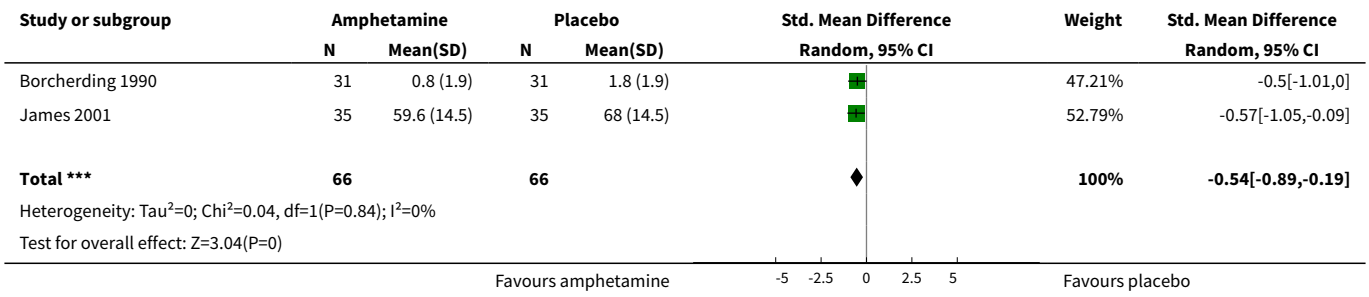
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Hyperactivity/impulsivity - teacher ratings	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5 Inattention - teacher ratings	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6 Total ADHD symptom score - clinician ratings	3	813	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.32, -0.36]
7 Hyperactivity/impulsivity - clinician ratings	3	813	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.28, -0.23]
8 Inattention - clinician ratings	3	813	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-1.26, -0.30]
9 Total ADHD symptom score - investigator/research personnel ratings	3	630	Std. Mean Difference (IV, Random, 95% CI)	-1.15 [-1.87, -0.44]
10 Hyperactivity/impulsivity - investigator/research personnel ratings	2	280	Std. Mean Difference (IV, Random, 95% CI)	-1.46 [-1.83, -1.08]
11 Inattention - investigator/research personnel ratings	4	634	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-1.42, -0.04]
12 Proportion of responders (Clinical Global Impression - Improvement; CGI - I)	9	2207	Risk Ratio (M-H, Random, 95% CI)	3.36 [2.48, 4.55]
13 Clinical Global Impression - Severity (CGI - S) score	2	86	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.72, -0.01]
14 Academic performance	8	826	Std. Mean Difference (IV, Random, 95% CI)	0.56 [0.39, 0.73]
15 Quality of life	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
16 Retention: proportion of participants who completed the trial	11	2381	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.97, 1.10]
17 Proportion of participants experiencing decreased appetite	11	2467	Risk Ratio (M-H, Random, 95% CI)	6.31 [2.58, 15.46]
18 Proportion of participants experiencing insomnia/trouble sleeping	10	2429	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.12, 6.83]
19 Proportion of participants experiencing abdominal pain	10	2155	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.03, 2.00]
20 Proportion of participants experiencing nausea/vomiting	6	1579	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.04, 2.56]
21 Proportion of participants experiencing headaches	9	2091	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Proportion of participants experiencing anxiety/nervousness	5	1088	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.78, 1.93]
23 Proportion of participants who experienced at least one adverse event	6	1742	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.18, 1.44]
24 Proportion of participants who dropped out/withdrew due to an adverse event	9	2160	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.86, 2.98]

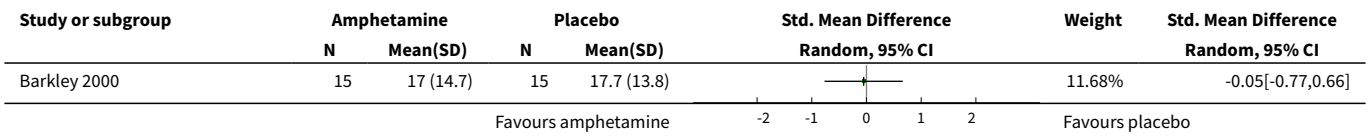
Analysis 1.1. Comparison 1 Amphetamines versus placebo, Outcome 1 Total ADHD symptom score - parent ratings.



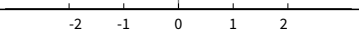
Analysis 1.2. Comparison 1 Amphetamines versus placebo, Outcome 2 Hyperactivity/impulsivity - parent ratings.



Analysis 1.3. Comparison 1 Amphetamines versus placebo, Outcome 3 Total ADHD symptom score - teacher ratings.



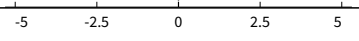
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Biederman 2002	360	5.8 (11)	203	9.9 (9.4)		42.39%	-0.39[-0.57,-0.22]
Donnelly 1989	20	7.8 (3.1)	20	10.9 (3.8)		13.45%	-0.88[-1.53,-0.22]
Manos 1999	42	51.5 (10.4)	42	62 (13.6)		21.96%	-0.86[-1.31,-0.42]
Nemzer 1986	14	30.2 (18.9)	14	43.6 (18.6)		10.51%	-0.69[-1.46,0.08]
Total ***	**451**		**294**			**100%**	**-0.55[-0.83,-0.27]**
Heterogeneity: Tau^2=0.04; Chi^2=6.82, df=4(P=0.15); I^2=41.37%							
Test for overall effect: Z=3.89(P=0)							



Favours amphetamine — Favours placebo

Analysis 1.4. Comparison 1 Amphetamines versus placebo, Outcome 4 Hyperactivity/impulsivity - teacher ratings.

Study or subgroup	Favours amphetamine N	Favours amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
James 2001	35	51.6 (6.7)	35	63.1 (12.6)		0%	-1.13[-1.63,-0.62]



Favours amphetamine — Favours placebo

Analysis 1.5. Comparison 1 Amphetamines versus placebo, Outcome 5 Inattention - teacher ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Pliszka 2000	12	0.5 (0.4)	12	1.5 (0.9)		0%	-1.43[-2.35,-0.52]

Favours amphetamine — Favours placebo

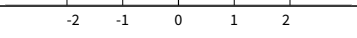
Analysis 1.6. Comparison 1 Amphetamines versus placebo, Outcome 6 Total ADHD symptom score - clinician ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Findling 2011	232	17.6 (11.4)	77	25.7 (12.9)		33.93%	-0.69[-0.95,-0.42]
Spencer 2006a	226	-17.8 (16.6)	52	-9.4 (16.6)		32.81%	-0.5[-0.81,-0.2]
Wigal 2009a	113	-25.8 (12.8)	113	-8.7 (12.8)		33.25%	-1.33[-1.62,-1.04]
Total ***	**571**		**242**			**100%**	**-0.84[-1.32,-0.36]**
Heterogeneity: Tau^2=0.16; Chi^2=17.12, df=2(P=0); I^2=88.32%							
Test for overall effect: Z=3.42(P=0)							

Favours amphetamine — Favours placebo

Analysis 1.7. Comparison 1 Amphetamines versus placebo, Outcome 7 Hyperactivity/impulsivity - clinician ratings.

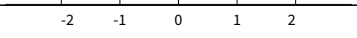
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Findling 2011	232	8.5 (6.6)	77	11.5 (6.6)		33.86%	-0.46[-0.72,-0.2]
Spencer 2006a	226	-7.6 (8.6)	52	-3.2 (8.6)		32.86%	-0.51[-0.81,-0.21]
Wigal 2009a	113	-13.3 (6.8)	113	-4.5 (6.8)		33.27%	-1.29[-1.58,-1]
Total ***	**571**		**242**			**100%**	**-0.75[-1.28,-0.23]**
Heterogeneity: Tau^2=0.2; Chi^2=20.7, df=2(P<0.0001); I^2=90.34%							
Test for overall effect: Z=2.8(P=0.01)							



Favours amphetamine | Favours placebo

Analysis 1.8. Comparison 1 Amphetamines versus placebo, Outcome 8 Inattention - clinician ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Findling 2011	232	12.5 (7.8)	77	16.8 (7.8)		33.95%	-0.55[-0.81,-0.29]
Spencer 2006a	226	-10.2 (8)	52	-6.1 (8)		32.77%	-0.51[-0.82,-0.21]
Wigal 2009a	113	-12.5 (6.6)	113	-4.1 (6.6)		33.28%	-1.27[-1.56,-0.98]
Total ***	**571**		**242**			**100%**	**-0.78[-1.26,-0.3]**
Heterogeneity: Tau^2=0.16; Chi^2=17.24, df=2(P=0); I^2=88.4%							
Test for overall effect: Z=3.17(P=0)							



Favours amphetamine | Favours placebo

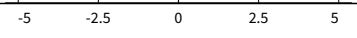
Analysis 1.9. Comparison 1 Amphetamines versus placebo, Outcome 9 Total ADHD symptom score - investigator/research personnel ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Childress 2015	97	10 (8.2)	97	17.8 (1.9)		33.17%	-1.3[-1.61,-0.99]
Coghill 2013	104	16.3 (10)	106	34.9 (12)		33.09%	-1.68[-2,-1.37]
Wigal 2009a	113	1.4 (0.9)	113	1.9 (0.9)		33.74%	-0.49[-0.76,-0.23]
Total ***	**314**		**316**			**100%**	**-1.15[-1.87,-0.44]**
Heterogeneity: Tau^2=0.37; Chi^2=34.79, df=2(P<0.0001); I^2=94.25%							
Test for overall effect: Z=3.17(P=0)							

Favours amphetamine | Favours placebo

Analysis 1.10. Comparison 1 Amphetamines versus placebo, Outcome 10 Hyperactivity/impulsivity - investigator/research personnel ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Coghill 2013	104	7.4 (5.9)	106	16.7 (5.7)		63.62%	-1.6[-1.91,-1.29]
James 2001	35	2.5 (1)	35	3.8 (1.1)		36.38%	-1.21[-1.72,-0.69]

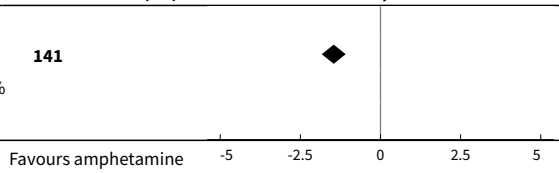


Favours amphetamine | Favours placebo

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Total * **	**139**		**141**			**100%**	**-1.46[-1.83,-1.08]**

Heterogeneity: Tau²=0.03; Chi²=1.68, df=1(P=0.19); I²=40.62%

Test for overall effect: Z=7.64(P<0.0001)

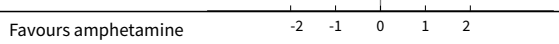


Analysis 1.11. Comparison 1 Amphetamines versus placebo, Outcome 11 Inattention - investigator/research personnel ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Biederman 2007a	50	1.2 (1)	50	1.8 (1)		24.49%	-0.6[-1,-0.19]
Coghill 2013	104	8.8 (5.9)	106	19 (5.9)		25.27%	-1.72[-2.04,-1.4]
McCracken 2003	49	1.3 (1.1)	49	1.4 (0.9)		24.54%	-0.16[-0.55,0.24]
Wigal 2009a	113	1.1 (1.1)	113	1.6 (1.1)		25.7%	-0.44[-0.71,-0.18]
Total * **	**316**		**318**			**100%**	**-0.73[-1.42,-0.04]**

Heterogeneity: Tau²=0.46; Chi²=50.15, df=3(P<0.0001); I²=94.02%

Test for overall effect: Z=2.08(P=0.04)



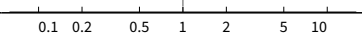
Analysis 1.12. Comparison 1 Amphetamines versus placebo, Outcome 12 Proportion of responders (Clinical Global Impression - Improvement; CGI - I).

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Barkley 2000	16/46	5/46		6.58%	3.2[1.28,8.01]
Biederman 2002	148/374	35/210		13.97%	2.37[1.71,3.29]
Biederman 2007a	36/52	9/52		9.79%	4[2.15,7.44]
Biederman 2007b	156/218	12/72		11.13%	4.29[2.54,7.25]
Coghill 2013	81/104	15/106		11.75%	5.5[3.41,8.89]
Findling 2011	160/232	30/77		14.44%	1.77[1.32,2.37]
Sharp 1999	27/32	5/32		7.5%	5.4[2.38,12.25]
Spencer 2006a	143/233	14/63		11.85%	2.76[1.72,4.43]
Wigal 2009a	93/129	22/129		12.99%	4.23[2.85,6.28]
Total (95% CI)	**1420**	**787**		**100%**	**3.36[2.48,4.55]**

Total events: 860 (Amphetamine), 147 (Placebo)

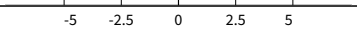
Heterogeneity: Tau²=0.14; Chi²=28.71, df=8(P=0); I²=72.13%

Test for overall effect: Z=7.86(P<0.0001)



Analysis 1.13. Comparison 1 Amphetamines versus placebo, Outcome 13 Clinical Global Impression - Severity (CGI - S) score.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Borcherding 1990	31	2.5 (3.9)	31	4.5 (3.9)		59.39%	-0.5[-1.01,0]
Pliszka 2000	12	1.6 (0.7)	12	3.2 (1.4)		40.61%	-1.39[-2.3,-0.48]
Total ***	**43**		**43**			**100%**	**-0.86[-1.72,-0.01]**
Heterogeneity: Tau^2=0.25; Chi^2=2.8, df=1(P=0.09); I^2=64.29%							
Test for overall effect: Z=1.98(P=0.05)							



Favours amphetamine — Favours placebo

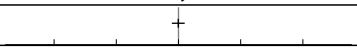
Analysis 1.14. Comparison 1 Amphetamines versus placebo, Outcome 14 Academic performance.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Biederman 2007a	50	129.5 (76)	50	84.1 (76)		13.22%	0.59[0.19,0.99]
Borcherding 1990	33	97.1 (4.6)	33	94 (7.9)		9.78%	0.47[-0.02,0.96]
Childress 2015	97	110.4 (37.4)	97	82.8 (35.8)		19.95%	0.75[0.46,1.04]
James 2001	35	169.9 (52.7)	35	140.2 (51.3)		10.15%	0.56[0.09,1.04]
McCracken 2003	49	79.1 (52)	49	64.9 (50.3)		13.36%	0.28[-0.12,0.67]
Nemzer 1986	14	45.8 (16.7)	14	37.8 (17.4)		4.72%	0.46[-0.3,1.21]
Shekim 1986	22	95.1 (9.5)	22	95.1 (11.7)		7.19%	-0.01[-0.6,0.59]
Wigal 2009a	113	109.2 (36.3)	113	80.8 (36.3)		21.64%	0.78[0.51,1.05]
Total ***	**413**		**413**			**100%**	**0.56[0.39,0.73]**
Heterogeneity: Tau^2=0.02; Chi^2=9.71, df=7(P=0.21); I^2=27.9%							
Test for overall effect: Z=6.35(P<0.0001)							

Favours placebo — Favours amphetamine

Analysis 1.15. Comparison 1 Amphetamines versus placebo, Outcome 15 Quality of life.

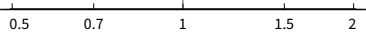
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Findling 2011	232	81.2 (12.5)	77	81.3 (12.2)		0%	-0.01[-0.27,0.25]



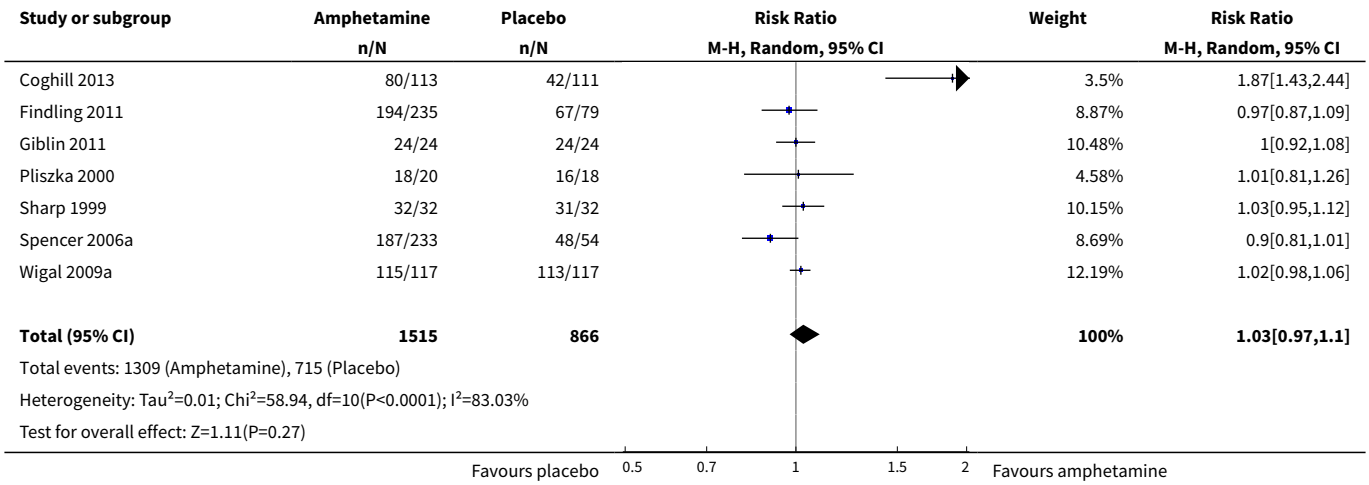
Favours placebo — Favours amphetamine

Analysis 1.16. Comparison 1 Amphetamines versus placebo, Outcome 16 Retention: proportion of participants who completed the trial.

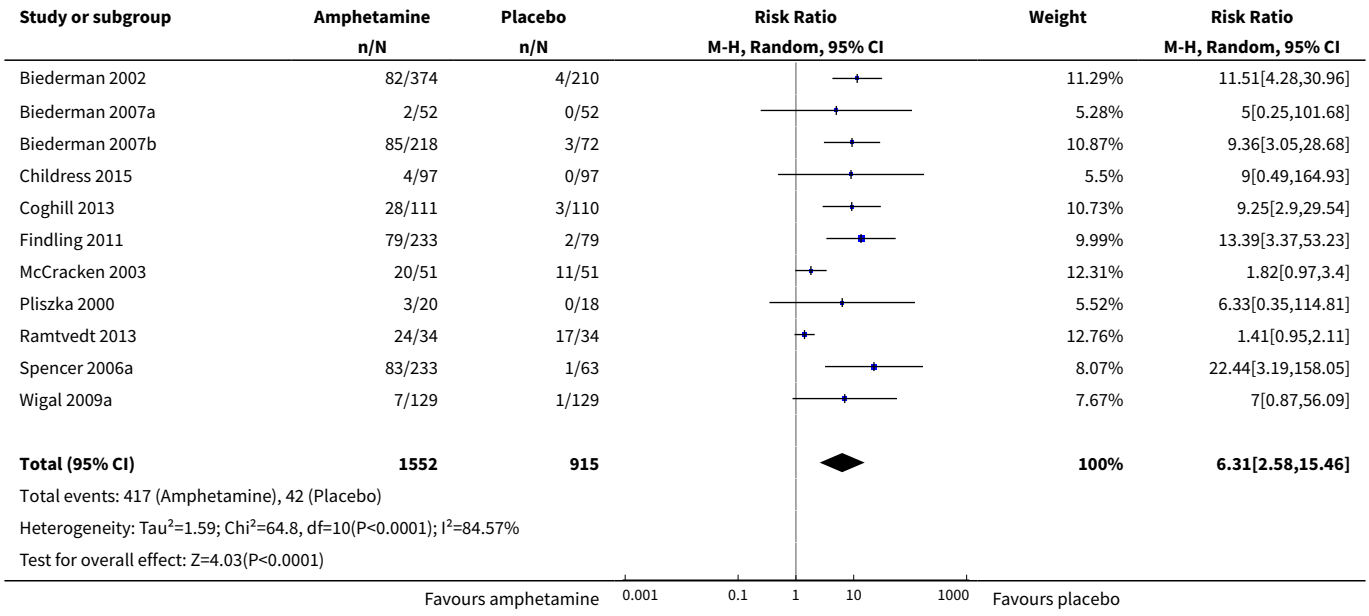
Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biederman 2002	336/374	173/210		10.88%	1.09[1.02,1.17]
Biederman 2007a	52/52	50/52		11.17%	1.04[0.97,1.11]
Biederman 2007b	176/218	54/72		7.06%	1.08[0.93,1.25]
Childress 2015	95/97	97/97		12.41%	0.98[0.95,1.01]



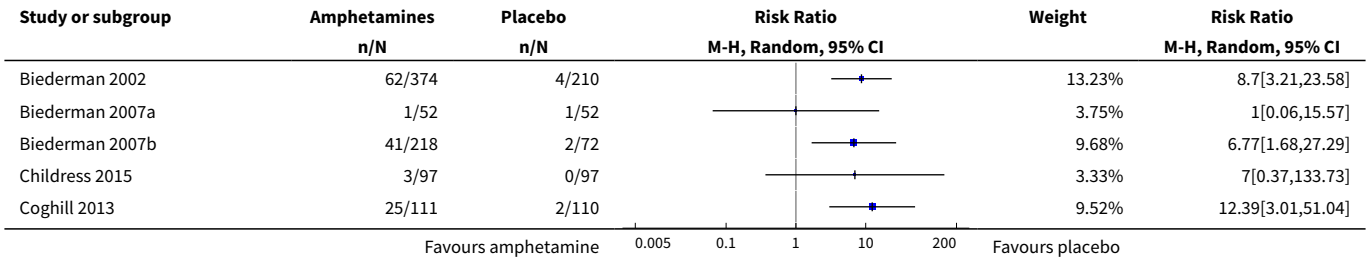
Favours placebo — Favours amphetamine



Analysis 1.17. Comparison 1 Amphetamines versus placebo, Outcome 17 Proportion of participants experiencing decreased appetite.



Analysis 1.18. Comparison 1 Amphetamines versus placebo, Outcome 18 Proportion of participants experiencing insomnia/trouble sleeping.

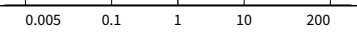


Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Findling 2011	26/233	3/79		11.58%	2.94[0.91,9.44]
McCracken 2003	16/51	10/51		16.55%	1.6[0.8,3.18]
Ramtvedt 2013	30/34	14/34		19.33%	2.14[1.41,3.26]
Spencer 2006a	28/233	2/63		9.58%	3.79[0.93,15.46]
Wigal 2009a	5/129	0/129		3.45%	11[0.61,196.91]
Total (95% CI)	**1532**	**897**		**100%**	**3.8[2.12,6.83]**
Total events: 237 (Amphetamines), 38 (Placebo)					
Heterogeneity: Tau^2=0.42; Chi^2=21.75, df=9(P=0.01); I^2=58.63%					
Test for overall effect: Z=4.47(P<0.0001)					

Favours amphetamine | Favours placebo

Analysis 1.19. Comparison 1 Amphetamines versus placebo, Outcome 19 Proportion of participants experiencing abdominal pain.

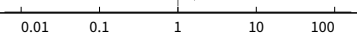
Study or subgroup	Amphetamines n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biederman 2002	54/374	20/210		29.32%	1.52[0.93,2.46]
Biederman 2007a	2/52	1/52		1.9%	2[0.19,21.38]
Biederman 2007b	26/218	4/72		9.3%	2.15[0.78,5.94]
Childress 2015	3/97	0/97		1.24%	7[0.37,133.73]
Coghill 2013	16/111	14/110		18.74%	1.13[0.58,2.21]
McCracken 2003	18/51	12/51		20.98%	1.5[0.81,2.78]
Pliszka 2000	5/20	0/18		1.34%	9.95[0.59,168.27]
Ramtvedt 2013	6/34	9/34		11.16%	0.67[0.27,1.67]
Spencer 2006a	25/233	1/63		2.69%	6.76[0.93,48.92]
Wigal 2009a	2/129	3/129		3.33%	0.67[0.11,3.92]
Total (95% CI)	**1319**	**836**		**100%**	**1.44[1.03,2]**
Total events: 157 (Amphetamines), 64 (Placebo)					
Heterogeneity: Tau^2=0.04; Chi^2=10.32, df=9(P=0.32); I^2=12.83%					
Test for overall effect: Z=2.15(P=0.03)					



Favours amphetamine | Favours placebo

Analysis 1.20. Comparison 1 Amphetamines versus placebo, Outcome 20 Proportion of participants experiencing nausea/vomiting.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biederman 2002	46/374	14/210		31.84%	1.84[1.04,3.27]
Biederman 2007a	1/52	2/52		3.47%	0.5[0.05,5.35]
Biederman 2007b	32/218	5/72		18.14%	2.11[0.86,5.22]
Coghill 2013	12/111	3/110		11.13%	3.96[1.15,13.66]
Findling 2011	12/233	6/79		16.97%	0.68[0.26,1.75]
Ramtvedt 2013	10/34	6/34		18.45%	1.67[0.68,4.07]
Total (95% CI)	**1022**	**557**		**100%**	**1.63[1.04,2.56]**



Favours amphetamine | Favours placebo

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 113 (Amphetamine), 36 (Placebo)					
Heterogeneity: Tau²=0.08; Chi²=6.77, df=5(P=0.24); I²=26.13%					
Test for overall effect: Z=2.11(P=0.03)					

Analysis 1.21. Comparison 1 Amphetamines versus placebo, Outcome 21 Proportion of participants experiencing headaches.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biederman 2002	67/374	45/210		42.35%	0.84[0.6,1.17]
Biederman 2007b	26/218	7/72		7.73%	1.23[0.56,2.71]
Coghill 2013	16/111	22/110		14.01%	0.72[0.4,1.3]
Findling 2011	34/233	10/79		11.19%	1.15[0.6,2.22]
Giblin 2011	5/16	1/8		1.24%	2.5[0.35,17.97]
Pliszka 2000	2/20	1/18		0.9%	1.8[0.18,18.21]
Ramtvedt 2013	8/34	8/34		6.58%	1[0.42,2.36]
Spencer 2006a	38/233	12/63		14.06%	0.86[0.48,1.54]
Wigal 2009a	6/129	2/129		1.93%	3[0.62,14.59]
Total (95% CI)	**1368**	**723**		**100%**	**0.93[0.75,1.16]**
Total events: 202 (Amphetamine), 108 (Placebo)					
Heterogeneity: Tau²=0; Chi²=5.52, df=8(P=0.7); I²=0%					
Test for overall effect: Z=0.66(P=0.51)					

Analysis 1.22. Comparison 1 Amphetamines versus placebo, Outcome 22 Proportion of participants experiencing anxiety/nervousness.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biederman 2002	21/374	4/210		14.28%	2.95[1.03,8.47]
McCracken 2003	39/51	39/51		53.38%	1[0.81,1.24]
Pliszka 2000	1/20	1/18		2.73%	0.9[0.06,13.36]
Ramtvedt 2013	8/34	7/34		18.17%	1.14[0.47,2.8]
Spencer 2006a	14/233	3/63		11.44%	1.26[0.37,4.25]
Total (95% CI)	**712**	**376**		**100%**	**1.22[0.78,1.93]**
Total events: 83 (Amphetamine), 54 (Placebo)					
Heterogeneity: Tau²=0.09; Chi²=5.87, df=4(P=0.21); I²=31.88%					
Test for overall effect: Z=0.87(P=0.38)					

Analysis 1.23. Comparison 1 Amphetamines versus placebo, Outcome 23 Proportion of participants who experienced at least one adverse event.

Study or subgroup	Favours amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biederman 2002	263/374	119/210		54.23%	1.24[1.08,1.42]
Biederman 2007a	9/52	8/52		1.36%	1.13[0.47,2.69]
Biederman 2007b	162/218	34/72		15.56%	1.57[1.22,2.03]
Childress 2015	10/97	6/97		1.09%	1.67[0.63,4.41]
Findling 2011	160/233	45/79		22.98%	1.21[0.98,1.49]
Wigal 2009a	38/129	22/129		4.77%	1.73[1.09,2.75]
Total (95% CI)	**1103**	**639**		**100%**	**1.3[1.18,1.44]**
Total events: 642 (Favours amphetamine), 234 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.05, df=5(P=0.41); I^2=0.93%					
Test for overall effect: Z=5.08(P<0.0001)					

Analysis 1.24. Comparison 1 Amphetamines versus placebo, Outcome 24 Proportion of participants who dropped out/withdrew due to an adverse event.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biederman 2002	9/374	6/210		37.02%	0.84[0.3,2.33]
Biederman 2007b	21/218	1/72		9.73%	6.94[0.95,50.65]
Borcherding 1990	1/46	0/46		3.81%	3[0.13,71.78]
Coghill 2013	5/113	4/111		23.16%	1.23[0.34,4.45]
Findling 2011	10/233	1/79		9.24%	3.39[0.44,26.07]
Pliszka 2000	2/20	0/18		4.35%	4.52[0.23,88.38]
Spencer 2006a	5/233	0/63		4.63%	3.01[0.17,53.69]
Swanson 1998a	2/33	0/33		4.28%	5[0.25,100.32]
Wigal 2009a	0/129	1/129		3.78%	0.33[0.01,8.11]
Total (95% CI)	**1399**	**761**		**100%**	**1.6[0.86,2.98]**
Total events: 55 (Amphetamine), 13 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.97, df=8(P=0.54); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					

Comparison 2. Subgroup analysis 1: Type of amphetamine

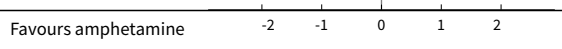
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total ADHD symptom score - parent ratings	7	1247	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.86, -0.27]
1.1 Dexamphetamine	1	28	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-1.36, 0.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Lisdexamphetamine	2	486	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-1.59, 0.14]
1.3 Mixed amphetamine salts	4	733	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.63, -0.24]
2 Proportion of responders (CGI - I)	9	2205	Risk Ratio (M-H, Random, 95% CI)	3.38 [2.51, 4.55]
2.1 Dexamphetamine	1	64	Risk Ratio (M-H, Random, 95% CI)	5.4 [2.38, 12.25]
2.2 Lisdexamphetamine	4	1065	Risk Ratio (M-H, Random, 95% CI)	3.62 [2.04, 6.41]
2.3 Mixed amphetamine salts	4	1076	Risk Ratio (M-H, Random, 95% CI)	2.72 [2.14, 3.45]
3 Academic performance	8	826	Std. Mean Difference (IV, Random, 95% CI)	0.56 [0.39, 0.73]
3.1 Dexamphetamine	4	208	Std. Mean Difference (IV, Random, 95% CI)	0.40 [0.12, 0.67]
3.2 Lisdexamphetamine	1	226	Std. Mean Difference (IV, Random, 95% CI)	0.78 [0.51, 1.05]
3.3 Mixed amphetamine salts	3	392	Std. Mean Difference (IV, Random, 95% CI)	0.56 [0.29, 0.84]
4 Retention: proportion of participants who completed the trial	10	2364	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.12]
4.1 Dexamphetamine	1	64	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.95, 1.12]
4.2 Lisdexamphetamine	4	1084	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.92, 1.42]
4.3 Mixed amphetamine salts	5	1216	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.11]
5 Proportion of participants who dropped out/withdrew due to an adverse event	9	2161	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.86, 2.98]
5.1 Dexamphetamine	1	92	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 71.78]
5.2 Lisdexamphetamine	4	1085	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.70, 5.91]
5.3 Mixed amphetamine salts	4	984	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.53, 3.06]
6 Proportion of participants experiencing decreased appetite	10	2273	Risk Ratio (M-H, Random, 95% CI)	6.20 [2.44, 15.71]
6.1 Dexamphetamine	1	68	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.95, 2.11]
6.2 Lisdexampheatmine	4	1081	Risk Ratio (M-H, Random, 95% CI)	9.83 [5.08, 19.02]

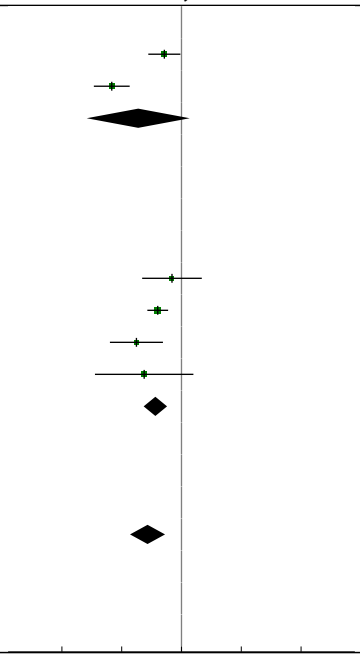
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Mixed amphetamine salts	5	1124	Risk Ratio (M-H, Random, 95% CI)	6.42 [1.56, 26.52]
7 Proportion of participants experiencing insomnia/trouble sleeping	10	2429	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.12, 6.83]
7.1 Dexamphetamine	1	68	Risk Ratio (M-H, Random, 95% CI)	2.14 [1.41, 3.26]
7.2 Lisdexamphetamine	4	1081	Risk Ratio (M-H, Random, 95% CI)	5.91 [2.84, 12.29]
7.3 Mixed amphetamine salts	5	1280	Risk Ratio (M-H, Random, 95% CI)	3.34 [1.25, 8.96]
8 Proportion of participants experiencing abdominal pain	10	2155	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.03, 2.00]
8.1 Dexamphetamine	1	68	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.27, 1.67]
8.2 Lisdexamphetamine	3	769	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.76, 2.19]
8.3 Mixed amphetamine salts	6	1318	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.17, 2.45]
9 Proportion of participants experiencing headaches	9	2063	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.16]
9.1 Dexamphetamine	1	68	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.42, 2.36]
9.2 Lisdexamphetamine	5	1077	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.73, 1.57]
9.3 Mixed amphetamine salts	3	918	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.14]
10 Proportion of participants experiencing nausea/vomiting	6	1579	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.04, 2.56]
10.1 Dexamphetamine	1	68	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.68, 4.07]
10.2 Lisdexamphetamine	4	927	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.61, 3.61]
10.3 Mixed amphetamine salts	1	584	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.04, 3.27]

Analysis 2.1. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 1 Total ADHD symptom score - parent ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.1.1 Dexamphetamine							
Nemzer 1986	14	13.3 (6.4)	14	17.2 (6.2)		8.77%	-0.6[-1.36,0.16]
Subtotal ***	**14**		**14**			**8.77%**	**-0.6[-1.36,0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.56(P=0.12)							

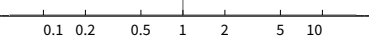


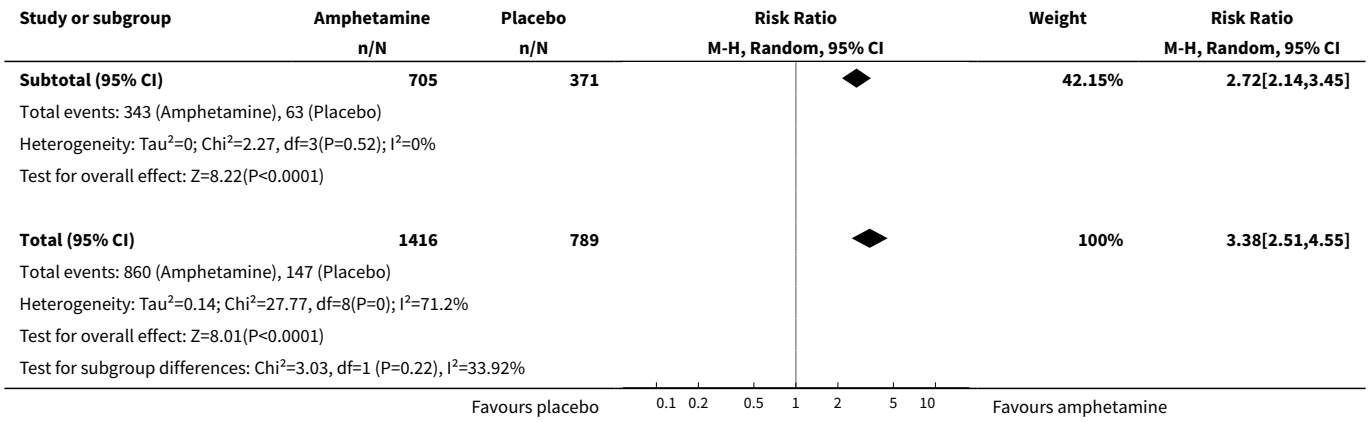
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.1.2 Lisdexamphetamine							
Biederman 2007b	213	18.6 (59.8)	72	34.3 (34.8)		18.18%	-0.29[-0.55,-0.02]
Coghill 2013	98	28.7 (17.6)	103	49.5 (18)		17.52%	-1.17[-1.47,-0.87]
Subtotal ***	**311**		**175**			**35.71%**	**-0.72[-1.59,0.14]**
Heterogeneity: Tau^2=0.37; Chi^2=18.37, df=1(P<0.0001); I^2=94.56%							
Test for overall effect: Z=1.65(P=0.1)							
2.1.3 Mixed amphetamine salts							
Barkley 2000	31	20.2 (9)	31	21.9 (12.5)		13.23%	-0.16[-0.66,0.34]
Biederman 2002	360	7.8 (10.7)	203	11.8 (8.8)		19.95%	-0.4[-0.57,-0.22]
Manos 1999	42	11.8 (9.9)	42	20 (11.7)		14.38%	-0.75[-1.2,-0.31]
Pliszka 2000	12	1 (0.7)	12	1.5 (0.9)		7.96%	-0.62[-1.45,0.2]
Subtotal ***	**445**		**288**			**55.52%**	**-0.44[-0.63,-0.24]**
Heterogeneity: Tau^2=0.01; Chi^2=3.53, df=3(P=0.32); I^2=14.92%							
Test for overall effect: Z=4.37(P<0.0001)							
Total ***	**770**		**477**			**100%**	**-0.57[-0.86,-0.27]**
Heterogeneity: Tau^2=0.1; Chi^2=25.88, df=6(P=0); I^2=76.82%							
Test for overall effect: Z=3.8(P=0)							
Test for subgroup differences: Chi^2=0.55, df=1 (P=0.76), I^2=0%							



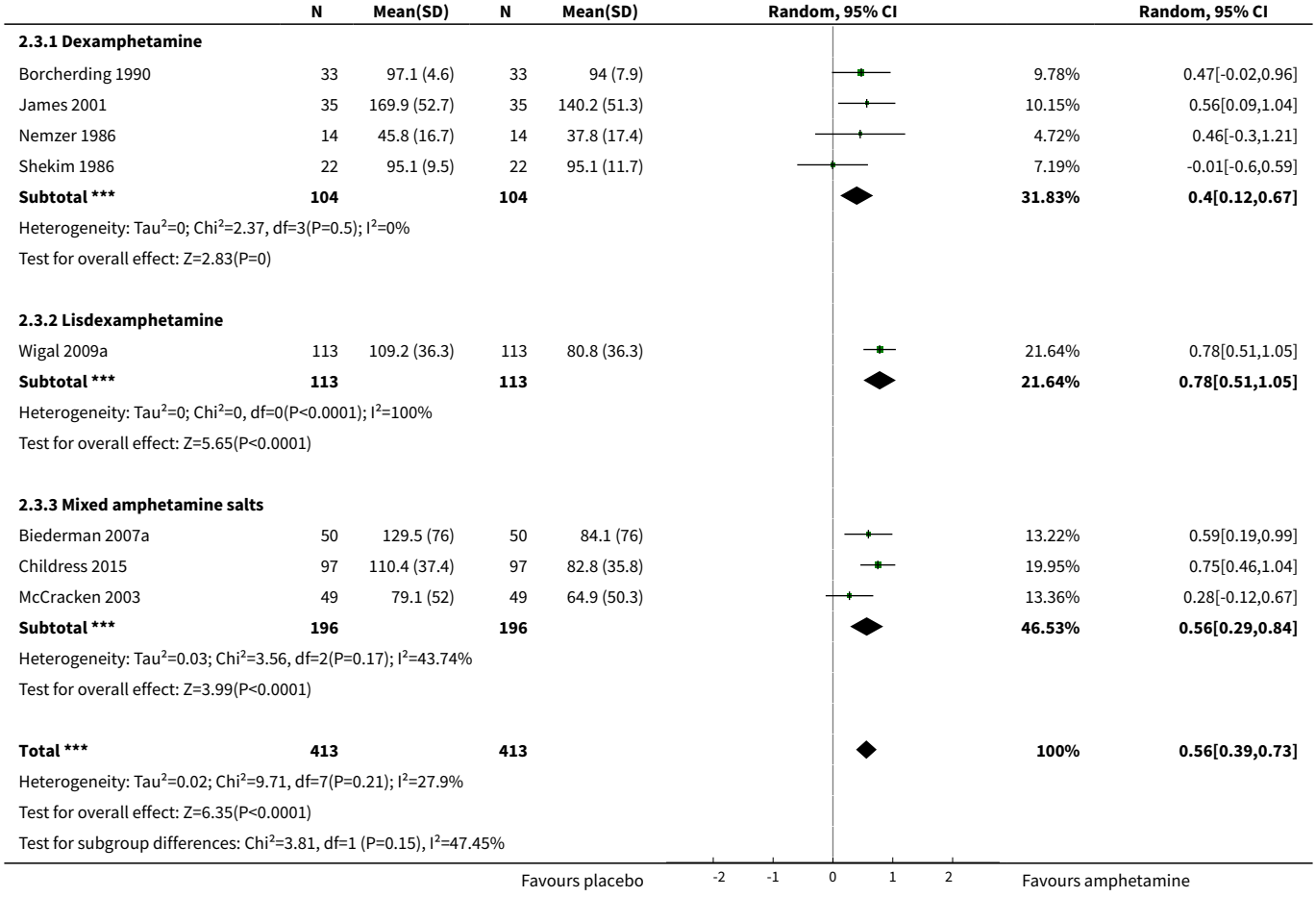
Analysis 2.2. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 2 Proportion of responders (CGI - I).

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Dexamphetamine					
Sharp 1999	27/32	5/32		7.42%	5.4[2.38,12.25]
Subtotal (95% CI)	**32**	**32**		**7.42%**	**5.4[2.38,12.25]**
Total events: 27 (Amphetamine), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.04(P<0.0001)					
2.2.2 Lisdexamphetamine					
Biederman 2007b	156/213	12/72		11.12%	4.39[2.61,7.41]
Coghill 2013	81/104	15/106		11.76%	5.5[3.41,8.89]
Findling 2011	160/233	30/79		14.52%	1.81[1.35,2.43]
Wigal 2009a	93/129	22/129		13.04%	4.23[2.85,6.28]
Subtotal (95% CI)	**679**	**386**		**50.43%**	**3.62[2.04,6.41]**
Total events: 490 (Amphetamine), 79 (Placebo)					
Heterogeneity: Tau^2=0.29; Chi^2=23.33, df=3(P<0.0001); I^2=87.14%					
Test for overall effect: Z=4.39(P<0.0001)					
2.2.3 Mixed amphetamine salts					
Barkley 2000	16/46	5/46		6.49%	3.2[1.28,8.01]
Biederman 2002	148/374	35/210		14.05%	2.37[1.71,3.29]
Biederman 2007a	36/52	9/52		9.75%	4[2.15,7.44]
Spencer 2006a	143/233	14/63		11.86%	2.76[1.72,4.43]

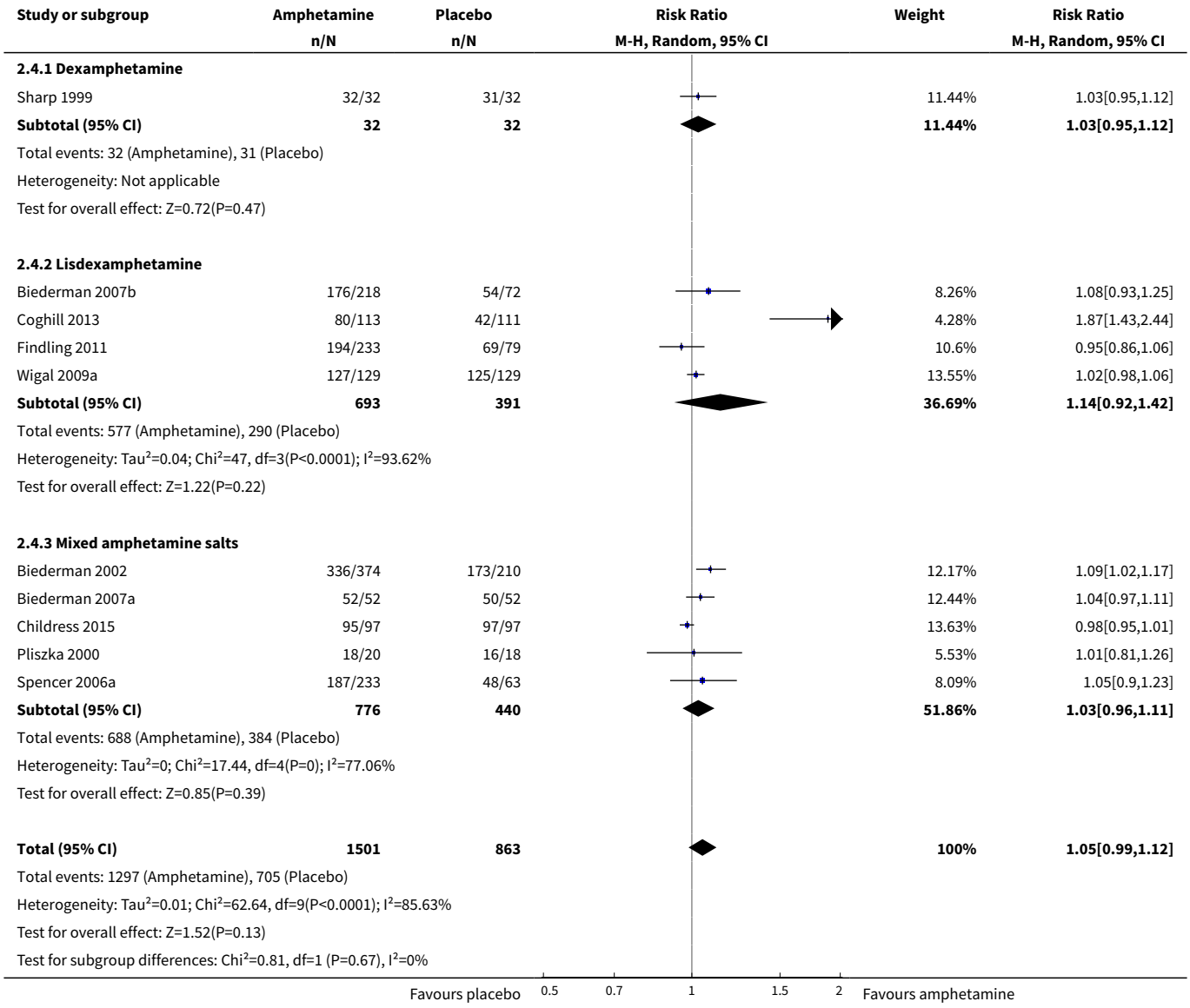




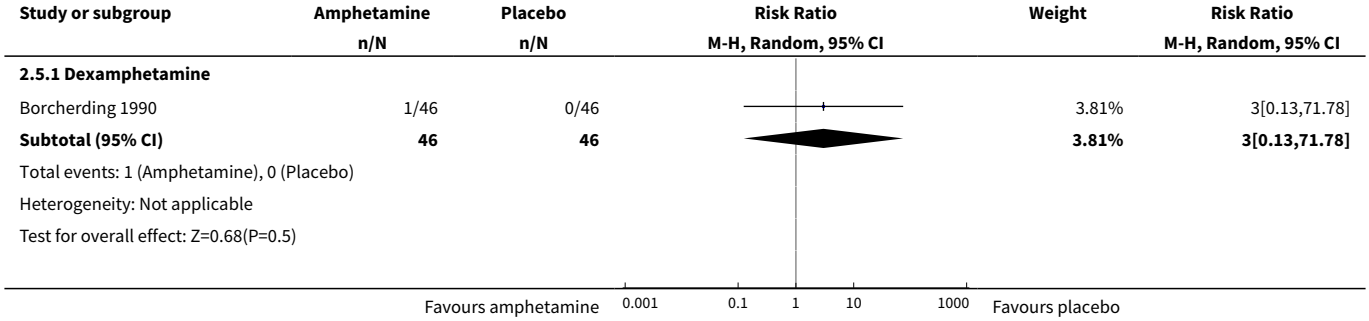
Analysis 2.3. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 3 Academic performance.

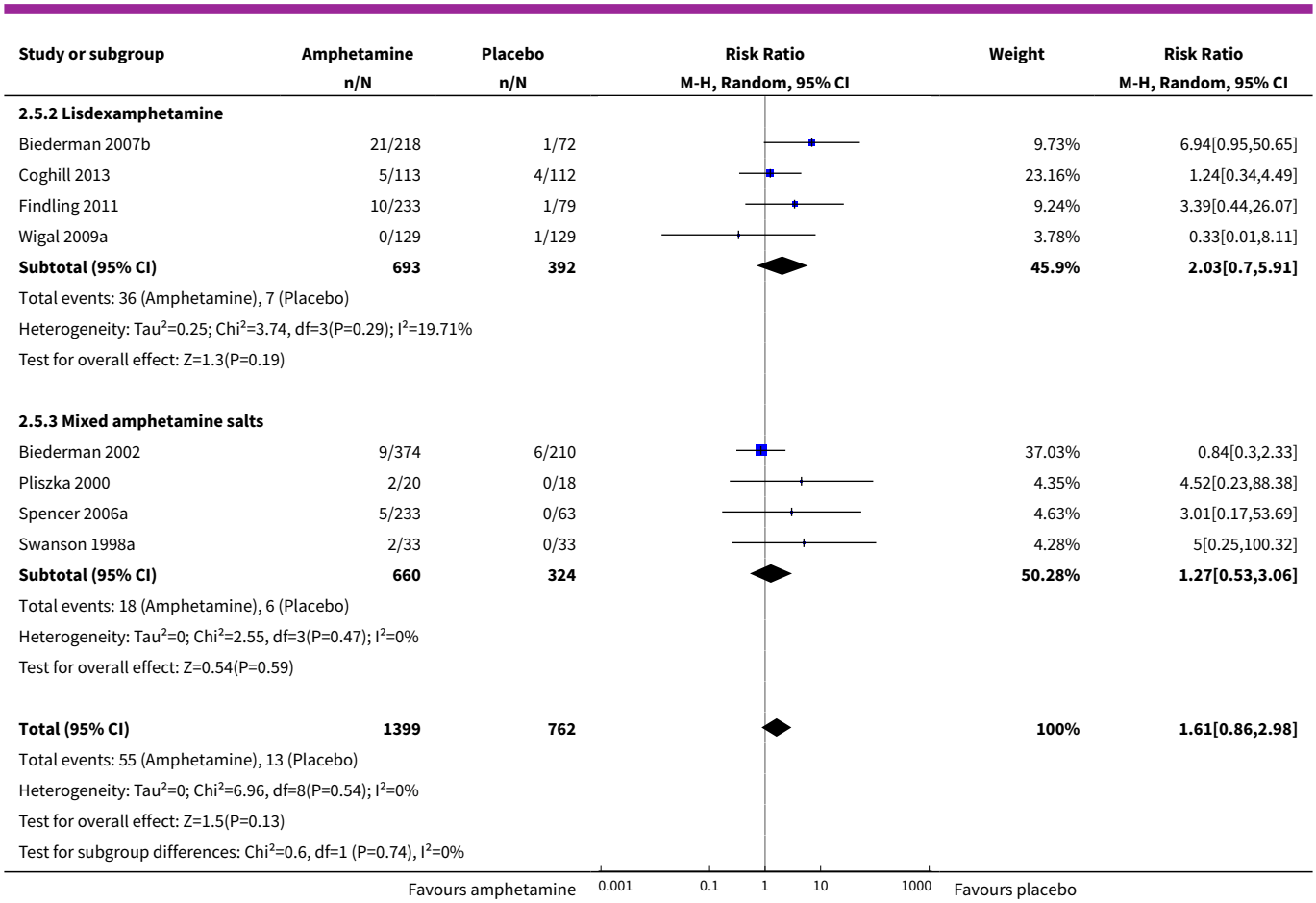


Analysis 2.4. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 4 Retention: proportion of participants who completed the trial.

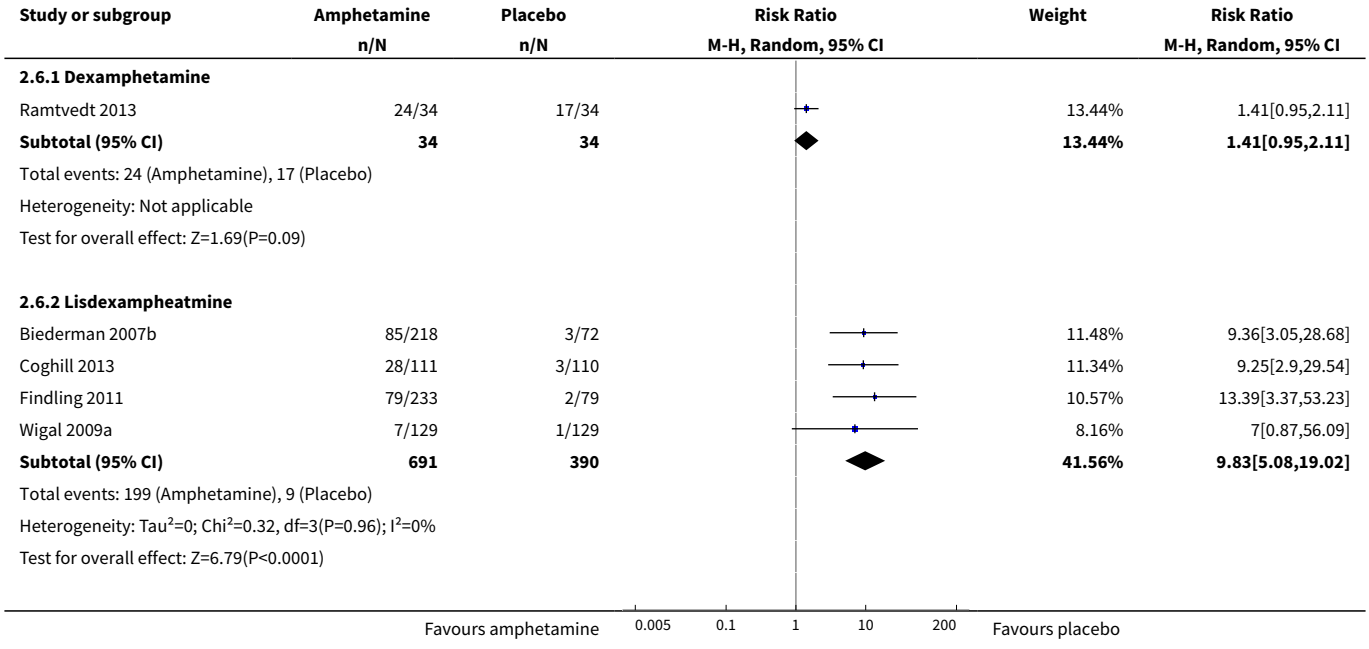


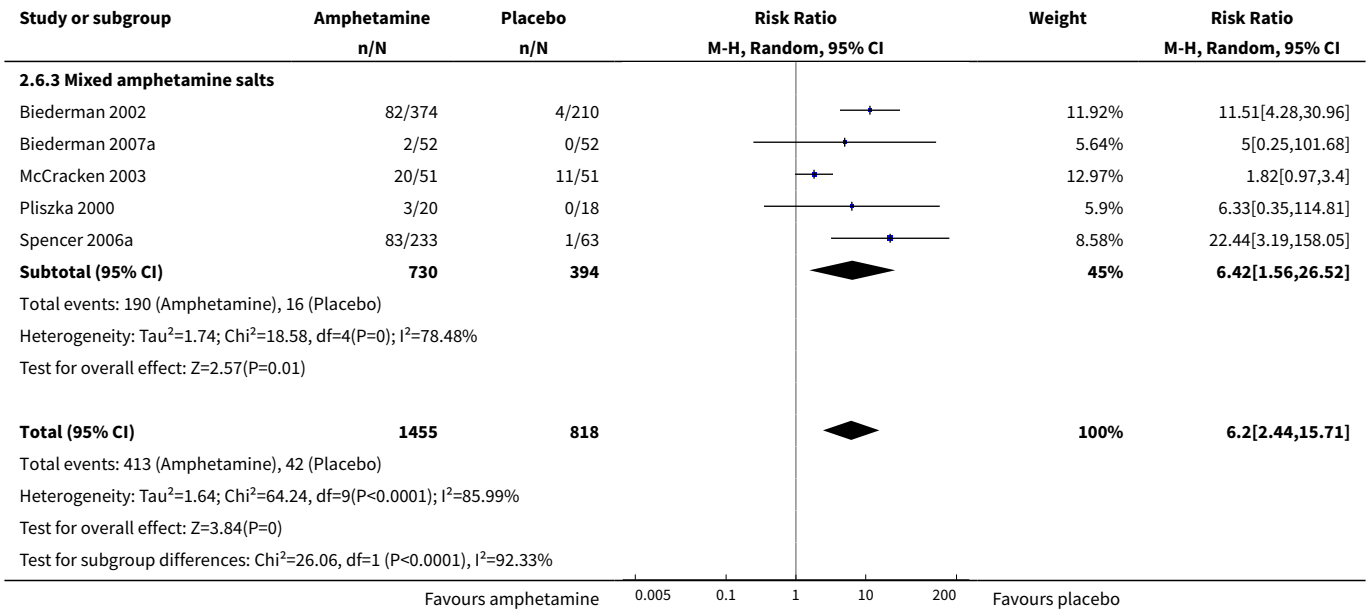
Analysis 2.5. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 5 Proportion of participants who dropped out/withdrew due to an adverse event.



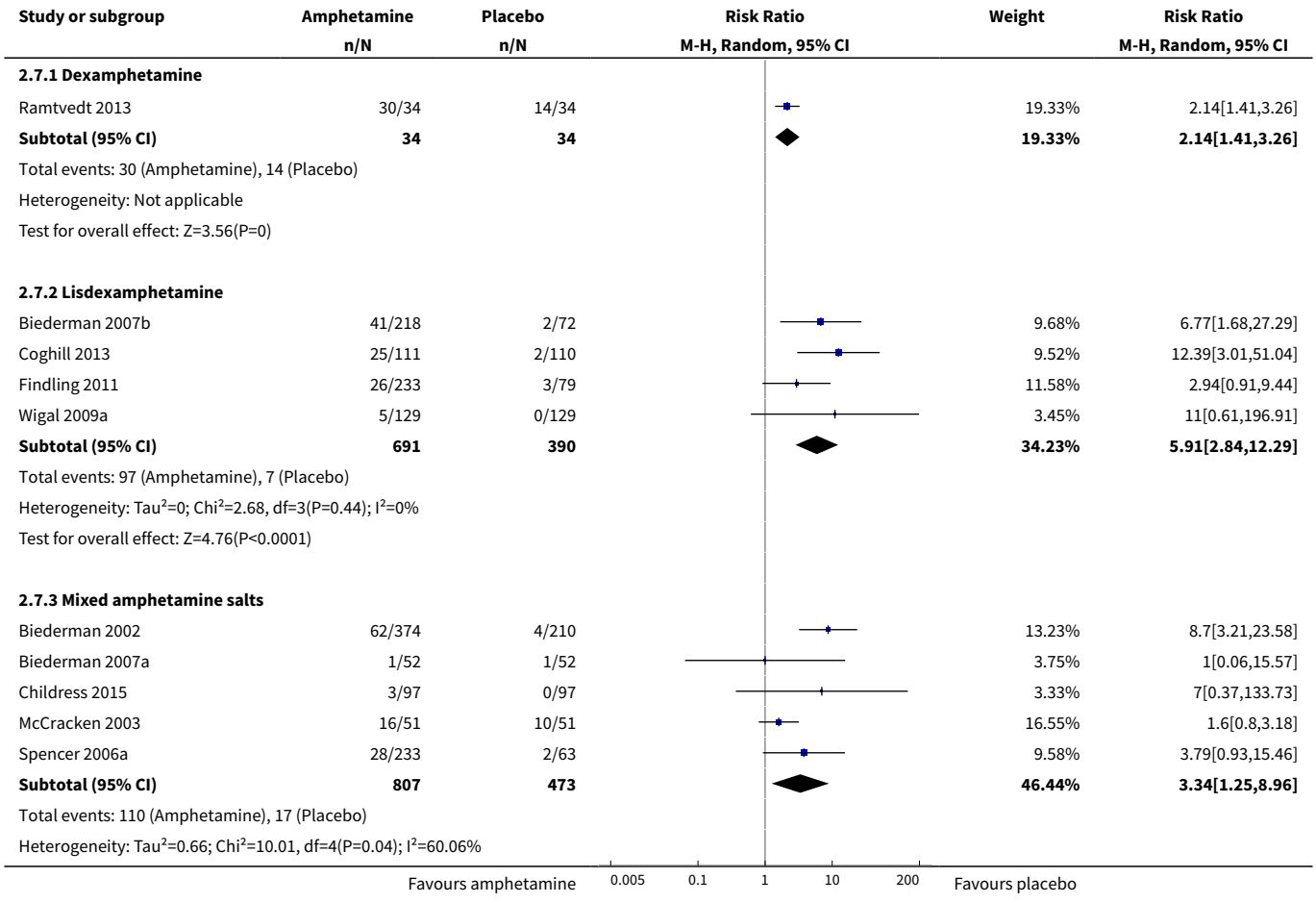


Analysis 2.6. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 6 Proportion of participants experiencing decreased appetite.





Analysis 2.7. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 7 Proportion of participants experiencing insomnia/trouble sleeping.



Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.4(P=0.02)					
Total (95% CI)	**1532**	**897**		**100%**	**3.8[2.12,6.83]**
Total events: 237 (Amphetamine), 38 (Placebo)					
Heterogeneity: Tau^2=0.42; Chi^2=21.75, df=9(P=0.01); I^2=58.63%					
Test for overall effect: Z=4.47(P<0.0001)					
Test for subgroup differences: Chi^2=5.69, df=1 (P=0.06), I^2=64.84%					

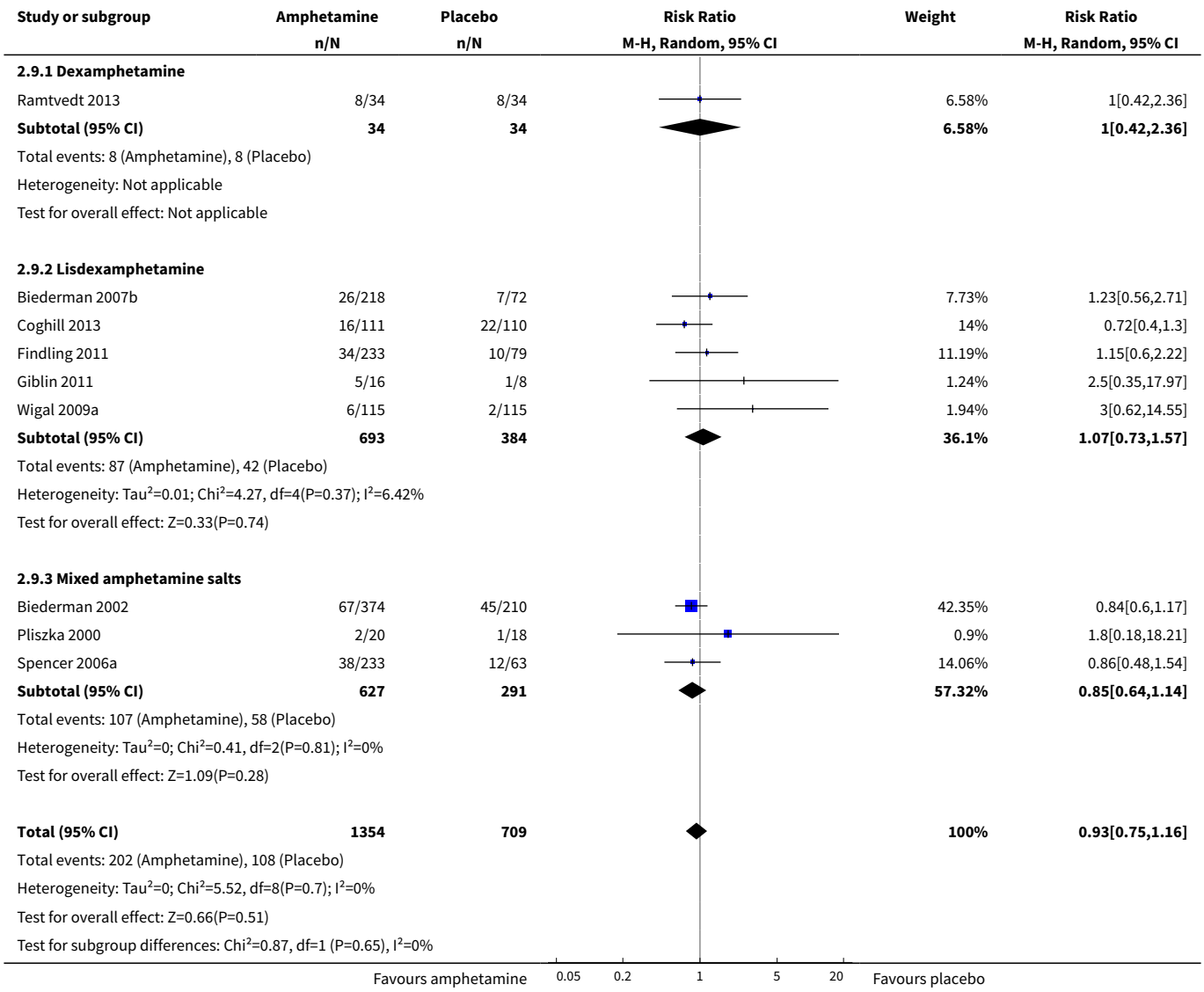
Favours amphetamine 0.005 0.1 1 10 200 Favours placebo

Analysis 2.8. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 8 Proportion of participants experiencing abdominal pain.

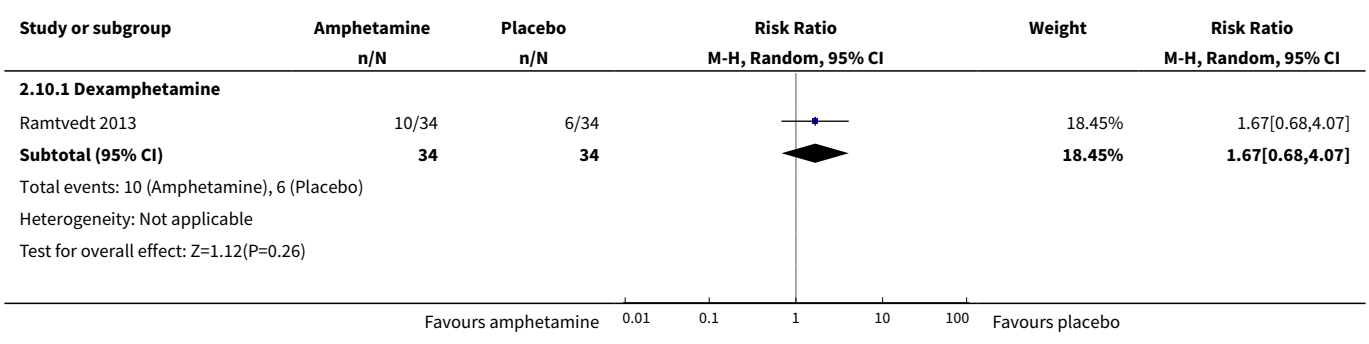
Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Dexamphetamine					
Ramtvedt 2013	6/34	9/34		11.16%	0.67[0.27,1.67]
Subtotal (95% CI)	**34**	**34**		**11.16%**	**0.67[0.27,1.67]**
Total events: 6 (Amphetamine), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.39)					
2.8.2 Lisdexamphetamine					
Biederman 2007b	26/218	4/72		9.3%	2.15[0.78,5.94]
Coghill 2013	16/111	14/110		18.74%	1.13[0.58,2.21]
Wigal 2009a	2/129	3/129		3.33%	0.67[0.11,3.92]
Subtotal (95% CI)	**458**	**311**		**31.37%**	**1.29[0.76,2.19]**
Total events: 44 (Amphetamine), 21 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.66, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					
2.8.3 Mixed amphetamine salts					
Biederman 2002	54/374	20/210		29.32%	1.52[0.93,2.46]
Biederman 2007a	2/52	1/52		1.9%	2[0.19,21.38]
Childress 2015	3/97	0/97		1.24%	7[0.37,133.73]
McCracken 2003	18/51	12/51		20.98%	1.5[0.81,2.78]
Pliszka 2000	5/20	0/18		1.34%	9.95[0.59,168.27]
Spencer 2006a	25/233	1/63		2.69%	6.76[0.93,48.92]
Subtotal (95% CI)	**827**	**491**		**57.47%**	**1.69[1.17,2.45]**
Total events: 107 (Amphetamine), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.03, df=5(P=0.41); I^2=0.69%					
Test for overall effect: Z=2.8(P=0.01)					
Total (95% CI)	**1319**	**836**		**100%**	**1.44[1.03,2]**
Total events: 157 (Amphetamine), 64 (Placebo)					
Heterogeneity: Tau^2=0.04; Chi^2=10.32, df=9(P=0.32); I^2=12.83%					
Test for overall effect: Z=2.15(P=0.03)					
Test for subgroup differences: Chi^2=3.62, df=1 (P=0.16), I^2=44.76%					

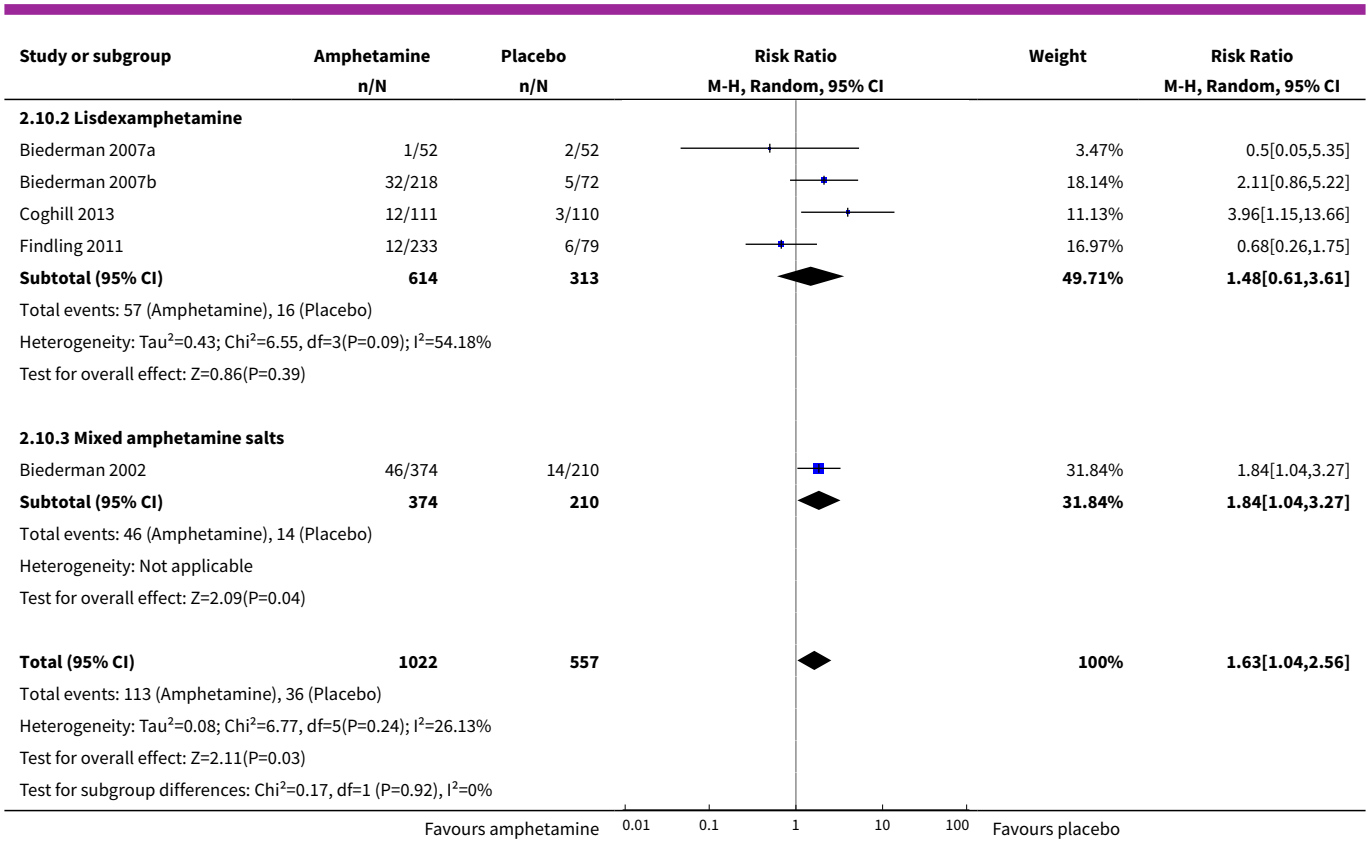
Favours amphetamine 0.005 0.1 1 10 200 Favours placebo

Analysis 2.9. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 9 Proportion of participants experiencing headaches.



Analysis 2.10. Comparison 2 Subgroup analysis 1: Type of amphetamine, Outcome 10 Proportion of participants experiencing nausea/vomiting.





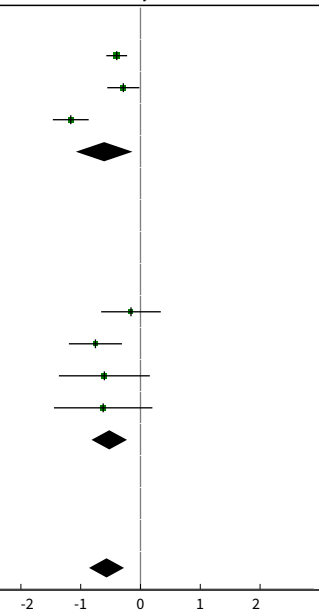
Comparison 3. Subgroup analysis 2: Type of amphetamine release formulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total ADHD symptom score - parent ratings	7	1247	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.86, -0.27]
1.1 Long acting	3	1049	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.08, -0.13]
1.2 Short acting	4	198	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.82, -0.23]
2 Proportion of responders (CGI - I)	9	2105	Risk Ratio (M-H, Random, 95% CI)	3.31 [2.44, 4.49]
2.1 Long acting	6	1662	Risk Ratio (M-H, Random, 95% CI)	3.55 [2.63, 4.79]
2.2 Short acting	3	443	Risk Ratio (M-H, Random, 95% CI)	2.89 [1.39, 6.02]
3 Academic performance	8	826	Std. Mean Difference (IV, Random, 95% CI)	0.56 [0.39, 0.73]
3.1 Long acting	4	494	Std. Mean Difference (IV, Random, 95% CI)	0.59 [0.36, 0.81]

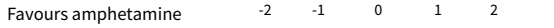
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Short acting	4	332	Std. Mean Difference (IV, Random, 95% CI)	0.48 [0.15, 0.81]
4 Retention: proportion of participants who completed the trial	10	2364	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.12]
4.1 Long acting	6	1756	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.00, 1.24]
4.2 Short acting	4	608	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
5 Proportion of participants experiencing decreased appetite	10	2271	Risk Ratio (M-H, Random, 95% CI)	6.18 [2.44, 15.63]
5.1 Long acting	8	2165	Risk Ratio (M-H, Random, 95% CI)	7.67 [3.33, 17.65]
5.2 Short acting	2	106	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.69, 3.62]
6 Proportion of participants experiencing abdominal pain	10	2155	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.03, 2.00]
6.1 Long acting	7	1855	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.10, 2.02]
6.2 Short acting	3	300	Risk Ratio (M-H, Random, 95% CI)	2.54 [0.30, 21.39]

Analysis 3.1. Comparison 3 Subgroup analysis 2: Type of amphetamine release formulation, Outcome 1 Total ADHD symptom score - parent ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.1.1 Long acting							
Biederman 2002	360	7.8 (10.7)	203	11.8 (8.8)		19.95%	-0.4[-0.57,-0.22]
Biederman 2007b	213	18.6 (59.8)	72	34.3 (34.8)		18.18%	-0.29[-0.55,-0.02]
Coghill 2013	98	28.7 (17.6)	103	49.5 (18)		17.52%	-1.17[-1.47,-0.87]
Subtotal ***	**671**		**378**			**55.66%**	**-0.61[-1.08,-0.13]**
Heterogeneity: Tau^2=0.16; Chi^2=22.7, df=2(P<0.0001); I^2=91.19%							
Test for overall effect: Z=2.51(P=0.01)							
3.1.2 Short acting							
Barkley 2000	31	20.2 (9)	31	21.9 (12.5)		13.23%	-0.16[-0.66,0.34]
Manos 1999	42	11.8 (9.9)	42	20 (11.7)		14.38%	-0.75[-1.2,-0.31]
Nemzer 1986	14	13.3 (6.4)	14	17.2 (6.2)		8.77%	-0.6[-1.36,0.16]
Pliszka 2000	12	1 (0.7)	12	1.5 (0.9)		7.96%	-0.62[-1.45,0.2]
Subtotal ***	**99**		**99**			**44.34%**	**-0.52[-0.82,-0.23]**
Heterogeneity: Tau^2=0.01; Chi^2=3.19, df=3(P=0.36); I^2=5.88%							
Test for overall effect: Z=3.45(P=0)							
Total ***	**770**		**477**			**100%**	**-0.57[-0.86,-0.27]**



Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Heterogeneity: Tau²=0.1; Chi²=25.88, df=6(P=0); I²=76.82%							
Test for overall effect: Z=3.8(P=0)							
Test for subgroup differences: Chi²=0.09, df=1 (P=0.76), I²=0%							

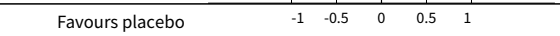


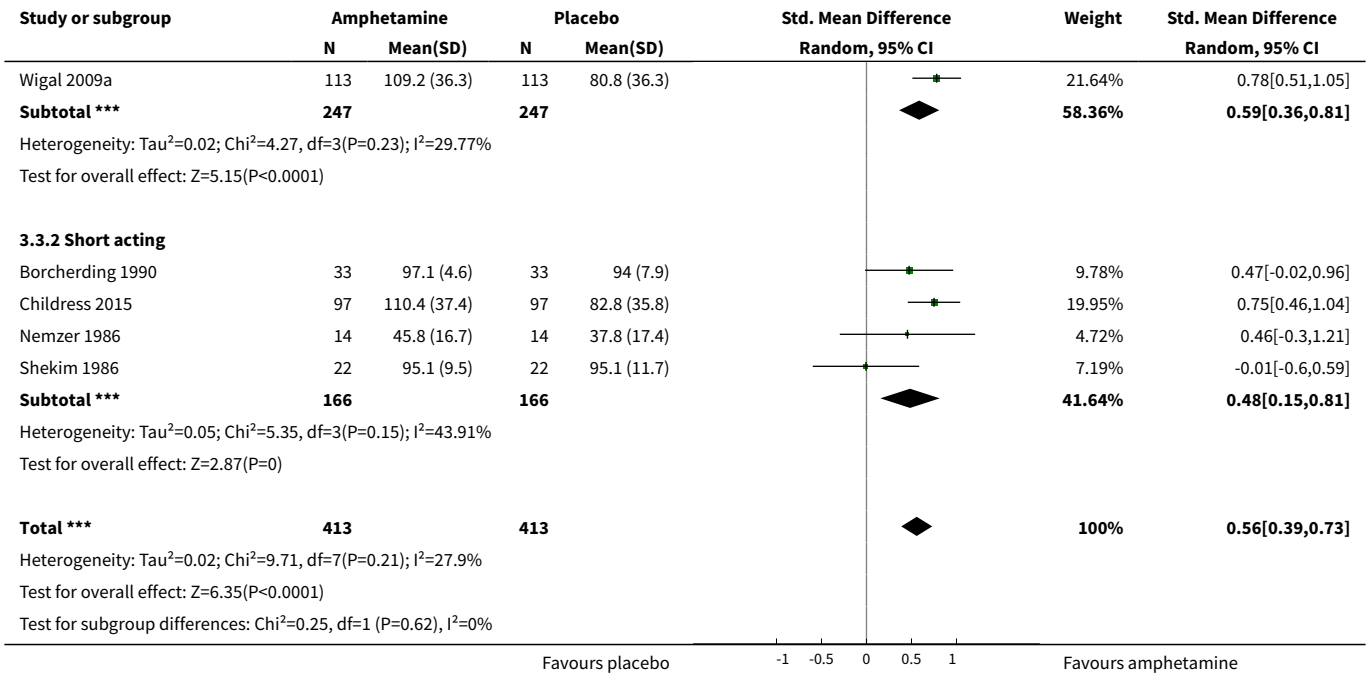
Analysis 3.2. Comparison 3 Subgroup analysis 2: Type of amphetamine release formulation, Outcome 2 Proportion of responders (CGI - I).

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Long acting					
Biederman 2002	148/360	35/203		13.82%	2.38[1.72,3.3]
Biederman 2007a	36/50	9/50		9.82%	4[2.16,7.41]
Biederman 2007b	156/213	12/72		11.07%	4.39[2.61,7.41]
Coghill 2013	81/104	15/106		11.67%	5.5[3.41,8.89]
Spencer 2006a	143/226	14/52		11.97%	2.35[1.49,3.72]
Wigal 2009a	93/113	22/113		13.01%	4.23[2.88,6.21]
Subtotal (95% CI)	**1066**	**596**		**71.37%**	**3.55[2.63,4.79]**
Total events: 657 (Amphetamine), 107 (Placebo)					
Heterogeneity: Tau²=0.09; Chi²=13.36, df=5(P=0.02); I²=62.56%					
Test for overall effect: Z=8.27(P<0.0001)					
3.2.2 Short acting					
Barkley 2000	16/35	5/35		6.86%	3.2[1.32,7.78]
Findling 2011	160/232	30/77		14.26%	1.77[1.32,2.37]
Sharp 1999	27/32	5/32		7.52%	5.4[2.38,12.25]
Subtotal (95% CI)	**299**	**144**		**28.63%**	**2.89[1.39,6.02]**
Total events: 203 (Amphetamine), 40 (Placebo)					
Heterogeneity: Tau²=0.3; Chi²=7.51, df=2(P=0.02); I²=73.37%					
Test for overall effect: Z=2.83(P=0)					
Total (95% CI)	**1365**	**740**		**100%**	**3.31[2.44,4.49]**
Total events: 860 (Amphetamine), 147 (Placebo)					
Heterogeneity: Tau²=0.15; Chi²=29.93, df=8(P=0); I²=73.27%					
Test for overall effect: Z=7.69(P<0.0001)					
Test for subgroup differences: Chi²=0.26, df=1 (P=0.61), I²=0%					

Analysis 3.3. Comparison 3 Subgroup analysis 2: Type of amphetamine release formulation, Outcome 3 Academic performance.

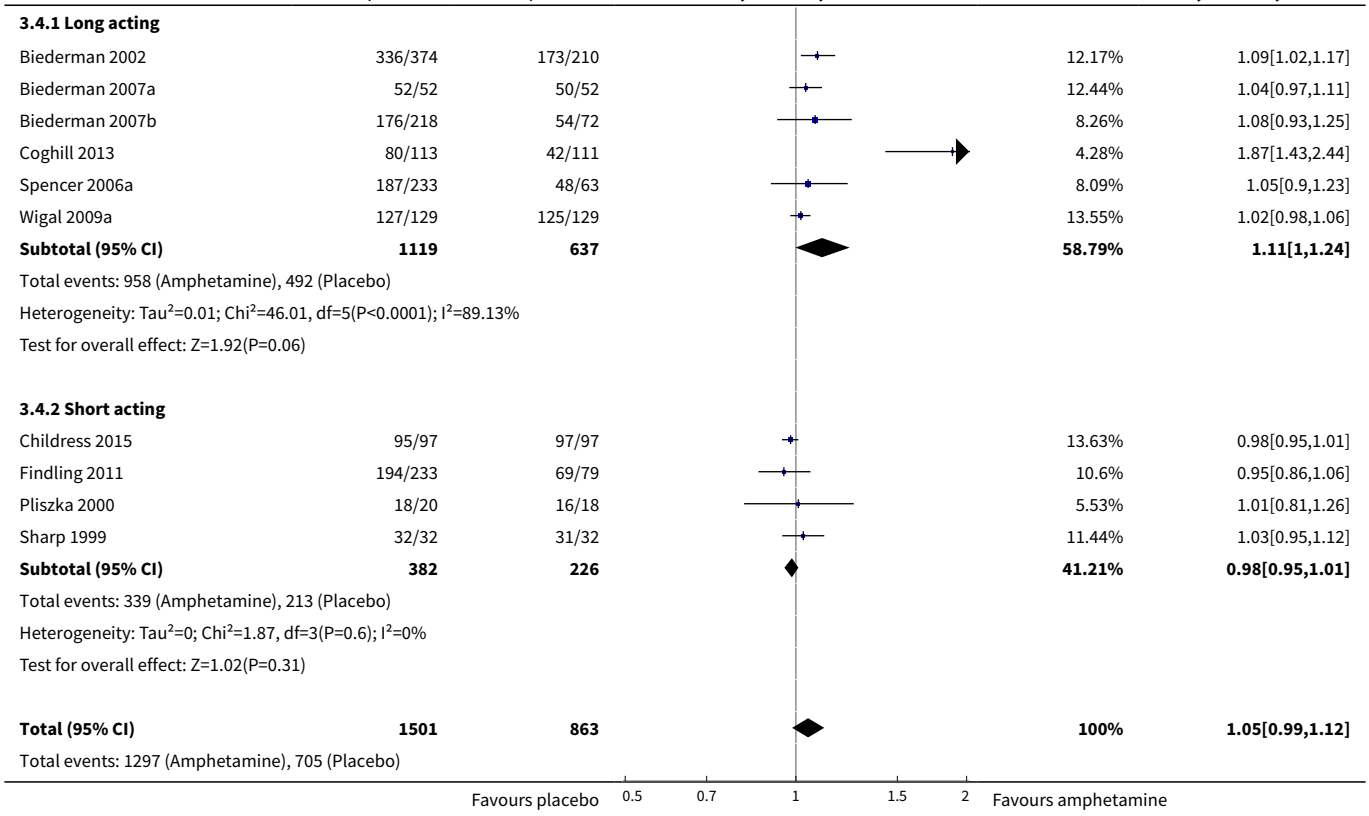
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.3.1 Long acting							
Biederman 2007a	50	129.5 (76)	50	84.1 (76)		13.22%	0.59[0.19,0.99]
James 2001	35	169.9 (52.7)	35	140.2 (51.3)		10.15%	0.56[0.09,1.04]
McCracken 2003	49	79.1 (52)	49	64.9 (50.3)		13.36%	0.28[-0.12,0.67]





Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Wigal 2009a	113	109.2 (36.3)	113	80.8 (36.3)		21.64%	0.78[0.51,1.05]
Subtotal ***	**247**		**247**			**58.36%**	**0.59[0.36,0.81]**
Heterogeneity: Tau²=0.02; Chi²=4.27, df=3(P=0.23); I²=29.77%							
Test for overall effect: Z=5.15(P<0.0001)							
3.3.2 Short acting							
Borcherding 1990	33	97.1 (4.6)	33	94 (7.9)		9.78%	0.47[-0.02,0.96]
Childress 2015	97	110.4 (37.4)	97	82.8 (35.8)		19.95%	0.75[0.46,1.04]
Nemzer 1986	14	45.8 (16.7)	14	37.8 (17.4)		4.72%	0.46[-0.3,1.21]
Shekim 1986	22	95.1 (9.5)	22	95.1 (11.7)		7.19%	-0.01[-0.6,0.59]
Subtotal ***	**166**		**166**			**41.64%**	**0.48[0.15,0.81]**
Heterogeneity: Tau²=0.05; Chi²=5.35, df=3(P=0.15); I²=43.91%							
Test for overall effect: Z=2.87(P=0)							
Total ***	**413**		**413**			**100%**	**0.56[0.39,0.73]**
Heterogeneity: Tau²=0.02; Chi²=9.71, df=7(P=0.21); I²=27.9%							
Test for overall effect: Z=6.35(P<0.0001)							
Test for subgroup differences: Chi²=0.25, df=1 (P=0.62), I²=0%							

Analysis 3.4. Comparison 3 Subgroup analysis 2: Type of amphetamine release formulation, Outcome 4 Retention: proportion of participants who completed the trial.



Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Long acting					
Biederman 2002	336/374	173/210		12.17%	1.09[1.02,1.17]
Biederman 2007a	52/52	50/52		12.44%	1.04[0.97,1.11]
Biederman 2007b	176/218	54/72		8.26%	1.08[0.93,1.25]
Coghill 2013	80/113	42/111		4.28%	1.87[1.43,2.44]
Spencer 2006a	187/233	48/63		8.09%	1.05[0.9,1.23]
Wigal 2009a	127/129	125/129		13.55%	1.02[0.98,1.06]
Subtotal (95% CI)	**1119**	**637**		**58.79%**	**1.11[1,1.24]**
Total events: 958 (Amphetamine), 492 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=46.01, df=5(P<0.0001); I²=89.13%					
Test for overall effect: Z=1.92(P=0.06)					
3.4.2 Short acting					
Childress 2015	95/97	97/97		13.63%	0.98[0.95,1.01]
Findling 2011	194/233	69/79		10.6%	0.95[0.86,1.06]
Pliszka 2000	18/20	16/18		5.53%	1.01[0.81,1.26]
Sharp 1999	32/32	31/32		11.44%	1.03[0.95,1.12]
Subtotal (95% CI)	**382**	**226**		**41.21%**	**0.98[0.95,1.01]**
Total events: 339 (Amphetamine), 213 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.87, df=3(P=0.6); I²=0%					
Test for overall effect: Z=1.02(P=0.31)					
Total (95% CI)	**1501**	**863**		**100%**	**1.05[0.99,1.12]**
Total events: 1297 (Amphetamine), 705 (Placebo)					

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.01; Chi²=62.64, df=9(P<0.0001); I²=85.63%					
Test for overall effect: Z=1.52(P=0.13)					
Test for subgroup differences: Chi²=4.5, df=1 (P=0.03), I²=77.77%					

Favours placebo 0.5 0.7 1 1.5 2 Favours amphetamine

Analysis 3.5. Comparison 3 Subgroup analysis 2: Type of amphetamine release formulation, Outcome 5 Proportion of participants experiencing decreased appetite.

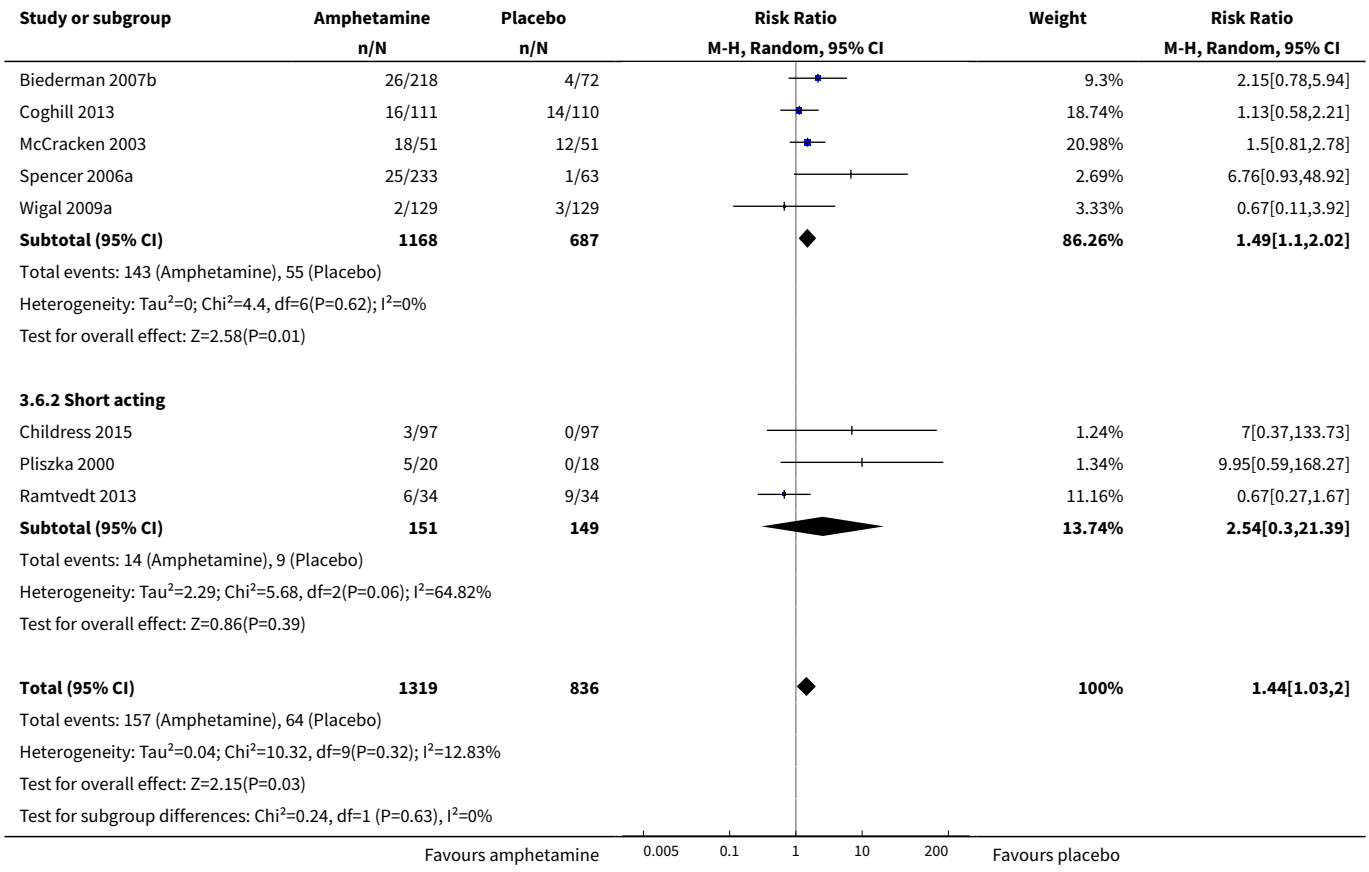
Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Long acting					
Biederman 2002	82/374	4/210		11.93%	11.51[4.28,30.96]
Biederman 2007a	2/52	0/52		5.62%	5[0.25,101.68]
Biederman 2007b	85/218	3/72		11.49%	9.36[3.05,28.68]
Coghill 2013	28/111	3/110		11.35%	9.25[2.9,29.54]
Findling 2011	79/233	2/77		10.57%	13.05[3.29,51.86]
McCracken 2003	20/51	11/51		12.98%	1.82[0.97,3.4]
Spencer 2006a	83/233	1/63		8.57%	22.44[3.19,158.05]
Wigal 2009a	7/129	1/129		8.15%	7[0.87,56.09]
Subtotal (95% CI)	**1401**	**764**		**80.66%**	**7.67[3.33,17.65]**
Total events: 386 (Amphetamine), 25 (Placebo)					
Heterogeneity: Tau²=0.9; Chi²=23.5, df=7(P=0); I²=70.21%					
Test for overall effect: Z=4.79(P<0.0001)					
3.5.2 Short acting					
Pliszka 2000	3/20	0/18		5.89%	6.33[0.35,114.81]
Ramtvedt 2013	24/34	17/34		13.45%	1.41[0.95,2.11]
Subtotal (95% CI)	**54**	**52**		**19.34%**	**1.58[0.69,3.62]**
Total events: 27 (Amphetamine), 17 (Placebo)					
Heterogeneity: Tau²=0.15; Chi²=1.14, df=1(P=0.29); I²=11.95%					
Test for overall effect: Z=1.09(P=0.28)					
Total (95% CI)	**1455**	**816**		**100%**	**6.18[2.44,15.63]**
Total events: 413 (Amphetamine), 42 (Placebo)					
Heterogeneity: Tau²=1.63; Chi²=63.92, df=9(P<0.0001); I²=85.92%					
Test for overall effect: Z=3.84(P=0)					
Test for subgroup differences: Chi²=6.93, df=1 (P=0.01), I²=85.58%					

Favours amphetamine 0.005 0.1 1 10 200 Favours placebo

Analysis 3.6. Comparison 3 Subgroup analysis 2: Type of amphetamine release formulation, Outcome 6 Proportion of participants experiencing abdominal pain.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Long acting					
Biederman 2002	54/374	20/210		29.32%	1.52[0.93,2.46]
Biederman 2007a	2/52	1/52		1.9%	2[0.19,21.38]

Favours amphetamine 0.005 0.1 1 10 200 Favours placebo



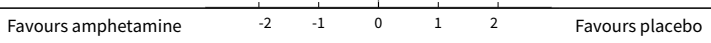
Comparison 4. Subgroup analysis 3: Funding source

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total ADHD symptom score - parent ratings	7	1247	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.86, -0.27]
1.1 Industry	5	1135	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.89, -0.16]
1.2 Public	1	84	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-1.20, -0.31]
1.3 Not reported	1	28	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-1.36, 0.16]
2 Proportion of responders (CGI - I)	9	2210	Risk Ratio (M-H, Random, 95% CI)	3.37 [2.50, 4.53]
2.1 Industry	8	2146	Risk Ratio (M-H, Random, 95% CI)	3.24 [2.39, 4.40]
2.2 Not reported	1	64	Risk Ratio (M-H, Random, 95% CI)	5.4 [2.38, 12.25]
3 Academic performance	8	826	Std. Mean Difference (IV, Random, 95% CI)	0.56 [0.39, 0.73]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Industry	5	688	Std. Mean Difference (IV, Random, 95% CI)	0.64 [0.46, 0.81]
3.2 Public	1	44	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.60, 0.59]
3.3 Not reported	2	94	Std. Mean Difference (IV, Random, 95% CI)	0.47 [0.06, 0.88]

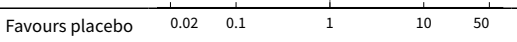
Analysis 4.1. Comparison 4 Subgroup analysis 3: Funding source, Outcome 1 Total ADHD symptom score - parent ratings.

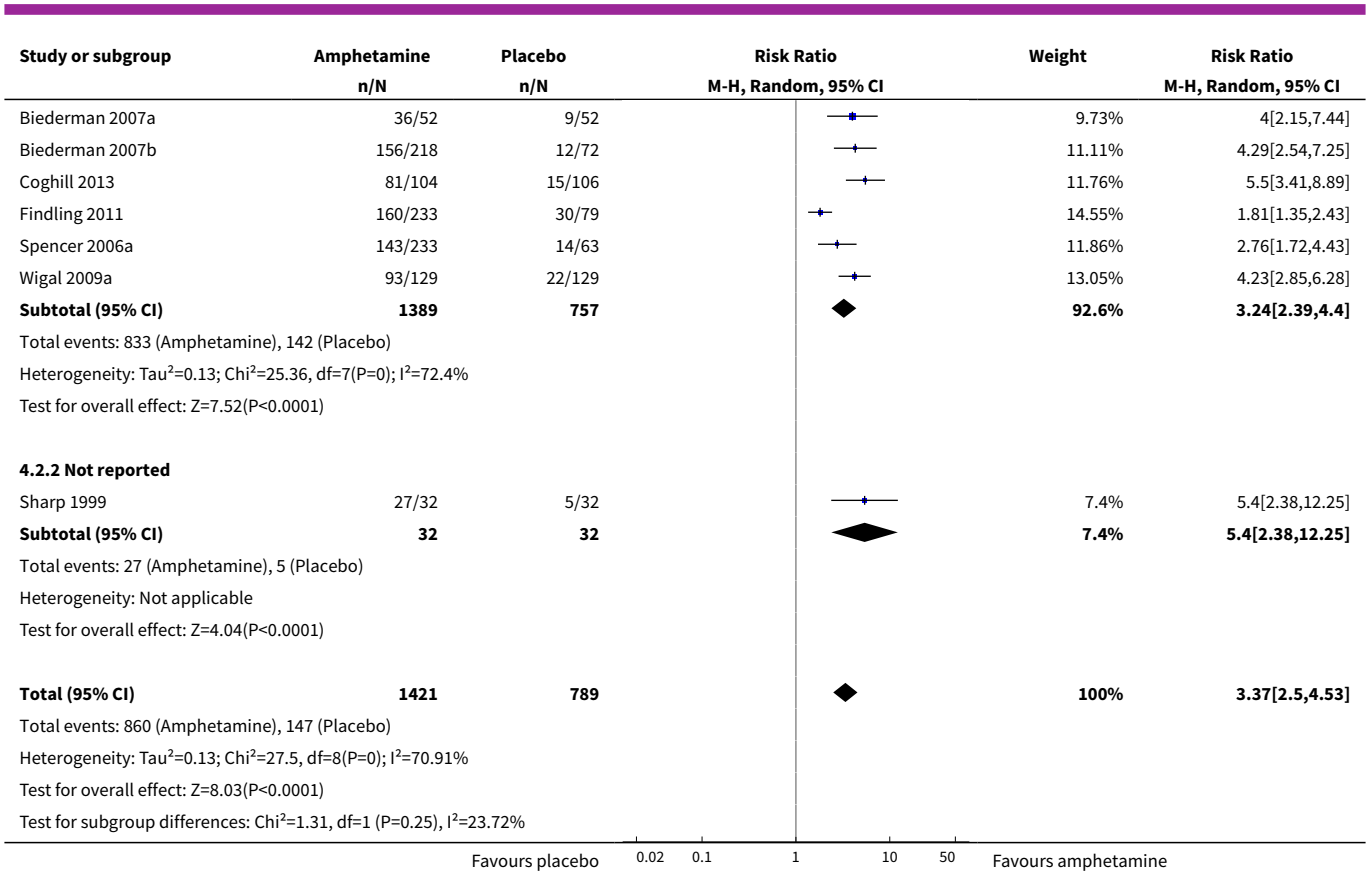
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
4.1.1 Industry							
Barkley 2000	31	20.2 (9)	31	21.9 (12.5)		13.23%	-0.16[-0.66,0.34]
Biederman 2002	360	7.8 (10.7)	203	11.8 (8.8)		19.95%	-0.4[-0.57,-0.22]
Biederman 2007b	213	18.6 (59.8)	72	34.3 (34.8)		18.18%	-0.29[-0.55,-0.02]
Coghill 2013	98	28.7 (17.6)	103	49.5 (18)		17.52%	-1.17[-1.47,-0.87]
Pliszka 2000	12	1 (0.7)	12	1.5 (0.9)		7.96%	-0.62[-1.45,0.2]
Subtotal ***	**714**		**421**			**76.85%**	**-0.53[-0.89,-0.16]**
Heterogeneity: Tau²=0.13; Chi²=24.65, df=4(P<0.0001); I²=83.77%							
Test for overall effect: Z=2.83(P=0)							
4.1.2 Public							
Manos 1999	42	11.8 (9.9)	42	20 (11.7)		14.38%	-0.75[-1.2,-0.31]
Subtotal ***	**42**		**42**			**14.38%**	**-0.75[-1.2,-0.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.33(P=0)							
4.1.3 Not reported							
Nemzer 1986	14	13.3 (6.4)	14	17.2 (6.2)		8.77%	-0.6[-1.36,0.16]
Subtotal ***	**14**		**14**			**8.77%**	**-0.6[-1.36,0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.56(P=0.12)							
Total ***	**770**		**477**			**100%**	**-0.57[-0.86,-0.27]**
Heterogeneity: Tau²=0.1; Chi²=25.88, df=6(P=0); I²=76.82%							
Test for overall effect: Z=3.8(P=0)							
Test for subgroup differences: Chi²=0.59, df=1 (P=0.74), I²=0%							



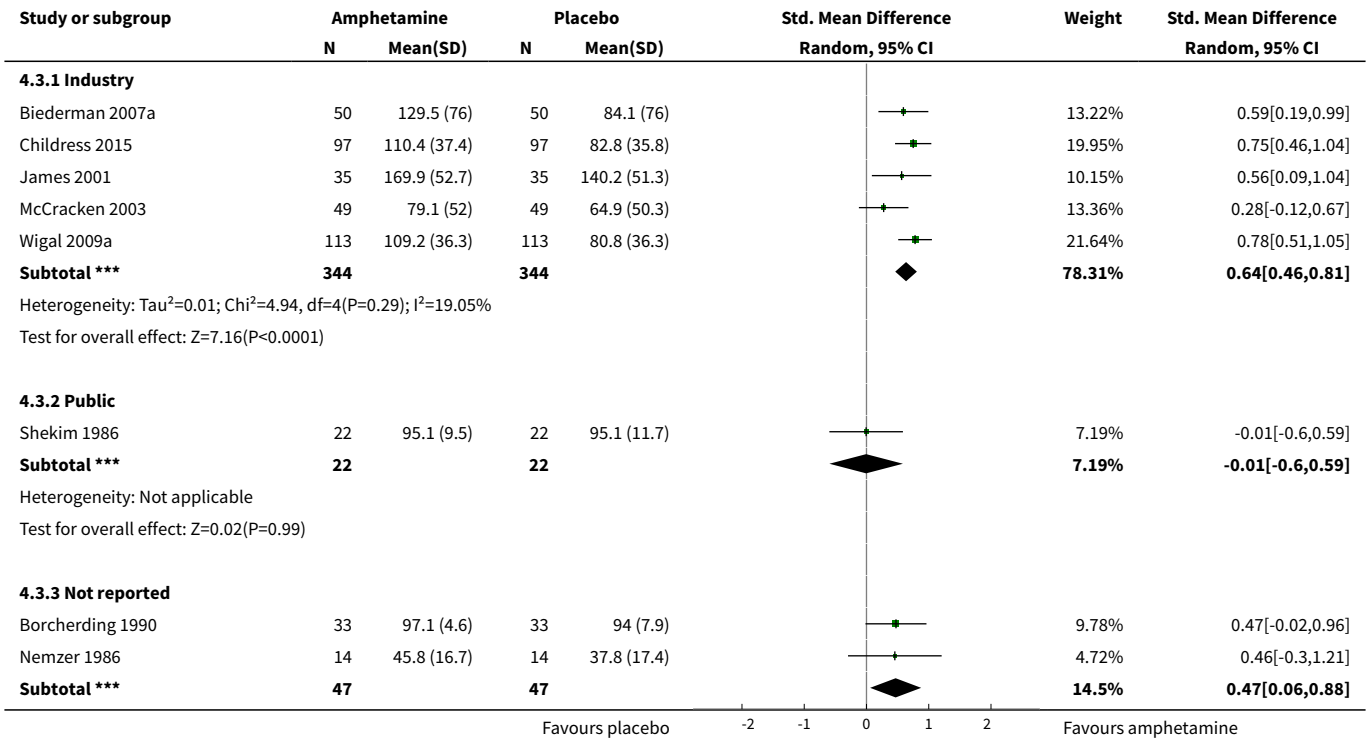
Analysis 4.2. Comparison 4 Subgroup analysis 3: Funding source, Outcome 2 Proportion of responders (CGI - I).

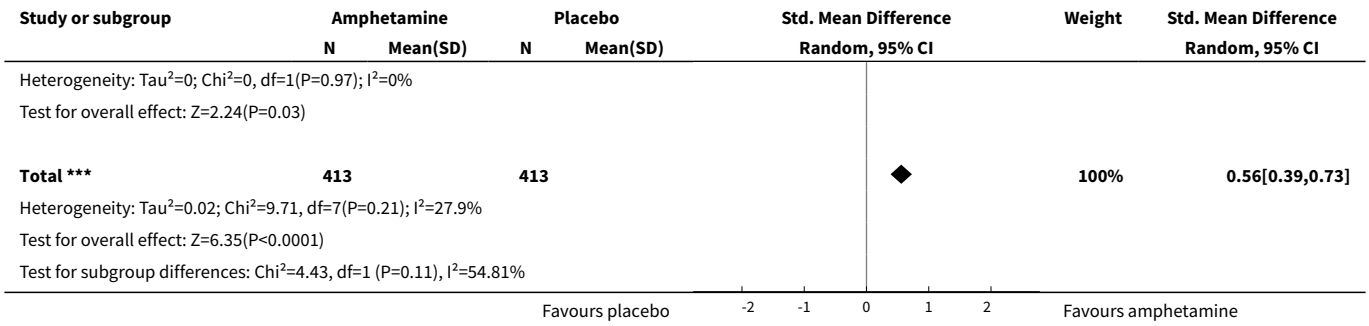
Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Industry					
Barkley 2000	16/46	5/46		6.46%	3.2[1.28,8.01]
Biederman 2002	148/374	35/210		14.08%	2.37[1.71,3.29]





Analysis 4.3. Comparison 4 Subgroup analysis 3: Funding source, Outcome 3 Academic performance.





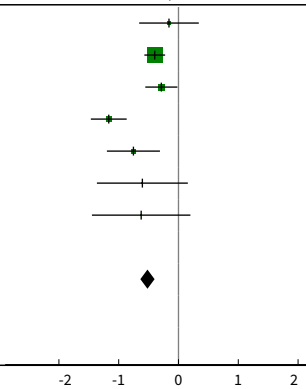
Comparison 5. Sensitivity analysis 1: Fixed-effect model

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total ADHD symptom score - parent ratings	7	1247	Std. Mean Difference (IV, Fixed, 95% CI)	-0.52 [-0.64, -0.40]
2 Hyperactivity/impulsivity - parent ratings	2	132	Std. Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.89, -0.19]
3 Total ADHD symptom score - teacher ratings	5	745	Std. Mean Difference (IV, Fixed, 95% CI)	-0.47 [-0.62, -0.32]
4 Hyperactivity/impulsivity - teacher ratings	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Inattention - teacher ratings	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Total ADHD symptom score - clinician ratings	3	813	Std. Mean Difference (IV, Fixed, 95% CI)	-0.84 [-1.01, -0.68]
7 Hyperactivity/impulsivity - clinician ratings	3	813	Std. Mean Difference (IV, Fixed, 95% CI)	-0.74 [-0.90, -0.58]
8 Inattention - clinician ratings	3	813	Std. Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.94, -0.61]
9 Total ADHD symptom score - investigator/research personnel ratings	3	630	Std. Mean Difference (IV, Fixed, 95% CI)	-1.08 [-1.25, -0.91]
10 Hyperactivity/impulsivity - Investigator/research personnel ratings	2	280	Std. Mean Difference (IV, Fixed, 95% CI)	-1.50 [-1.76, -1.23]
11 Inattention - investigator/research personnel ratings	4	634	Std. Mean Difference (IV, Fixed, 95% CI)	-0.76 [-0.93, -0.60]
12 Proportion of responders (CGI - I)	9	2207	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [2.68, 3.61]
13 CGI - S score	2	86	Std. Mean Difference (IV, Fixed, 95% CI)	-0.71 [-1.15, -0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Quality of life	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15 Academic performance	8	826	Std. Mean Difference (IV, Fixed, 95% CI)	0.59 [0.45, 0.73]
16 Retention: proportion of participants who completed the trial	10	2364	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [1.04, 1.12]
17 Proportion of participants who experienced at least one adverse event	6	1742	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.20, 1.47]
18 Proportion of participants who dropped out/withdrew due to an adverse event	9	2160	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.08, 3.51]
19 Proportion of participants experiencing decreased appetite	11	2467	Risk Ratio (M-H, Fixed, 95% CI)	5.57 [4.03, 7.68]
20 Proportion of participants experiencing insomnia/trouble sleeping	10	2429	Risk Ratio (M-H, Fixed, 95% CI)	3.91 [2.82, 5.41]
21 Proportion of participants experiencing abdominal pain	10	2155	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.18, 2.08]
22 Proportion of participants experiencing headaches	9	2091	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.18]
23 Proportion of participants experiencing anxiety/nervousness	5	1088	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.94, 1.56]
24 Proportion of participants experiencing nausea/vomiting	6	1579	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.20, 2.46]

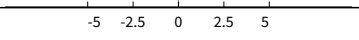
Analysis 5.1. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 1 Total ADHD symptom score - parent ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Barkley 2000	31	20.2 (9)	31	21.9 (12.5)		5.7%	-0.16[-0.66,0.34]
Biederman 2002	360	7.8 (10.7)	203	11.8 (8.8)		47.04%	-0.4[-0.57,-0.22]
Biederman 2007b	213	18.6 (59.8)	72	34.3 (34.8)		19.7%	-0.29[-0.55,-0.02]
Coghill 2013	98	28.7 (17.6)	103	49.5 (18)		15.8%	-1.17[-1.47,-0.87]
Manos 1999	42	11.8 (9.9)	42	20 (11.7)		7.21%	-0.75[-1.2,-0.31]
Nemzer 1986	14	13.3 (6.4)	14	17.2 (6.2)		2.45%	-0.6[-1.36,0.16]
Pliszka 2000	12	1 (0.7)	12	1.5 (0.9)		2.09%	-0.62[-1.45,0.2]
Total ***	**770**		**477**			**100%**	**-0.52[-0.64,-0.4]**
Heterogeneity: Tau^2=0; Chi^2=25.88, df=6(P=0); I^2=76.82%							
Test for overall effect: Z=8.54(P<0.0001)							



Analysis 5.2. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 2 Hyperactivity/impulsivity - parent ratings.

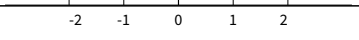
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Borcherding 1990	31	0.8 (1.9)	31	1.8 (1.9)		47.21%	-0.5[-1.01,0]
James 2001	35	59.6 (14.5)	35	68 (14.5)		52.79%	-0.57[-1.05,-0.09]
Total ***	**66**		**66**			**100%**	**-0.54[-0.89,-0.19]**
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%							
Test for overall effect: Z=3.04(P=0)							



Favours amphetamine — Favours placebo

Analysis 5.3. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 3 Total ADHD symptom score - teacher ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Barkley 2000	15	17 (14.7)	15	17.7 (13.8)		4.42%	-0.05[-0.77,0.66]
Biederman 2002	360	5.8 (11)	203	9.9 (9.4)		75.13%	-0.39[-0.57,-0.22]
Donnelly 1989	20	7.8 (3.1)	20	10.9 (3.8)		5.33%	-0.88[-1.53,-0.22]
Manos 1999	42	51.5 (10.4)	42	62 (13.6)		11.27%	-0.86[-1.31,-0.42]
Nemzer 1986	14	30.2 (18.9)	14	43.6 (18.6)		3.86%	-0.69[-1.46,0.08]
Total ***	**451**		**294**			**100%**	**-0.47[-0.62,-0.32]**
Heterogeneity: Tau²=0; Chi²=6.82, df=4(P=0.15); I²=41.37%							
Test for overall effect: Z=6.12(P<0.0001)							



Favours amphetamine — Favours placebo

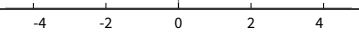
Analysis 5.4. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 4 Hyperactivity/impulsivity - teacher ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
James 2001	35	51.6 (6.7)	35	63.1 (12.6)		0%	-1.13[-1.63,-0.62]

Favours amphetamine — Favours placebo

Analysis 5.5. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 5 Inattention - teacher ratings.

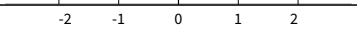
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Pliszka 2000	12	0.5 (0.4)	12	1.5 (0.9)		0%	-1.43[-2.35,-0.52]



Favours amphetamine — Favours placebo

Analysis 5.6. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 6 Total ADHD symptom score - clinician ratings.

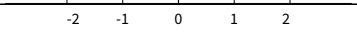
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Findling 2011	232	17.6 (11.4)	77	25.7 (12.9)		38.73%	-0.69[-0.95,-0.42]
Spencer 2006a	226	-17.8 (16.6)	52	-9.4 (16.6)		29.01%	-0.5[-0.81,-0.2]
Wigal 2009a	113	-25.8 (12.8)	113	-8.7 (12.8)		32.26%	-1.33[-1.62,-1.04]
Total ***	**571**		**242**			**100%**	**-0.84[-1.01,-0.68]**
Heterogeneity: Tau^2=0; Chi^2=17.12, df=2(P=0); I^2=88.32%							
Test for overall effect: Z=10.06(P<0.0001)							



Favours amphetamine — Favours placebo

Analysis 5.7. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 7 Hyperactivity/impulsivity - clinician ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Findling 2011	232	8.5 (6.6)	77	11.5 (6.6)		39.15%	-0.46[-0.72,-0.2]
Spencer 2006a	226	-7.6 (8.6)	52	-3.2 (8.6)		28.63%	-0.51[-0.81,-0.21]
Wigal 2009a	113	-13.3 (6.8)	113	-4.5 (6.8)		32.22%	-1.29[-1.58,-1]
Total ***	**571**		**242**			**100%**	**-0.74[-0.9,-0.58]**
Heterogeneity: Tau^2=0; Chi^2=20.7, df=2(P<0.0001); I^2=90.34%							
Test for overall effect: Z=8.93(P<0.0001)							



Favours amphetamine — Favours placebo

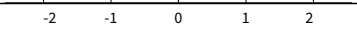
Analysis 5.8. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 8 Inattention - clinician ratings.

Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Findling 2011	232	12.5 (7.8)	77	16.8 (7.8)		38.89%	-0.55[-0.81,-0.29]
Spencer 2006a	226	-10.2 (8)	52	-6.1 (8)		28.67%	-0.51[-0.82,-0.21]
Wigal 2009a	113	-12.5 (6.6)	113	-4.1 (6.6)		32.44%	-1.27[-1.56,-0.98]
Total ***	**571**		**242**			**100%**	**-0.77[-0.94,-0.61]**
Heterogeneity: Tau^2=0; Chi^2=17.24, df=2(P=0); I^2=88.4%							
Test for overall effect: Z=9.29(P<0.0001)							

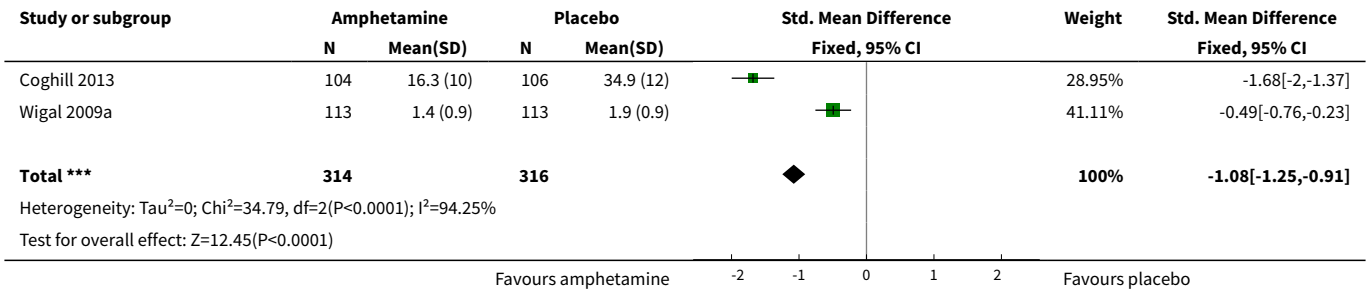
Favours amphetamine — Favours placebo

Analysis 5.9. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 9 Total ADHD symptom score - investigator/research personnel ratings.

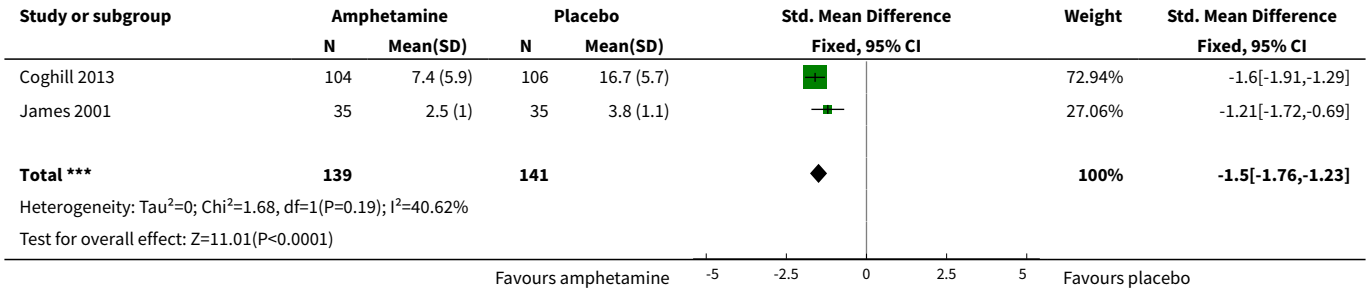
Study or subgroup	Amphetamine N	Amphetamine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Childress 2015	97	10 (8.2)	97	17.8 (1.9)		29.94%	-1.3[-1.61,-0.99]



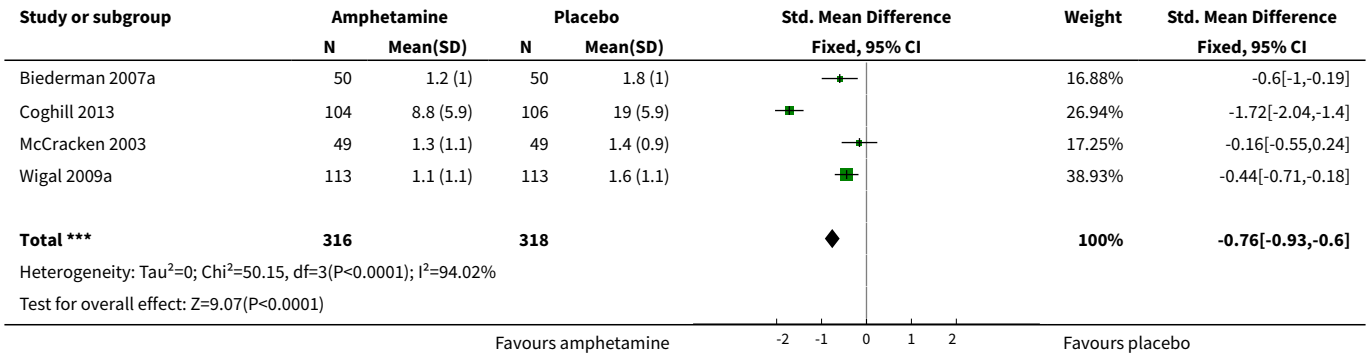
Favours amphetamine — Favours placebo



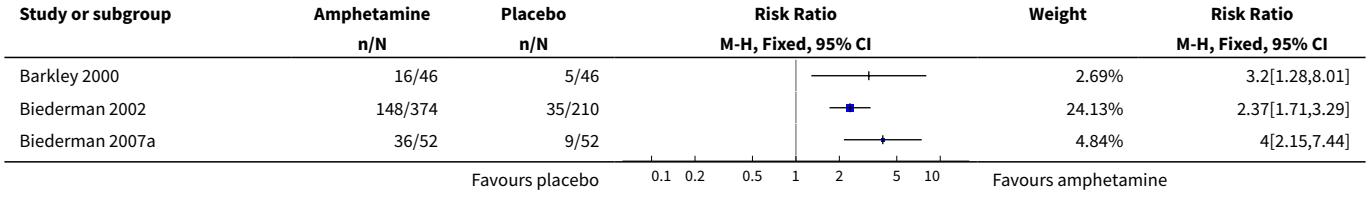
Analysis 5.10. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 10 Hyperactivity/impulsivity - Investigator/research personnel ratings.

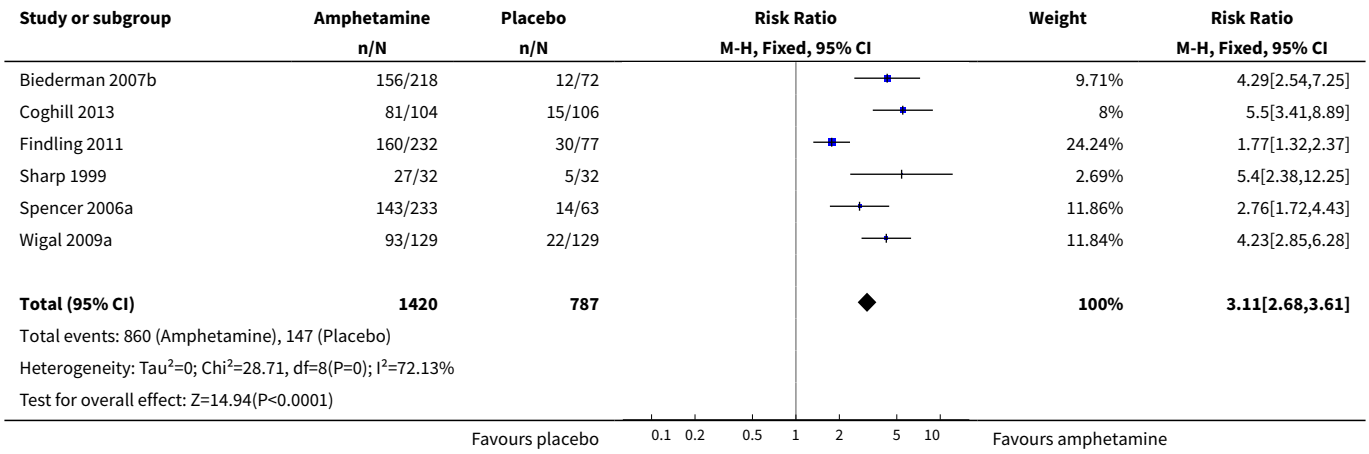


Analysis 5.11. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 11 Inattention - investigator/research personnel ratings.

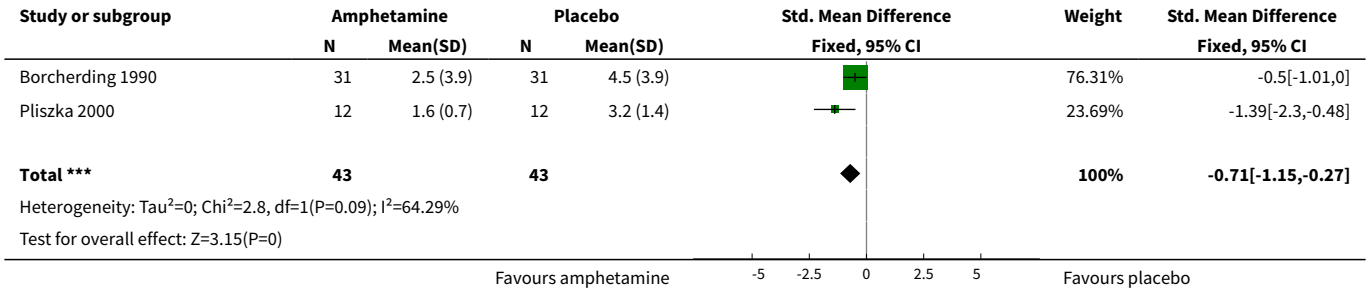


Analysis 5.12. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 12 Proportion of responders (CGI - I).

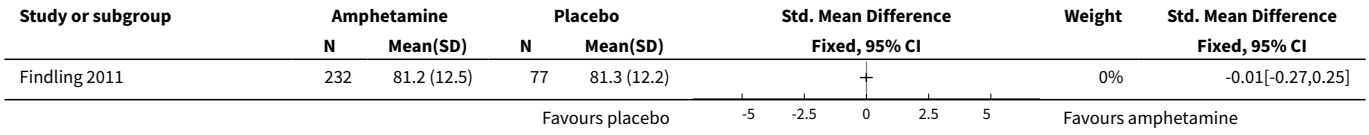




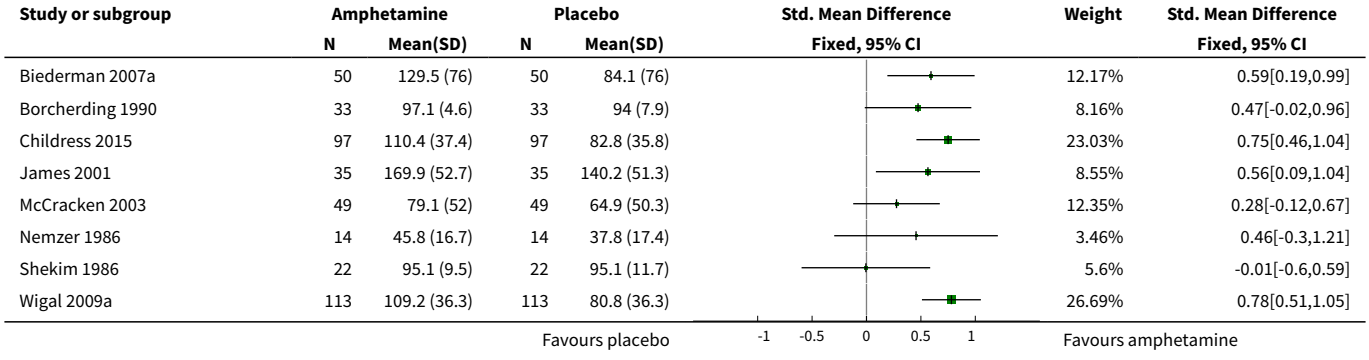
Analysis 5.13. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 13 CGI - S score.

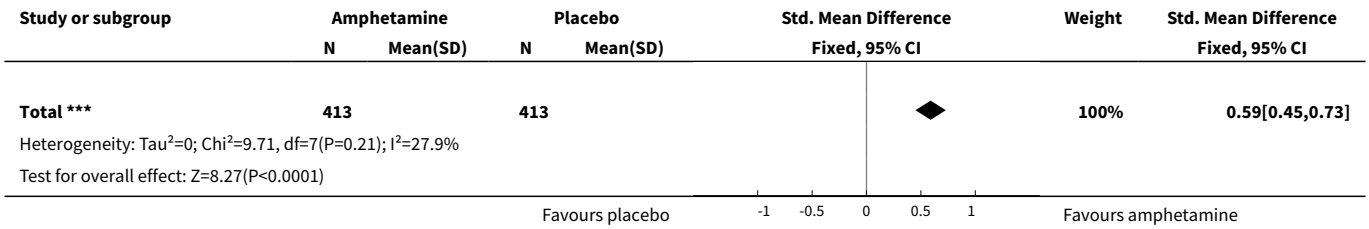


Analysis 5.14. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 14 Quality of life.

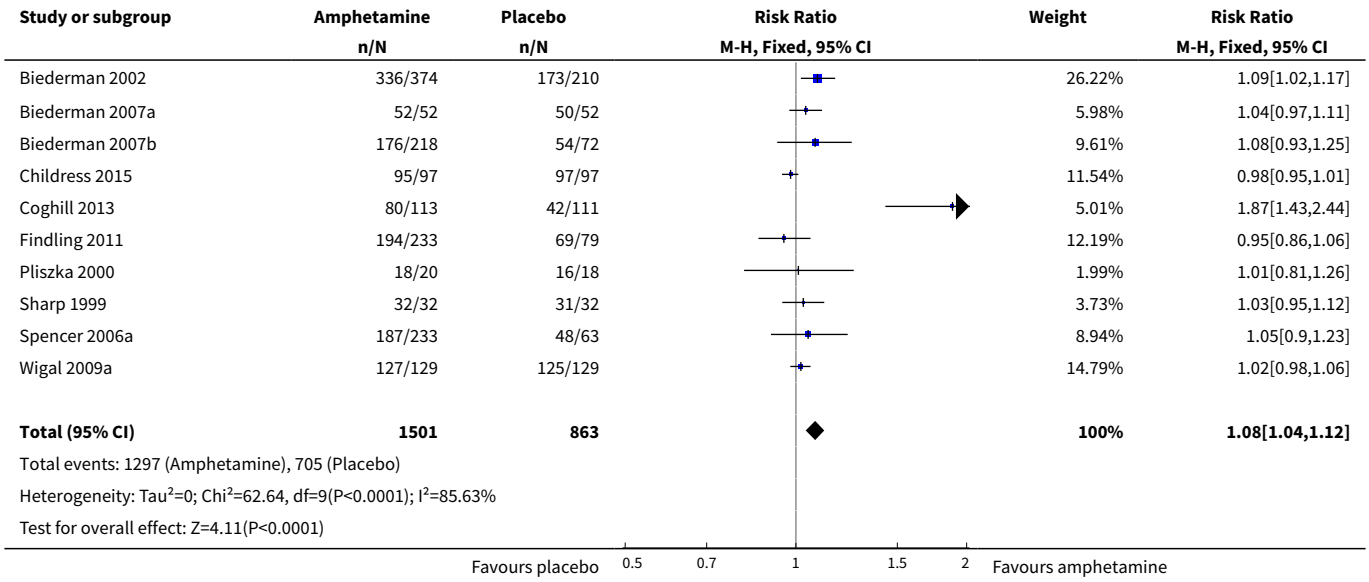


Analysis 5.15. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 15 Academic performance.

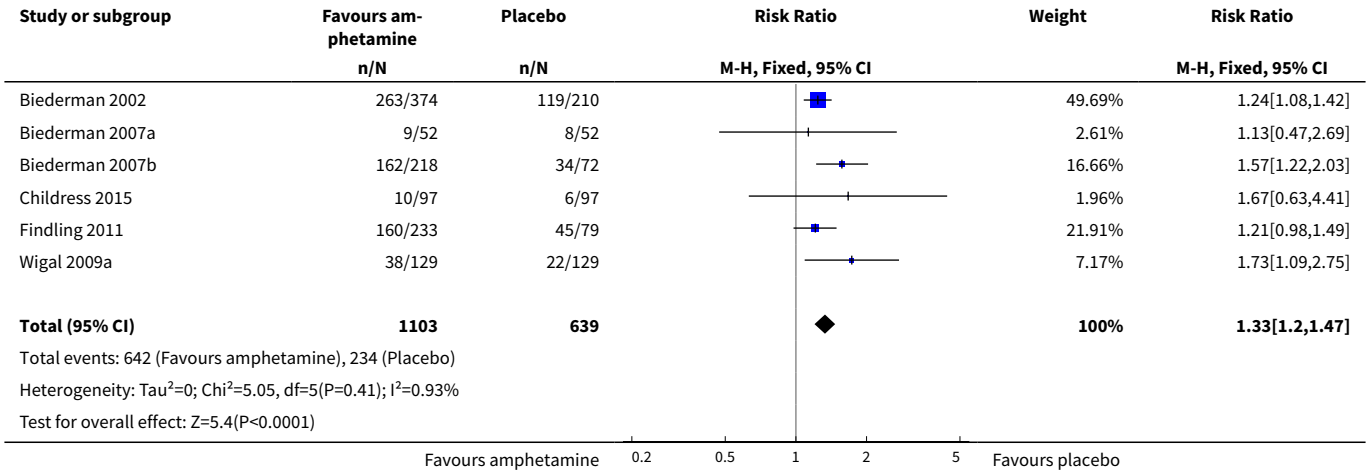




Analysis 5.16. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 16 Retention: proportion of participants who completed the trial.

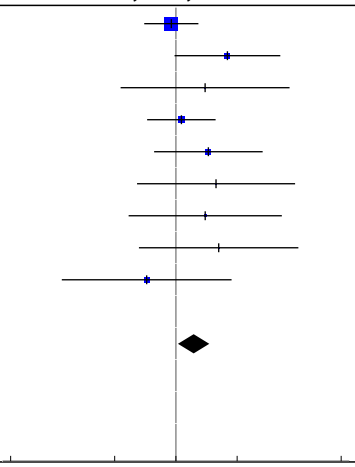


Analysis 5.17. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 17 Proportion of participants who experienced at least one adverse event.



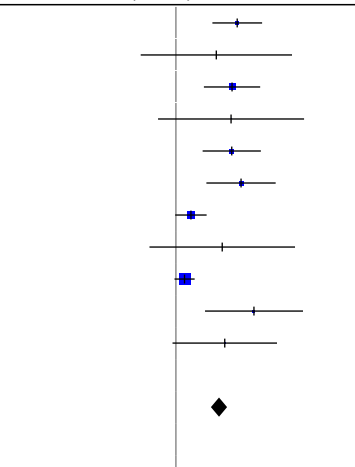
Analysis 5.18. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 18 Proportion of participants who dropped out/withdrew due to an adverse event.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Biederman 2002	9/374	6/210		41.48%	0.84[0.3,2.33]
Biederman 2007b	21/218	1/72		8.11%	6.94[0.95,50.65]
Borcherding 1990	1/46	0/46		2.7%	3[0.13,71.78]
Coghill 2013	5/113	4/111		21.78%	1.23[0.34,4.45]
Findling 2011	10/233	1/79		8.06%	3.39[0.44,26.07]
Pliszka 2000	2/20	0/18		2.83%	4.52[0.23,88.38]
Spencer 2006a	5/233	0/63		4.24%	3.01[0.17,53.69]
Swanson 1998a	2/33	0/33		2.7%	5[0.25,100.32]
Wigal 2009a	0/129	1/129		8.1%	0.33[0.01,8.11]
Total (95% CI)	**1399**	**761**		**100%**	**1.95[1.08,3.51]**
Total events: 55 (Amphetamine), 13 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.97, df=8(P=0.54); I^2=0%					
Test for overall effect: Z=2.23(P=0.03)					



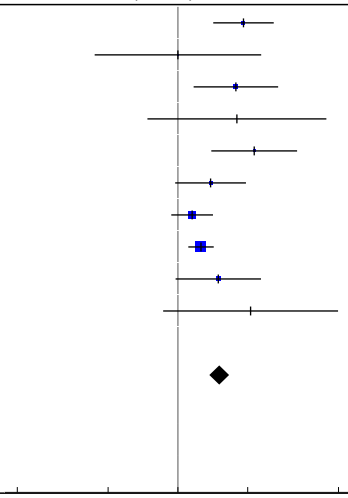
Analysis 5.19. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 19 Proportion of participants experiencing decreased appetite.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Biederman 2002	82/374	4/210		10.73%	11.51[4.28,30.96]
Biederman 2007a	2/52	0/52		1.05%	5[0.25,101.68]
Biederman 2007b	85/218	3/72		9.45%	9.36[3.05,28.68]
Childress 2015	4/97	0/97		1.05%	9[0.49,164.93]
Coghill 2013	28/111	3/110		6.31%	9.25[2.9,29.54]
Findling 2011	79/233	2/79		6.26%	13.39[3.37,53.23]
McCracken 2003	20/51	11/51		23.04%	1.82[0.97,3.4]
Pliszka 2000	3/20	0/18		1.1%	6.33[0.35,114.81]
Ramtvedt 2013	24/34	17/34		35.61%	1.41[0.95,2.11]
Spencer 2006a	83/233	1/63		3.3%	22.44[3.19,158.05]
Wigal 2009a	7/129	1/129		2.09%	7[0.87,56.09]
Total (95% CI)	**1552**	**915**		**100%**	**5.57[4.03,7.68]**
Total events: 417 (Amphetamine), 42 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=64.8, df=10(P<0.0001); I^2=84.57%					
Test for overall effect: Z=10.45(P<0.0001)					



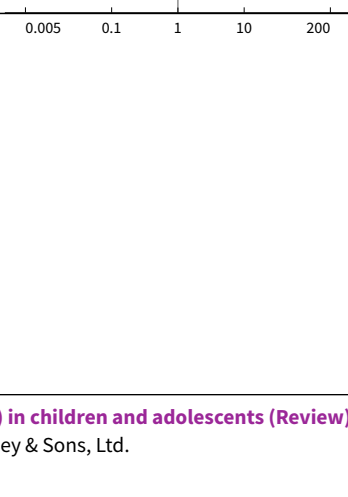
Analysis 5.20. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 20 Proportion of participants experiencing insomnia/trouble sleeping.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Biederman 2002	62/374	4/210		11.71%	8.7[3.21,23.58]
Biederman 2007a	1/52	1/52		2.28%	1[0.06,15.57]
Biederman 2007b	41/218	2/72		6.87%	6.77[1.68,27.29]
Childress 2015	3/97	0/97		1.14%	7[0.37,133.73]
Coghill 2013	25/111	2/110		4.59%	12.39[3.01,51.04]
Findling 2011	26/233	3/79		10.24%	2.94[0.91,9.44]
McCracken 2003	16/51	10/51		22.85%	1.6[0.8,3.18]
Ramtvedt 2013	30/34	14/34		31.99%	2.14[1.41,3.26]
Spencer 2006a	28/233	2/63		7.19%	3.79[0.93,15.46]
Wigal 2009a	5/129	0/129		1.14%	11[0.61,196.91]
Total (95% CI)	**1532**	**897**		**100%**	**3.91[2.82,5.41]**
Total events: 237 (Amphetamine), 38 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=21.75, df=9(P=0.01); I^2=58.63%					
Test for overall effect: Z=8.18(P<0.0001)					



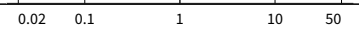
Analysis 5.21. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 21 Proportion of participants experiencing abdominal pain.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Biederman 2002	54/374	20/210		34.95%	1.52[0.93,2.46]
Biederman 2007a	2/52	1/52		1.36%	2[0.19,21.38]
Biederman 2007b	26/218	4/72		8.21%	2.15[0.78,5.94]
Childress 2015	3/97	0/97		0.68%	7[0.37,133.73]
Coghill 2013	16/111	14/110		19.19%	1.13[0.58,2.21]
McCracken 2003	18/51	12/51		16.37%	1.5[0.81,2.78]
Pliszka 2000	5/20	0/18		0.72%	9.95[0.59,168.27]
Ramtvedt 2013	6/34	9/34		12.28%	0.67[0.27,1.67]
Spencer 2006a	25/233	1/63		2.15%	6.76[0.93,48.92]
Wigal 2009a	2/129	3/129		4.09%	0.67[0.11,3.92]
Total (95% CI)	**1319**	**836**		**100%**	**1.57[1.18,2.08]**
Total events: 157 (Amphetamine), 64 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.32, df=9(P=0.32); I^2=12.83%					
Test for overall effect: Z=3.12(P=0)					



Analysis 5.22. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 22 Proportion of participants experiencing headaches.

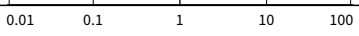
Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Biederman 2002	67/374	45/210		42.23%	0.84[0.6,1.17]
Biederman 2007b	26/218	7/72		7.71%	1.23[0.56,2.71]
Coghill 2013	16/111	22/110		16.19%	0.72[0.4,1.3]
Findling 2011	34/233	10/79		10.94%	1.15[0.6,2.22]
Giblin 2011	5/16	1/8		0.98%	2.5[0.35,17.97]
Pliszka 2000	2/20	1/18		0.77%	1.8[0.18,18.21]
Ramtvedt 2013	8/34	8/34		5.86%	1[0.42,2.36]
Spencer 2006a	38/233	12/63		13.84%	0.86[0.48,1.54]
Wigal 2009a	6/129	2/129		1.47%	3[0.62,14.59]
Total (95% CI)	**1368**	**723**		**100%**	**0.95[0.76,1.18]**
Total events: 202 (Amphetamine), 108 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.52, df=8(P=0.7); I^2=0%					
Test for overall effect: Z=0.46(P=0.65)					



Favours amphetamine — Favours placebo

Analysis 5.23. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 23 Proportion of participants experiencing anxiety/nervousness.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Biederman 2002	21/374	4/210		9%	2.95[1.03,8.47]
McCracken 2003	39/51	39/51		68.54%	1[0.81,1.24]
Pliszka 2000	1/20	1/18		1.85%	0.9[0.06,13.36]
Ramtvedt 2013	8/34	7/34		12.3%	1.14[0.47,2.8]
Spencer 2006a	14/233	3/63		8.3%	1.26[0.37,4.25]
Total (95% CI)	**712**	**376**		**100%**	**1.21[0.94,1.56]**
Total events: 83 (Amphetamine), 54 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.87, df=4(P=0.21); I^2=31.88%					
Test for overall effect: Z=1.5(P=0.13)					

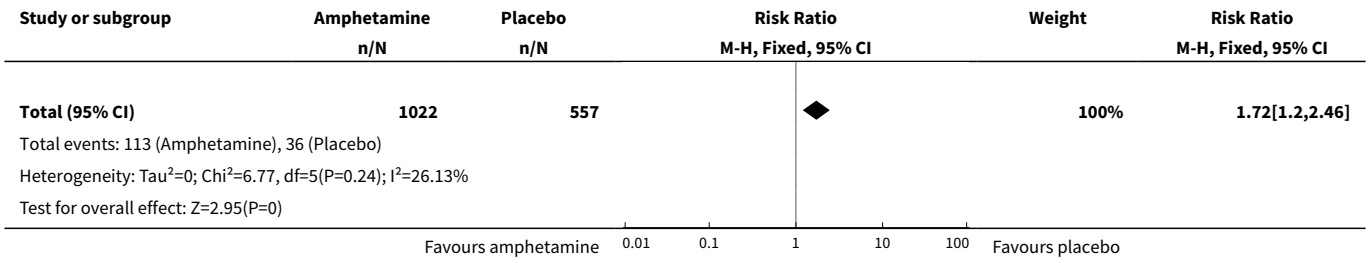


Favours amphetamine — Favours placebo

Analysis 5.24. Comparison 5 Sensitivity analysis 1: Fixed-effect model, Outcome 24 Proportion of participants experiencing nausea/vomiting.

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Biederman 2002	46/374	14/210		39.48%	1.84[1.04,3.27]
Biederman 2007a	1/52	2/52		4.4%	0.5[0.05,5.35]
Biederman 2007b	32/218	5/72		16.55%	2.11[0.86,5.22]
Coghill 2013	12/111	3/110		6.63%	3.96[1.15,13.66]
Findling 2011	12/233	6/79		19.73%	0.68[0.26,1.75]
Ramtvedt 2013	10/34	6/34		13.21%	1.67[0.68,4.07]

Favours amphetamine — Favours placebo



ADDITIONAL TABLES

Table 1. Protocol decisions not used in this review

Types of outcome measures	**Primary outcomes** Multiple perspectives (i.e. teacher, parent, clinician) are considered the gold standard when assessing the core symptoms of ADHD. As such, we will not favor one perspective over another. In the event that reports do not agree with one another, for example, teacher reports disagree with parent reports on the improvement of core symptoms, this may be quite telling about how a child's environment impacts their ADHD given the varying demands between a school environment and home environment. This will be interpreted accordingly in the discussion. **Secondary outcomes** We will assess 'parental stress' as a secondary outcome.
Measures of treatment effect	**Dichotomous outcome data** When a single study has utilized more than one measure to assess the same construct (e.g. ADHD core symptoms as assessed by teacher-rated ADHD-RS-IV and teacher ratings of the Conners' ADHD Rating Scale), treatment effects will be averaged across outcome measures in order to arrive at a single treatment effect for use in the meta-analysis. **Continuous outcome data** For continuous outcomes, where the same rating scale has been used for all studies, we will calculate mean differences.
Unit of analysis issues	**Cross-over trials** For meta-analyses that use that use a mean difference, we will compute standard deviations for the cross-over trials taking into account correlation. If correlation coefficients are not available, we will impute them from other studies or use 0.5 as a conservative estimate (Follman 1992). For cross-over trials where carry-over is thought to be a problem, where no washout period is present, or when only data from the first period are available, we will analyze data from the first period only. **Studies with multiple time points** In studies where results are presented for several periods of follow-up, we will analyze each outcome at each point in a separate meta-analysis with other comparable studies taking measures at a similar time frame post-randomization. Time frames will reflect short-term (up to six months), medium-term (between 6 months and 12 months), and long-term (over 12 months) outcomes.
Assessment of reporting biases	For each primary meta-analysis in which we have identified a sufficient number of studies (n ≥ 10) for inclusion, we will draw funnel plots in order to assess the possibility of publication bias.

Table 1. Protocol decisions not used in this review *(Continued)*

Subgroup analysis and investigation of heterogeneity	We will conduct the following subgroup analyses. 1. Presence of comorbidities (i.e. oppositional defiant disorder, conduct disorder, or both) versus no comorbid conditions. 2. ADHD subtype: inattentive type versus hyperactive-impulsive type versus combined type
Sensitivity analysis	We will conduct the following sensitivity analyses. 1. Based on the risk of bias assessment of the studies: we will restrict each outcome meta-analysis to those studies with a low risk of bias. A study is defined as having a low risk of bias if all domains of the risk of bias tool score a low risk of bias. 2. Based on publication status: unpublished versus published studies. 3. Missing data: we will conduct a sensitivity analysis of the imputed standard deviation versus a lower imputed standard deviation.

ADHD: attention deficit hyperactivity disorder.
ADHD-RS-IV: Attention Deficit Hyperactivity Rating Scale, Fourth Version.

Table 2. ADHD core symptom outcome measures by study

Outcome	Outcome measure (respondent)	Studies	Measure used in meta-analysis
Inattention	ADHD Rating Scale, Fourth Version (parent ratings)	Biederman 2007b	No (data presented in an unusable format)
	ADHD Rating Scale, Fourth Version (clinician ratings)	Findling 2011	Yes
		Spencer 2006a	Yes
		Wigal 2009a	Yes
	ADHD Rating Scale, Fourth Version (investigator/research personnel ratings)	Coghill 2013	Yes
	Conners' Rating Scale (parent ratings)	Borcherding 1990	Yes
		Gillberg 1997	No (only study that included long-term data)
	Conners' Rating Scale (teacher ratings)	Gillberg 1997	No (only study that included long-term data)
	IOWA Conners' Rating Scale	Pliszka 2000	Yes
	SKAMP scale (teacher ratings)	Swanson 1998a	No (data not available)
	SKAMP scale (investigator/research personnel ratings)	Biederman 2007a	Yes
		McCracken 2003	Yes
Hyperactivity/impulsivity	ADHD Rating Scale, Fourth Version (parent ratings)	Biederman 2007b	No (data presented in an unusable format)
	ADHD Rating Scale, Fourth Version (clinician ratings)	Findling 2011	Yes

Table 2. ADHD core symptom outcome measures by study *(Continued)*

		Spencer 2006a	Yes
		Wigal 2009a	Yes
	ADHD Rating Scale, Fourth Version (investigator/research personnel ratings)	Coghill 2013	Yes
	Conners' Rating Scale (parent ratings)	Gillberg 1997	No (only study that included long-term data)
		James 2001	Yes
	Conners' Rating Scale (teacher ratings)	Gillberg 1997	No (only study that included long-term data)
		James 2001	Yes
Total core symptom score	ADHD Rating Scale, Fourth Version (parent ratings)	Barkley 2000	Yes
		Biederman 2007b	Yes
	ADHD Rating Scale, Fourth Version (teacher ratings)	Barkley 2000	Yes
	ADHD Rating Scale, Fourth Version (clinician ratings)	Findling 2011	Yes
		Spencer 2006a	Yes
		Wigal 2009a	Yes
	ADHD Rating Scale, Fourth Version (investigator/research personnel ratings)	Coghill 2013	Yes
		Giblin 2011	No (no data available)
	Conners' Rating Scale (parent ratings)	Biederman 2007b	No (data presented in an unusable format)
		Coghill 2013	Yes
		Giblin 2011	No (data not available)
		Gillberg 1997	No (only study that included long-term data)
		Nemzer 1986	Yes
		Sharp 1999	No (data not available)
		Short 2004	No (data presented in an unusable format)
	Conners' Rating Scale (teacher ratings)	Borcherding 1990	No (no data available)
		Donnelly 1989	Yes

Table 2. ADHD core symptom outcome measures by study *(Continued)*

	Gillberg 1997	No (only study that included long-term data)
	Nemzer 1986	Yes
	Sharp 1999	No (data not available)
	Short 2004	No (data presented in an unusable format)
Conners' Global Index (parent ratings)	Biederman 2002	Yes
	Pliszka 2000	Yes
Conners' Global Index (teacher ratings)	Biederman 2002	Yes
Conners' Abbreviated Symptom Questionnaire (parent ratings)	Manos 1999	Yes
Conners' Abbreviated Symptom Questionnaire (teacher ratings)	Manos 1999	Yes
ADHD Questionnaire (developed within study) (parent ratings)	Ramtvedt 2013	No (data presented in an unusable format)
ADHD Questionnaire (developed within study) (teacher ratings)	Ramtvedt 2013	No (data presented in an unusable format)
SKAMP scale (investigator/research personnel ratings)	Childress 2015	Yes

ADHD: attention deficit hyperactivity disorder.
IOWA: inattention/overactivity with aggression.
SKAMP: Swanson, Kotkin, Agler, M-Flynn and Pelham scale.

APPENDICES

Appendix 1. CENTRAL search strategy

1. exp Amphetamines/
2. (amphetamine$ or dexamphetamine$ or methamphetamine$ or dextroamphetamine$ or lisdexamphetamine$ or vyvanase$ or Dexedrin3 or desoxyn$ or adderall$).mp.
3. Central Nervous System Stimulants/
4. 1 or 2 or 3
5. exp Attention Deficit Disorder with Hyperactivity/
6. Child Behavior Disorders/
7. adhd.tw.
8. addh.tw.
9. adhs.tw.
10. "ad/hd".tw.
11. hyperactiv$.tw.
12. hyper-activ$.tw.
13. overactiv$.tw.
14. over-activ$.tw.
15. hyperkinesis/
16. hyperkin$.tw.

17. hyper-kin$.tw.
18. hkd.tw.
19. (minimal adj3 brain$ adj3 (damag$ or disorder$ or dysfunc$)).tw.
20. (attention$ adj3 (deficit$ or disorder$ or dysfunc$)).tw.
21. (behav$ adj3 (dysfunc$ or disorder$)).tw.
22. (impulsiv$ or inattentiv$ or inattention$).tw.
23. disruptiv$.tw.
24. or/5-23
25. exp child/
26. adolescent/
27. (adoles$ or teen$ or youth$ or young people or young person$).tw.
28. (child$ or toddler$ or preschool$ or pre-school or schoolchild$ or schoolgirl$ or schoolboy$ or girl$ or boy$).tw.
29. Pediatrics/
30. p?ediatric$.tw.
31. or/25-30
32. 4 and 24 and 31

Appendix 2. Ovid MEDLINE search strategy

1. exp Amphetamines
2. (amphetamine$ or dexamphetamine$ or methamphetamine$ or dextroamphetamine$ or lisdexamphetamine$ or vyvanase$ or Dexedrin3 or desoxyn$ or adderall$).mp.
3. Central Nervous System Stimulants/
4. 1 or 2 or 3
5. exp Attention Deficit Disorder with Hyperactivity/
6. Child Behavior Disorders/
7. adhd.tw.
8. addh.tw.
9. adhs.tw
10. "ad/hd".tw.
11. hyperactiv$.tw.
12. hyper-activ$.tw.
13. overactiv$.tw.
14. over-activ$.tw.
15. hyperkinesis/
16. hyperkin$.tw.
17. hyper-kin$.tw.
18. hkd.tw.
19. (minimal adj3 brain$ adj3 (damag$ or disorder$ or dysfunc$)).tw.
20. (attention$ adj3 (deficit$ or disorder$ or dysfunc$)).tw.
21. (behav$ adj3 (dysfunc$ or disorder$)).tw.
22. (impulsiv$ or inattentiv$ or inattention$).tw.
23. disruptiv$.tw.
24. or/5-23
25. exp child/
26. adolescent/
27. (adoles$ or teen$ or youth$ or young people or young person$).tw.
28. (child$ or toddler$ or preschool$ or pre-school or schoolchild$ or schoolgirl$ or schoolboy$ or girl$ or boy$).tw.
29. Pediatrics/
30. p?ediatric$.tw.
31. or/25-30
32. 4 and 24 and 31
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomi#ed.ab.
36. placebo$.ab.
37. drug therapy.fs.
38. randomly.ab.
39. trial.ab.
40. groups.ab.
41. or/33-40
42. exp animals/ not humans.sh.

43. 41 not 42
44. 32 and 43

Lines 33 to 43 are the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE (Ovid version) (Lefebvre 2011).

Appendix 3. Embase search strategy

1. exp amphetamine/
2. (amphetamine$ or dexamphetamine$ or methamphetamine$ or dextroamphetamine$ or lisdexamphetamine$ or vyvanase$ or Dexedrin3 or desoxyn$ or adderall$).mp.
3. central stimulant agent/
4. 1 or 2 or 3
5. exp attention deficit disorder/
6. behavior disorder/
7. adhd.tw.
8. addh.tw.
9. adhs.tw.
10. "ad/hd".tw.
11. hyper-activ$.tw.
12. hyperactiv$.tw.
13. overactiv$.tw.
14. over-activ$.tw.
15. hyperkinesia/
16. hyperkin$.tw.
17. hyper-kin$.tw.
18. hkd.tw.
19. (minimal adj3 brain$ adj3 (damag$ or disorder$ or dysfunc$)).tw.
20. (attention$ adj3 (deficit$ or disorder$ or dysfunc$)).tw.
21. (behav$ adj3 (dysfunc$ or disorder$)).tw.
22. (impulsiv$ or inattentiv$ or inattention$).tw.
23. disruptiv$.tw.
24. or/5-23
25. child/
26. adolescent/
27. (adoles$ or teen$ or youth$ or young people or young person$).tw.
28. (child$ or toddler$ or preschool$ or pre-school or schoolchild$ or schoolgirl$ or schoolboy$ or girl$ or boy$).tw.
29. pediatrics/
30. p?ediatric$.tw.
31. or/25-30
32. 4 and 24 and 31
33. randomized controlled trial/
34. controlled clinical trial/
35. randomi#ed.ab.
36. placebo$.ab.
37. drug therapy/
38. randomly.ab.
39. trial.ab.
40. single blind procedure/
41. double blind procedure/
42. or/33-41
43. exp animal/ not human.sh.
44. 42 not 43

Appendix 4. PsycINFO search strategy

1. exp amphetamine/
2. (amphetamine$ or dexamphetamine$ or methamphetamine$ or dextroamphetamine$ or lisdexamphetamine$ or vyvanase$ or Dexedrin3 or desoxyn$ or adderall$).mp.
3. exp attention deficit disorder/
4. behavior disorder/
5. adhd.tw.
6. addh.tw.
7. adhs.tw.

8. "ad/hd".tw.
9. hyper-activ$.tw.
10. hyperactiv$.tw.
11. overactiv$.tw.
12. over-activ$.tw.
13. hyperkin$.tw.
14. hyper-kin$.tw.
15. hkd.tw.
16. (minimal adj3 brain$ adj3 (damag$ or disorder$ or dysfunc$)).tw.
17. (attention$ adj3 (deficit$ or disorder$ or dysfunc$)).tw.
18. (behav$ adj3 (dysfunc$ or disorder$)).tw.
19. (impulsiv$ or inattentiv$ or inattention$).tw.
20. disruptiv$.tw.
21. (adoles$ or teen$ or youth$ or young people or young person$).tw.
22. (child$ or toddler$ or preschool$ or pre-school or schoolchild$ or schoolgirl$ or schoolboy$ or girl$ or boy$).tw.
23. pediatrics/
24. p?ediatric$.tw.
25. randomi#ed.ab.
26. placebo$.ab.
27. drug therapy/
28. randomly.ab.
29. trial.ab.
30. (doubl$ adj blind$).mp.
31. (singl$ adj blind$).mp.
32. 1 or 2
33. or/3-20
34. or/21-24
35. 32 and 33 and 34
36. or/25-31
37. exp animals/ not humans.sh.
38. 36 not 37
39. 35 and 38

Appendix 5. Proquest Dissertations and Theses search strategy

Advanced search
(attention deficit disorder OR attention deficit hyperactivity disorder OR hyperactivity) AND all(amphetamine OR adderall) AND all(children OR youth OR adolescent)

Appendix 6. Networked Digital Library of Theses and Dissertations search strategy

Attention Deficit Hyperactivity Disorder AND amphetamine AND (child OR youth OR adolescent)

Appendix 7. ClinicalTrials.gov search strategy

Advanced search
Conditions: Attention Deficit Hyperactivity Disorder OR ADHD OR Attention Deficit Disorder OR ADD
Interventions: amphetamine OR dexamphetamine OR methamphetamine OR dextroamphetamine OR lisdexamphetamine OR vyvanase OR dexedrine OR adderall
Study results: All studies
Age group: Child

Appendix 8. Risk of bias domains

Domain	Description	Judgement
Random sequence generation	The method used to generate the allocation sequence is described in sufficient detail so as to assess whether it should have produced comparable groups.	What is the risk of selection bias due to inadequate generation of a randomized sequence?

(Continued)

Allocation concealment	The method used to conceal the allocation sequence is described in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	What is the risk of selection bias due to inadequate concealment of allocations prior to assignment?
Blinding of participants and personnel	The measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received and any information relating to whether the intended blinding was effective.	What is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study?
Blinding of outcome assessment	The measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received and any information relating to whether the intended blinding was effective.	What is the risk of detection bias due to knowledge of the allocated interventions by outcome assessors?
Incomplete outcome data	Assessment of the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis.	What is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?
Selective outcome reporting	Attempts made to assess the possibility of selective outcome reporting by investigators.	What is the risk of reporting bias due to selective outcome reporting?
Other sources of bias	Assessment of other sources of bias in other domains not covered by the tool, including validity of outcome measures utilized.	What is the risk of bias due to problems not covered elsewhere in the table?

CONTRIBUTIONS OF AUTHORS

SP and SV conceived this review and share overall responsibility for this review.
SP led the design and ongoing co-ordination of this review with oversight from LS, LH, LU, BV, CJN, and SV.
SP developed the additional search strategies and carried out the searches for this review.
SP and BV developed the analysis plan.
SP retrieved the papers for this review.
SP and LS independently assessed the retrieved papers against the eligibility criteria for this review.
SP and LS independently appraised the risk of bias in the papers for this review.
SP and LS independently extracted the data from the papers for this review.
SP wrote to authors of included studies for additional information for this review.
SP managed the data for this review, including entering data into RevMan and analysing the data under the guidance of BV.
SP interpreted the data for this review with input from all authors.
SP wrote the review.
All authors critically read and edited the review.

DECLARATIONS OF INTEREST

Salima Punja - none known.
Larissa Shamseer - none known.
Lisa Hartling - none known.
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Ben Vandermeer - none known.
Catherine Jane Nikles - published a paper in the area of amphetamines for ADHD (Nikles 2006). The study was excluded due to the nature of the design. Dr Nikles was not involved in assessing the eligibility of this study, which was performed by two independent authors.
Sunita Vohra - is the recipient of an Alberta Innovates - Health Scholar salary award. Dr Vohra's institution receives funds from Alberta Innovates - Health Solutions and protects 75% of her time for research. Other funders include Health Canada, Canadian Institutes of Health Research, Women & Children's Health Research Institute and National Health, Medical Research Council (Australia) and SERIN-ETD Acupuncture Research Fund. SERIN is a commercial entity who provided acupuncture needles for a trial. The population is not pediatric ADHD. None of these companies pose a conflict of interest as regards this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Please refer to Table 1 for a summary of protocol decisions not used in this review.

Methods. Data collection and analysis. Assessment of risk of bias in included studies.

In our protocol, we had included funding source in the risk of bias assessment. However, given the ongoing debate of the influence of funding source on treatment effect estimates, we removed this from the assessment. Instead, we explored the influence of industry on treatment effects by performing a subgroup analysis on funding source (industry versus publicly funded versus not reported).

Methods. Data collection and analysis. Unit of analysis issues.

Studies with multiple comparisons

For dichotomous outcomes of cross-over studies, we randomly dropped one arm and used the other in the meta-analysis.

Methods. Data collection and analysis. Assessment of heterogeneity

We added that we assessed statistical heterogeneity by examining "Chi^2 (P value less than 0.10 as evidence of heterogeneity)", and "Tau^2 estimates for each random-effects meta-analysis".

Methods. Data collection and analysis. 'Summary of findings'.

We added a description of what was included in the 'Summary of findings' table beneath the subsection on 'Data synthesis'.

Methods. Data collection and analysis. Subgroup analysis and investigation of heterogeneity.

We had planned to perform a subgroup analysis based on type of questionnaire used (teacher, parent, clinician, investigator). However, given the importance of each of these informants individually in the overall assessment of ADHD, these were separated in our primary analysis.

Methods. Data collection and analysis. Sensitivity analysis.

We did not conduct a sensitivity analysis according to study design (parallel-group versus cross-over trial) as planned, since all included cross-over studies were treated as if they were parallel-group studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Amphetamines [*therapeutic use]; Attention Deficit Disorder with Hyperactivity [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans