ClinicalEvidence

# ADHD in children and adolescents

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## ABSTRACT

INTRODUCTION: Prevalence estimates of attention deficit hyperactivity disorder (ADHD) vary according to the diagnostic criteria used and the population sampled. DSM-IV prevalence estimates among school children in the US are 3–5%, but other estimates vary from 1.7% to 16.0%. No objective test exists to confirm the diagnosis of ADHD, which remains a clinical diagnosis. Other conditions frequently co-exist with ADHD. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of pharmacological treatments for ADHD in children and adolescents? What are the effects of psychological treatments for ADHD in children and adolescents? What are the effects of combination treatments for ADHD in children and adolescents? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 34 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: atomoxetine, bupropion, clonidine, dexamfetamine sulphate, homeopathy, methylphenidate, modafinil, omega 3-polyunsaturated fatty acids, and psychological/behavioural treatment (either alone or in combination with a drug treatment).

## QUESTIONS



## INTERVENTIONS

### PHARMACOLOGICAL TREATMENTS

**Likely to be beneficial**



**Unknown effectiveness**



### PSYCHOLOGICAL TREATMENTS

**Unknown effectiveness**



### COMBINATION TREATMENTS

**Likely to be beneficial**



**Unknown effectiveness**



**To be covered in future updates**

Melatonin

Risperidone

## Key points

- Core symptoms of ADHD are inattention, hyperactivity, and impulsiveness, although other conditions frequently coexist with ADHD, including developmental disorders (especially motor, language, social communication, and specific learning disabilities) and psychiatric disorders (especially oppositional defiant and conduct disorder, anxiety, and depressive disorders).

  Symptoms must be present for at least 6 months, are generally observed in children before the age of 7 years, and cause clinically important impairment in social, academic, or occupational functioning which must be evident in more than one setting.

  Formal diagnostic criteria are most applicable to boys aged 6–12 years, and most research data relate to this group. Preschool children, adolescents, and females may present less-typical features, but similar levels of impairment.

  Prevalence estimates among school children range from 3% to 5%.

- Methylphenidate improves core symptoms and school performance in children with ADHD when used alone.
- Dexamfetamine and atomoxetine may also reduce symptoms of ADHD.

- We don't know how effective any treatment for ADHD is in the long term; people with ADHD may require treatment for many years.
- CAUTION: Atomoxetine may cause rare but serious liver injury.
- Clonidine and modafinil may improve symptoms of ADHD compared with placebo, but are associated with an increased risk of adverse effects compared with methylphenidate, dexamfetamine, and atomoxetine.
- We don't know whether homeopathy, bupropion, or polyunsaturated fatty acids are beneficial in the treatment of symptoms of ADHD.
- We don't know how effective psychological/behavioural treatments alone are compared with each other or with pharmacological treatments, as we found few high-quality studies.

  The combination of methylphenidate plus psychological treatment may enhance effectiveness of methylphenidate alone or behavioural treatment alone, but we don't know whether dexamfetamine plus psychological treatment is effective in treatment of ADHD compared with either intervention alone. Long-term outcome for both drug treatment alone and combination treatments is uncertain.

  We don't know whether parent training in conjunction with teacher involvement is more effective than parent training alone.

## DEFINITION

Attention deficit hyperactivity disorder (ADHD) is "a persistent pattern of inattention and hyperactivity and impulsivity that is more frequent and severe than is typically observed in people at a comparable level of development" (APA, DSM-IV). [1] Inattention, hyperactivity, and impulsivity are commonly known as the core symptoms of ADHD. Formal diagnostic criteria state that symptoms must be present for at least 6 months, observed before the age of 7 years, and "clinically important impairment in social, academic, or occupational functioning" must be evident in more than one setting. The symptoms must not be better explained by another disorder, such as an anxiety disorder, mood disorder, psychosis, or autistic disorder. [1] In clinical practice, symptoms are generally, but not always, observed before 7 years of age. The ICD-10 [2] uses the term "hyperkinetic disorder" for a more restricted diagnosis. It differs from the DSM-IV classification [3] in that: all three problems of attention, hyperactivity, and impulsiveness must be present; more stringent criteria for "pervasiveness" across situations must be met; and the presence of another disorder is an exclusion criterion. However, in clinical practice, the co-existence of anxiety and mood and autistic spectrum disorders is generally recognised. Formal diagnostic criteria are most applicable to boys aged 6–12 years, and most research data relate to this group. Preschool children, adolescents, and females may present with less typical features but similar levels of impairment. The evidence presented in this review largely relates to children and adolescents aged 3–18 years. There is no distinct boundary between the upper ranges of childhood, adolescence, and adulthood in terms of symptomatology and response to treatment. The research relating to adults is growing [4] but there is still a paucity of evidence of efficacy and safety of treatments in preschool children.

## INCIDENCE/ PREVALENCE

Prevalence estimates of ADHD vary according to the diagnostic criteria used and the population sampled. DSM-IV prevalence estimates among school children in the US are 3–5%, [1] but other estimates vary from 1.7% to 16.0%. [5] [6] In common with all mental health disorders, no objective test exists to confirm the diagnosis of ADHD, which remains a diagnosis based on clinical assessment of the nature of the behavioural disorder and functional impairment of cognitive processes. ADHD generally coexists with other developmental and mental health disorders. Oppositional defiant disorder is present in 35% (95% CI 27% to 44%) of children with ADHD, conduct disorder in 26% (95% CI 13% to 41%), anxiety disorder in 26% (95% CI 18% to 35%), and depressive disorder in 18% (95% CI 11% to 27%). [7] Of the developmental disorders, developmental coordination disorder has been found in just under 50% of children with ADHD, specific learning disabilities in around 40%, tics in 33%, and Asperger syndrome in 7%. [8]

## AETIOLOGY/ RISK FACTORS

The underlying causes of ADHD are not known. [7] There is some evidence that there is a genetic component: twin studies suggest an average heritability of 76%. [9] However, a high heritability does not exclude the important role of environment acting through gene–environment interactions. [10] [11] [12] [13] [14] The uneven distribution of ADHD in the population, which mirrors that of other mental health and behavioural disorders, also suggests that psychosocial factors are involved. Boys are at a greater risk of developing ADHD compared with girls, with a ratio of about 4:1. [3] Although the link between ADHD and dietary and nutritional factors (such as artificial food colours) is yet to be satisfactorily researched, studies suggest a correlation between artificial food colours and symptoms of hyperactivity in some young children. [15] In children with mild or moderate symptoms, it may be that the possible effects of dietary interventions could be initially explored.

## PROGNOSIS

More than 70% of hyperactive children may continue to meet criteria for ADHD in adolescence, and up to 65% of adolescents may continue to meet criteria for ADHD in adulthood. [6] Changes in diagnostic criteria cause difficulty with interpretation of the few outcome studies that exist. ADHD

is also a risk factor for psychiatric diagnosis, persistent hyperactivity, violence, and antisocial behaviours. Follow-up studies of children with ADHD into adulthood indicate an increased risk of antisocial, depressive, and anxiety disorders, [16] and of antisocial personality disorder. [17]

**AIMS OF INTERVENTION** To reduce inattention, hyperactivity, and impulsivity; and to improve psychosocial and educational functioning in affected children and adolescents, with minimal adverse effects of treatment.

**OUTCOMES** Measures of children's behaviour, such as Conners Teacher's Rating Scales; ADHD Rating Scale-IV SNAP, CLAM, SKAMP, school performance, such as School Situations Questionnaire; self-rated symptoms; adverse effects.

**METHODS** *Clinical Evidence* search and appraisal June 2007. The following databases were used to identify studies for this review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 children and adolescents of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded, unless blinding was impossible. We have searched for RCTs comparing each listed intervention versus placebo, no treatment, or each other, and have included all studies of sufficient quality. We also searched for RCTs of a combination of drug treatment plus psychological treatment versus usual care, drug treatment alone, or psychological treatment alone. Where we have included a systematic review, we have only reported comparisons for which the identified review found RCTs. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 29 ).

## QUESTION What are the effects of pharmacological treatments for ADHD in children and adolescents?

## OPTION ATOMOXETINE

**Symptom severity**
*Compared with placebo* Atomoxetine is more effective at improving ADHD symptoms (assessed using Attention Deficit Hyperactivity Disorder Rating Scale [ADHD-RS]) in children and adolescents aged 6–18 years (moderate-quality evidence).

*Compared with methylphenidate* Atomoxetine and low doses of methylphenidate seem equally effective at 8 weeks at improving response rates in children and adolescents aged 6–16 years (moderate-quality evidence).

**School performance**
*Compared with placebo* Atomoxetine may be no more effective at 7 weeks at improving academic productivity in children and adolescents aged 8–12 years as assessed using the Academic Performance Rating Scale (low-quality evidence).

**Adverse effects**
Atomoxetine has been associated with decreased appetite, nausea, vomiting, somnolence, suicidal ideation, depression, height and weight changes, liver disease, and seizures.

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:** **Atomoxetine versus placebo:**
We found one systematic review (search date 2004, 7 RCTs, 2019 people aged 6–18 years) [18] and one subsequent RCT [19] examining the effects of atomoxetine on symptoms of ADHD. The review searched for studies on atomoxetine from 1981 onwards, and built on two other systematic reviews of the effects of atomoxetine in ADHD. [20] [21] Quality and methodological issues precluded meta-analysis. The review assessed the effects of atomoxetine based on categorisation of low/medium (less than 1.5 mg/kg/day) and high dose (at least 1.5 mg/kg/day) of atomoxetine. The review concluded that atomoxetine improved symptoms of ADHD at doses above 0.5 mg/kg/day

compared with placebo. Five RCTs (reported in 4 papers) met *Clinical Evidence* inclusion criteria. The RCTs assessed mean differences in Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS). The results from the individual RCTs that met *Clinical Evidence* criteria [22] [23] [24] [25] are presented in table 1, p 23 . All RCTs found significant improvements in ADHD symptoms with atomoxetine at doses greater than 0.5 mg/kg/day (see table 1, p 23 ). One RCT [22] identified by the review found no significant difference between atomoxetine 0.5 mg/kg/day and placebo (see table 1, p 23 ). One RCT (416 children aged 6–15 years treated with open-label atomoxetine for 12 weeks, then randomised to 9 months' double-blind atomoxetine or placebo) identified by the review assessed the effects of atomoxetine on preventing symptom relapse. It found that atomoxetine was significantly more effective than placebo in preventing symptom relapse, defined as a return to 90% of baseline symptom severity ADHD-RS score (proportion relapsing: 65/292 [22%] with atomoxetine *v* 47/124 [38%] with placebo; P = 0.002). [26] The subsequent RCT (153 children aged 8–12 years) assessed mean differences in symptoms using teacher rather than parent reporting. [19] Symptom response was assessed using ADHD-RS-IV-Teacher Version (investigator-administered and scored). Secondary outcomes were measured using the clinician-rated CGI severity scale and Conners Parent Rating Scale-Revised ADHD Index T score. The RCT found that atomoxetine significantly reduced symptoms of ADHD at 7 weeks compared with placebo (see table 1, p 23 ). However, the RCT found no significant difference in academic productivity at 7 weeks between atomoxetine and placebo, as assessed using the Academic Performance Rating Scale. An extension of this RCT assessed the effects of atomoxetine on associated functional impairments at school. [27] The primary measure of symptom response in this analysis was also the ADHD-RS-IV-Teacher Version. The RCT found no significant difference in quality of life between atomoxetine and placebo, although greater improvements in quality-of-life scores were observed in children receiving atomoxetine (measured using the Children's Health Questionnaire: mean change in score from baseline: 7.1 with atomoxetine *v* 3.7 with placebo; P = 0.073).

**Atomoxetine versus methylphenidate:**
We found one systematic review (search date 2005, 4 RCTs, 1481 people) comparing atomoxetine versus methylphenidate. [28] The review did not pool data. The review included open-label studies and unpublished data. None of the RCTs identified by the review met *Clinical Evidence* inclusion criteria, and they are not discussed further. We found one subsequent RCT (330 children aged 6–16 years). [29] The RCT compared atomoxetine once daily (dose 0.8–1.8 mg/kg) versus methylphenidate twice daily (0.2–0.6 mg/kg) over 8 weeks. The primary outcome measure was response rate, which was defined as a reduction of 40% or more from baseline to end point in the parent-reported ADHD-RS-IV score (investigator-administered and scored). The RCT found no significant difference between atomoxetine and methylphenidate in response rate at 8 weeks (intention-to-treat analysis: 123/162 [76%] with atomoxetine *v* 133/164 [81%] with methylphenidate; P = 0.282). RCTs of methylphenidate suggest that optimal dosing of methylphenidate is 1 mg/kg three times daily, [30] and caution should be taken when interpreting data from trials in which the dosing of one arm may be suboptimal.

**Harms:**

**Atomoxetine versus placebo:**
The systematic review did not pool data on harms because of heterogeneity among studies. [18] The review reported that atomoxetine significantly reduced appetite compared with placebo (4 out of 6 RCTs) but had no effect on incidence of headache, stomach ache, or insomnia. One RCT identified by the review found that infection and pruritus increased with higher doses (infection: 1/83 [1%] with placebo *v* 0/44 [0%] with atomoxetine 0.5 mg/kg/day *v* 5/84 [6%] with atomoxetine 1.2 mg/kg/day *v* 6/83 [7%] with atomoxetine 1.8 mg/kg/day; pruritus: 0/83 [0%] with placebo *v* 0/44 [0%] with atomoxetine 0.5 mg/kg/day *v* 1/84 [1%] with atomoxetine 1.2 mg/kg/day *v* 5/83 [6%] with atomoxetine 1.8 mg/kg/day; significance not assessed). [22] Analyses of two RCTs (reported in 1 publication) [23] identified by the review found no significant difference between treatments for cardiovascular adverse effects (palpitations, tachycardia, murmur, extrasystole, and bradycardia; P less than 0.2 for all outcomes). [31] The fourth RCT identified by the review found that atomoxetine significantly increased nausea, vomiting, asthenia, and dyspepsia compared with placebo (vomiting: 13/85 [15%] with atomoxetine *v* 1/85 [1%] with placebo; P = 0.001; nausea: 10/85 [12%] with atomoxetine *v* 2/85 [2%] with placebo; P = 0.04; asthenia: 9/85 [11%] with atomoxetine *v* 1/85 [1%] with placebo; P = 0.02; dyspepsia: 8/85 [9%] with atomoxetine *v* 0/85 [0%] with placebo; P = 0.007). [24] The fifth RCT identified by the review found significantly higher incidences of somnolence and fatigue with atomoxetine compared with placebo (somnolence: 19/131 [15%] with atomoxetine *v* 1/63 [2%] with placebo; fatigue: 13/131 [10%] with atomoxetine *v* 1/63 [2%] with placebo; P less than 0.05 for all comparisons. [25] The subsequent RCT found that a greater proportion of people withdrew from the trial because of adverse effects associated with atomoxetine compared with placebo (discontinued: 6/101 [6%] with atomoxetine *v* 0/52 [0%] with placebo; significance not assessed). [19] Adverse effects associated with atomoxetine included abdominal pain, emotional disturbance, feeling abnormal, irritability, and vomiting. The RCT assessing relapse prevention reported a significant difference between atomoxetine and placebo in the incidence of gastroenteritis and

pharyngitis (each occurred in at least 5% of people; further data not reported; reported as significant). [26]

**Atomoxetine versus methylphenidate:**
The RCT found significantly higher rates of anorexia and nausea with atomoxetine compared with methylphenidate (anorexia: 61/164 [37%] with atomoxetine *v* 42/166 [25%] with methylphenidate; P = 0.024: nausea: 33/164 [20%] with atomoxetine *v* 17/166 [10%] with methylphenidate; P = 0.014). [29] Increased incidence of decreased appetite was reported with atomoxetine compared with methylphenidate, but this difference did not reach significance (46/164 [28%] with atomoxetine *v* 32/166 [19%] with methylphenidate; P = 0.07). Atomoxetine was associated with fewer incidences of insomnia compared with methylphenidate, but the difference was not significant (5/164 [3%] with atomoxetine *v* 9/166 [5%] with methylphenidate; P = 0.414).

**Atomoxetine and suicide:**
Regulatory authorities in both the UK (Medicines and Healthcare products Regulatory Agency [MHRA]) and USA (FDA) have recommended that people on Strattera (atomoxetine) should be monitored for signs of depression, suicidal thoughts, or suicidal behaviour, and referred for appropriate treatment if necessary; also, that patients and parents should be informed about this risk and advised to watch for any clinical worsening, irritability or agitation, suicidal thoughts or behaviour, or other unusual changes in behaviour. In addition, the prescribing information for atomoxetine was revised to include a boxed warning and additional warning statements to alert healthcare providers of an increased risk of suicidal thinking in children and adolescents being treated with this medication, and patient-information leaflets were to be revised to advise people of the risks associated with atomoxetine, and of precautions that can be taken when it is dispensed (see review on depression in children and adolescents).

**Atomoxetine and growth:**
A review examining the effect of atomoxetine on growth suggests that treatment with atomoxetine for two years has a minimal effect on height and weight. [32] Data were pooled from 13 multicentre trials conducted at 90 sites. The review assessed data for patients who had completed two years' treatment with atomoxetine and who had weight or height measurements at this time period. After 2 years, from a population of 419 children and adolescents (6–16 years old at the start of the treatment period, maximum dose of atomoxetine of 1.8 mg/kg/day), weight measurements were recorded for 412 people and height measurements for 382 people. The review found an absolute mean weight gain of 10.8 kg after 2 years' treatment with atomoxetine. This corresponds to a mean decrease, relative to baseline normative weights (–2.7 percentiles, P = 0.002). The decrease from predicted weight, assuming maintenance of the baseline weight percentile, is 0.87 kg at the end point. Regarding height, after 2 years' treatment, the review found a marked absolute mean height gain of 13.3 cm at the end point. This value corresponded to a slight decrease, relative to the baseline mean normative height value (–2.2 percentiles, P = 0.02). The decrease from the height predicted by assuming maintenance of the baseline height percentile is 0.44 cm at the 2-year end point. For both weight and height, the quartile of people who were smallest at baseline had an increase in end-point percentile, whereas people in the highest quartile had a decrease. The data presented here suggest that, at the group level, there is only a minimal effect on height after 2 years' treatment with atomoxetine. For those in the lowest quartile, and therefore those most at risk, atomoxetine does not seem to affect weight or height. However, individual patients could have more- or less-pronounced effects. For patients who seem to be growing more slowly than expected, clinicians should consider whether treatment with atomoxetine is a factor.

**Drug safety alert:**
A drug safety alert has been issued on the risk of psychotic or manic symptoms associated with atomoxetine (http://www.mhra.gov.uk).

**Comment:**

**Clinical guide:**
Atomoxetine is metabolised by the CYP 2D6 system of the liver. People with poor metabolism by this pathway may eliminate this drug more slowly and may be at greater risk of adverse effects. Atomoxetine was introduced under much stricter surveillance than other CNS stimulants have received, and as a result some uncommon, but potentially serious, adverse effects (e.g. liver disease and seizures) have been notified to regulatory authorities. As a result, it is uncertain whether this represents a true increase in risk of adverse effects compared with other CNS stimulants. The rate of sudden death with atomoxetine has been estimated as 0.5 per 100,000 patient-years, which is not clinically different from the rate for other CNS stimulants, and is not in excess of the baseline rate of sudden death in the paediatric population (estimated to be 1.3–1.85/100,000). [33] The FDA and its Pediatric Advisory Committee reviewed data regarding psychiatric adverse effects for the treatment of ADHD. The report revealed that rare events of toxic psychotic symptoms, specifically involving visual and tactile hallucinations of insects, have been reported for the pharmacological agents examined, which were all CNS stimulants, atomoxetine, and modafinil. [33]

## OPTION DEXAMFETAMINE SULPHATE

**Symptom severity**

*Compared with placebo* Dexamfetamine (dexamphetamine) may be more effective at improving hyperactivity and ADHD symptoms as measured by abbreviated Conners Teacher's Rating Scale (very low-quality evidence).

*Compared with dexamfetamine sulphate plus clonidine* Adding clonidine to dexamfetamine regimens may be more effective at improving response rates for conduct symptoms but not for hyperactivity, in children with comorbid oppositional defiant disorder or conduct disorder (very low-quality evidence).

*Compared with methylphenidate* We don't know whether dexamfetamine is more effective at improving ADHD symptoms in children and adolescents aged 5–18 years (very low-quality evidence).

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Dexamfetamine (dexamphetamine) sulphate versus placebo:**
We found three systematic reviews [6] [18] [21] No RCT was identified by all three reviews for this comparison. The first review (search date 1997, 4 RCTs, 61 children aged 6–12 years, dexamfetamine 0.46–0.75 mg/kg/day) found that dexamfetamine significantly improved outcomes measured by the abbreviated Conners Teacher's Rating Scale at up to 21 days compared with placebo (WMD –4.8 points, 95% CI –6.4 points to –2.9 points). [21] The second review (search date 1997, 3 RCTs, 150 children aged 6–16 years, dexamfetamine 5–20 mg/day) only evaluated longer-term studies (more than 12 weeks). [6] It found some evidence of positive outcomes (including improved concentration and hyperactivity) with dexamfetamine compared with placebo but did not pool data. However, some methodological problems were identified with the RCTs in this review. [6] The third review (5 RCTs, 125 children aged 4–12 years) found that, for medium-dose dexamfetamine (10–20 mg/day), results for hyperactivity varied with assessment scale used, but that high-dose dexamfetamine (more than 20 mg/day) seemed to improve hyperactivity compared with placebo. [18] The third review (search date 2004) [18] built on three other systematic reviews, one of which was the first review reported above. [20] [21] [34] The third review searched for studies on dexamfetamine from 1997 onwards. Quality and methodological issues precluded pooling of data in the third review.

**Dexamfetamine sulphate versus dexamfetamine sulphate plus clonidine:**
See benefits of clonidine, p 10 .

**Dexamfetamine sulphate versus methylphenidate:**
See benefits of methylphenidate, p 6 .

**Dexamfetamine sulphate versus psychological treatments:**
We found one systematic review (search date 2004, 1 RCT 34 children aged 4–6 years) comparing dexamfetamine versus psychological treatments. [18] The review built on three other systematic reviews. [20] [21] [34] The review searched for studies on dexamfetamine from 1997 onwards. The RCT identified by the review did not meet *Clinical Evidence* inclusion criteria and is not discussed further.

**Harms:**

**Dexamfetamine sulphate versus placebo:**
Two RCTs identified by two reviews reported people withdrawing from the trial because of adverse effects. [18] [21] The second review found that dexamfetamine increased anorexia and appetite disturbance in three RCTs (data not pooled; absolute numbers not reported). [6] The third review found a significant increase in loss of appetite with dexamfetamine compared with placebo (1 RCT, 17 people; RR 3.82, 95% CI 1.08 to 13.58). [18]

**Dexamfetamine sulphate versus dexamfetamine sulphate plus clonidine:**
See harms of clonidine, p 10 .

**Dexamfetamine sulphate versus methylphenidate:**
See harms of methylphenidate, p 6 .

**Dexamfetamine sulphate versus psychological treatments:**
We found no RCTs on adverse effects for this comparison.

**Comment:**

None.

## OPTION METHYLPHENIDATE

**Symptom severity**

*Compared with placebo* Methylphenidate (including transdermal formulations) may be more effective at reducing core symptoms of ADHD in children aged aged 5–18 years (low-quality evidence).

*Compared with atomoxetine* Low doses of methylphenidate and atomoxetine seem equally effective at improving response rates at 8 weeks in children and adolescents aged 6–16 years (moderate-quality evidence).

*Compared with dexamfetamine* We don't know whether methylphenidate is more effective at improving ADHD symptoms in children and adolescents aged 5–18 years (very low-quality evidence).

*Compared with clonidine* We don't know whether methylphenidate is more effective at reducing severity of ADHD symptoms in children aged 7–14 years with comorbid chronic tic disorders (very low-quality evidence).

*Compared with methylphenidate plus clonidine* Methylphenidate plus clonidine may be no more effective at reducing severity of ADHD symptoms in in children aged 7–14 years with comorbid chronic tic disorders and may increase the risk of bradycardia (very low-quality evidence).

*Compared with psychological/behavioural treatment* We don't know whether methylphenidate is more effective at improving ADHD symptoms in children and adolescents aged 5–18 years (very low-quality evidence).

*Compared with methylphenidate plus psychological/behavioural treatment* Methylphenidate plus multimodal psychological treatment (including parent training and counselling, social-skills training, psychological therapy and academic assistance) may be more effective at improving patient-rated SSRS (Social Skills Rating Scale) at 1 year, but not other parent or teacher rating scales in children aged 7–9 years (very low-quality evidence).

*Methylphenidate plus clonidine compared with clonidine alone* Methylphenidate plus clonidine plus may be no more effective at reducing severity of ADHD symptoms in children aged 7–14 years with comorbid chronic tic disorders, and may increase the risk of bradycardia (very low-quality evidence).

**School performance**
*Compared with placebo* Methylphenidate may be more effective at improving attention at 12 hours and at increasing attempts at and increasing correct completion of mathematical problems at 8 hours (low-quality evidence).

*Compared with methylphenidate plus psychological/behavioural treatment* Methylphenidate plus multimodal psychological treatment (including parent training and counselling, social-skills training, psychological therapy and academic assistance) may be no more effective at improving academic performance scores (Stanford Achievement Tests in total reading, math computation, and listening comprehension) at 1 year in children aged 7–9 years (very low-quality evidence).

**Adverse effects**
Methylphenidate has been associated with decreased appetite, insomnia, stomach ache, and decrease in growth rate affecting height and weight.

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

We found two systematic reviews (search date 2000 [34] and search date 2004 [18] ) examining the effects of methylphenidate on symptoms of ADHD. Quality and methodological issues precluded meta-analysis in both identified reviews. Because of differing inclusion/exclusion criteria and reporting in the reviews, there was some variation in the RCTs identified for some comparisons. We found four additional [35] [36] [37] [38] and four subsequent RCTs [39] [40] [41] [42] examining effects of methylphenidate on symptoms of ADHD. Most studies were done in the USA, used a diagnosis of attention deficit disorder (DSM-III) or ADHD (DSM-IIIR or DSM-IV), and included children aged 5–18 years, mostly recruited from psychiatric and other hospital outpatient clinics. The second review built on three other systematic reviews, one of which was the review identified with the earlier search date. [20] [21] [34] The review searched for studies on methylphenidate from 1999 onwards. In addition, we found one systematic review (search date not reported) attempting to assess the effects of methylphenidate on substance abuse in later life in children with ADHD; it identified no RCTs assessing this outcome. [43]

**Methylphenidate versus placebo:**
The first systematic review (search date 2000) found 13 rigorously selected short-term RCTs (1177 children aged 5–18 years). [34] The review did not pool results from the identified RCTs. Ten RCTs found that methylphenidate significantly improved scores on Conners Teacher's Rating Scale hyperactivity index (P less than 0.05) compared with placebo. This improvement was non-significant in three small RCTs (99 children) (see table 2, p 24 for all results from these RCTs). The same systematic review found similar results in 17 other RCTs (643 children), which were less stringent in terms of homogeneity of participants, outcome measures, and methodological quality. The second review identified nine RCTs subsequent to the search date of the first review. [18] The review re-

ported effects of methylphenidate based on dose (low-dose, up to 15 mg/day; medium-dose, 15–30 mg/day; and high-dose, more than 30 mg/day) and formulation of administration (immediate-release or extended-release). Some of the RCTs identified by the review did not assess improvement of symptoms of ADHD as an outcome, and some reported only on adverse effects. The review reported finding variable results in the effects of methylphenidate on the symptoms of ADHD compared with placebo (data reported for RCTs that meet *Clinical Evidence* inclusion criteria and report outcomes of interest: see table 2, p 24 ). The review reported that methodology was not reported adequately in many of the RCTs identified and that the results should be interpreted with caution. The first additional RCT (crossover design, 68 children aged 6–12 years) found similar benefit for extended-release (once-daily dosing) methylphenidate compared with placebo (see table 2, p 24 ). [35] Two other additional RCTs (crossover design, 1 RCT in 45 adolescents mean age 13.8 years and 1 RCT in 136 boys aged 7–12 years) also found that methylphenidate was significantly more effective than placebo at improving symptoms scores (both measured by the IOWA Conners rating) (see table 2, p 24 ). [36] [37] Another additional RCT (136 children aged 7–14 years with comorbid chronic tic disorders) compared methylphenidate, either alone or in combination with clonidine, versus placebo. [38] The RCT found that methylphenidate alone (average dose of 25.7 mg/day) significantly improved severity of ADHD symptoms at 16 weeks compared with placebo, as assessed by the Conners Abbreviated Symptom Questionnaire for Teachers (see table 2, p 24 ). The first subsequent RCT (318 children aged 6–12 years on a stable dose of methylphenidate) found that both extended-release (139 people; once-daily dosing: period of action: up to 8 hours) and immediate release (133 people; twice-daily dosing) formulations of methylphenidate significantly improved symptoms of ADHD compared with placebo (46 people) at 3 weeks (see table 2, p 24 ). [39] The second subsequent RCT (5-arm crossover design, 53 children, aged 6–12 years stabilised on methylphenidate 20–40 mg/day) compared two long-acting methylphenidate formulations (extended-release capsules [methylphenidate 20 and 40 mg] and modified-release tablets [methylphenidate 18 and 36 mg]) versus each other and placebo. [40] The RCT found significant improvements in attention at 12 hours and in attempts at and correct completion of mathematical problems at 8 hours for all formulations of methylphenidate compared with placebo (see table 2, p 24 ). Modified-release tablets comprised a methylphenidate immediate-release outer layer, and inner compartments, one of which contained methylphenidate. Children received treatment as a single dose on the same day of 5 consecutive weeks. They continued to take their prescribed medication 5 days after testing, and, to avoid carry over, to take no medication the day before testing. We found two subsequent RCTs that compared a methylphenidate transdermal system of administration versus placebo. [41] [42] In the first RCT (cross-over design, 80 children aged 6–12 years), children with ADHD first entered an open-label dose-optimisation phase, which took place over 5 weeks. [42] After dose optimisation, children were randomised to 1 week of methylphenidate at their optimised dose or placebo, followed by 1 week of the opposite treatment. The RCT found that methylphenidate (patches of 10, 16, 20 or 27 mg) significantly improved symptoms of ADHD at 12 hours compared with placebo (see table 2, p 24 ). Patches were applied in the morning and worn for 9 hours. Method of randomisation in this RCT was unclear, and pre-crossover results were not reported. The second RCT (36 children aged 6–13 years) took place over 8 days, and compared methylphenidate (patch worn for at least 12 hours; release rate of methylphenidate of 0.45, 0.9, or 1.8 mg/hour) versus placebo. [41] Behavioural outcomes were assessed using the Conners Rating Scale. The RCT found significant improvements in ADHD symptoms at all doses of methylphenidate compared with placebo, as rated by parents and teachers (see table 2, p 24 ). Counsellor-rated improvement of symptoms was significant for methylphenidate 0.9 and 1.8 mg/h, but not for methylphenidate 0.45 mg/h compared with placebo. Children were given each dose of methylphenidate and placebo twice, applied once 60 minutes and once 120 minutes before the start of the school day. The treatment sequence was randomised and concealed until the end of the study.

**Methylphenidate alone versus atomoxetine alone:**
See benefits of atomoxetine, p 3 .

**Methylphenidate alone versus dexamfetamine (dexamphetamine) sulphate alone:**
The first systematic review [34] identified four poorly reported crossover RCTs (224 children aged 5–18 years) comparing methylphenidate (dose range 0.6–4.5 mg/kg/day or 20 mg/day for trials reporting in those units) versus dexamfetamine (dose range 0.39–2.6 mg/kg/day or 10 mg/day for trials reporting in those units) but, because of heterogeneity, could not pool their results. The second systematic review identified no other RCTs for this comparison. [18] Three RCTs identified by the reviews (99 children aged 5–12 years) found no significant difference between methylphenidate and dexamfetamine in core symptoms score (see table 2, p 24 ). The fourth RCT found improvement with methylphenidate compared with dexamfetamine for teacher-reported, but not for parent-reported, outcomes. No firm conclusions can be drawn from these RCTs.

**Methylphenidate alone versus clonidine alone:**
See benefits of clonidine, p 10 .

**Methylphenidate alone versus methylphenidate plus clonidine:**
See benefits of clonidine, p 10 .

**Methylphenidate plus clonidine versus clonidine alone:**
See benefits of clonidine, p 10 .

**Methylphenidate versus psychological/behavioural treatment:**
We found two systematic reviews (search dates 2000 [34] and 2004 [18] ). Two RCTs were identified by both reviews. The first review identified four RCTs comparing methylphenidate versus psychological/behavioural treatment. Two of the RCTs reported Conners Teacher's Rating Scale scores (see table 2, p 24 ). Three of the RCTs (192 children aged 5–12 years) were poorly reported and compared a variety of psychological/behavioural treatments (individual cognitive training over 12 weeks; parent and teacher training; behaviour treatment for 8 weeks) versus methylphenidate (5–60 mg/day). Overall, these three RCTs found limited evidence that, in the medium term (12–52 weeks), methylphenidate improved symptoms compared with psychological/behavioural treatment. The fourth RCT (579 children aged 7–10 years) compared four interventions: drug treatment (144 children, double-blind titration of methylphenidate dose, switched to alternative medication, such as dexamfetamine [dexamphetamine], pemoline, or imipramine, after 28 days if response unsatisfactory, mean initial dose 30.5 mg/day); intensive behavioural management; drug treatment plus intensive behavioural management; and standard community care (treatments by community providers). [44] A total of 74% of the children randomised to drug treatment were taking methylphenidate at the end of the study. Initial results were not reported as the number of children who improved, but only as P values. Methylphenidate improved some, but not all symptoms of ADHD compared with intensive behavioural management. [44] Subsequent secondary analysis suggested that 56% of the children taking a pharmacological treatment improved compared with 34% in the intensive behavioural management group. [45] There is also a suggestion that children with comorbid behaviour problems (oppositional defiant disorder/conduct disorder) showed a stronger response to medication than those without comorbid behaviour problems, and that children with ADHD and anxiety disorders were likely to respond equally well to behavioural or medication treatments. [46] There are some concerns about the methods used in the RCT, and caution should be exercised when using the results of secondary analysis, as they are more susceptible to bias than the primary outcome analyses. [47] It should also be noted that the principal outcome measures were rating scales based on impressions of parents and teachers; they did not include the children's views or direct measures of their response to treatment. Long-term effects on psychosocial adjustment, educational success, or behavioural improvement are unclear. We found no evidence about methylphenidate for preschool children. The second review identified 6 RCTs (174 children aged 5–13 years) comparing methylphenidate versus psychological/behavioural treatment. [18] Inconsistent reporting of outcomes precluded pooling of data. The remaining four RCTs identified by the review do not meet *Clinical Evidence* inclusion criteria for this section and are not discussed further.

**Methylphenidate alone versus methylphenidate plus psychological/behavioural treatment:**
See benefits of methylphenidate plus psychological treatment, p 17 .

## Harms:

The first systematic review did not combine results on harms because of heterogeneity and incomplete data reporting. [34] It presented the number of RCTs that had found significant results, but did not report the number of adverse effects. The second systematic review did not combine results on harms because of heterogeneity. [18] The review reported the relative risks of headache, insomnia, and decreased appetite where data were available.

**Methylphenidate versus placebo:**
At least one RCT included in the first systematic review found that sleep disorders, anorexia or appetite disturbance, headache, motor tics, irritability, and abdominal pain were significantly more common in children receiving methylphenidate compared with placebo (see table 3, p 28 ). The second review found no differences in adverse effects between low-dose methylphenidate and placebo. [18] However, it reported that medium and high doses and extended-release formulations of methylphenidate were associated with higher incidences of headache, loss of appetite, stomach ache, and insomnia compared with placebo. One additional [35] and one subsequent RCT [39] reported similar adverse effects. Two other additional RCTs gave no information on adverse effects. [36] [37] One additional RCT found similar proportions of people reporting worsening of tics as an adverse effect for methylphenidate alone and placebo at 16 weeks (8/37 [22%] with methylphenidate *v* 7/32 [22%] with placebo: significance not assessed: P value not reported). [38] The RCT found higher rates of sedation for methylphenidate alone compared with placebo (14% with methylphenidate *v* 6% with placebo, significance not assessed; P value not reported). [38] One subsequent RCT reported that upper abdominal pain was the only adverse effect thought to be associated with methylphenidate (reported by 1 person receiving modified-release methylphenidate 36 mg; significance between groups not assessed). [40] Both RCTs assessing transdermal methylphenidate reported that the most common adverse effects associated with methylphenidate

were decreased appetite and insomnia (absolute numbers reported; significance not assessed in either RCT). [41] [42] No severe adverse effects were reported in either RCT. We found no good evidence about the effects of methylphenidate on growth rates in children.

**Methylphenidate alone versus atomoxetine alone:**
See harms of atomoxetine, p 3 .

**Methylphenidate alone versus dexamfetamine alone:**
Of the four RCTs identified by the first systematic review, [34] two reported no significant difference between methylphenidate and dexamfetamine in anorexia or appetite disturbance (absolute numbers not reported; reported as not significant; P values not reported), and one RCT reported no significant difference in motor tics, abdominal pain, and irritability (absolute numbers not reported; reported as not significant; P values not reported). The second systematic review gave no additional information on adverse effects. [18]

**Methylphenidate alone versus clonidine alone:**
See harms of clonidine, p 10 .

**Methylphenidate alone versus methylphenidate plus clonidine:**
See harms of clonidine, p 10 .

**Methylphenidate plus clonidine versus clonidine alone:**
See harms of clonidine, p 10 .

**Methylphenidate versus psychological/behavioural treatment:**
The RCT comparing methylphenidate versus intensive behavioural treatment found that, of the children receiving either drug treatment alone or drug treatment plus intensive behavioural treatment, 50% reported mild adverse effects, 11% had moderate adverse effects, and 3% had severe adverse effects (adverse effects not described further). [44] The study gave no information on adverse effects of non-drug intervention, but did comment that 6/11 reported severe adverse effects (depression, worrying, or irritability, with some children reporting more than 1) could have resulted from non-medication factors.

**Methylphenidate alone versus methylphenidate plus psychological/behavioural treatment:**
See harms of methylphenidate plus psychological treatment, p 17 .

**Comment:**

**Clinical guide:**
A review of MPH and its isomers has suggested that the largest transdermal system patch size of 37.5 $cm^2$ delivers approximately 30 mg of methylphenidate through the skin over a nine-hour period. [48] Therefore, a transdermal system can deliver the same systemic dose of methylphenidate as a 54 mg dose of the immediate-release formulation, which suggests that the transdermal system might be a satisfactory alternative mode of administration when oral dosing is contraindicated or unacceptable. There is insufficient evidence about any association between CNS stimulants and adverse effects, such as those uncommon adverse effects associated with atomoxetine (such as liver disease, suicidal thoughts, and seizures). Atomoxetine was introduced under much stricter surveillance than other CNS stimulants have received. The FDA and its Pediatric Advisory Committee reviewed data regarding psychiatric adverse effects for the treatment of ADHD. The report revealed that rare events of toxic psychotic symptoms (specifically involving visual and tactile hallucinations of insects) have been reported for the pharmacological agents examined, which were all the CNS stimulants, atomoxetine, and modafinil. Symptoms of aggression and suicidality (but no completed suicides) were also reported. [33] Twenty-eight cases of sudden death on CNS stimulant treatment have been reported by the FDA. The rate of sudden death with CNS stimulant and atomoxetine has been estimated, per 100,000 patient-years, [33] as 0.2 for MPH, 0.3 for amphetamine, and 0.5 for atomoxetine. The differences are not in excess of the baseline rate of sudden death in the paediatric population, which is estimated to be 1.3–1.85/100,000, and are considered not to be clinically meaningful.

## OPTION CLONIDINE

**Symptom severity**
*Compared with placebo* Clonidine may be more effective at improving symptoms of ADHD in children aged 6–16 years with comorbid conditions such as autism, tics, or conduct disorders (very low-quality evidence).

*Compared with methylphenidate* We don't know whether clonidine is more effective at reducing severity of ADHD symptoms in children aged 7–14 years with comorbid chronic tic disorders (very low-quality evidence).

*Clonidine plus methylphenidate/dexamfetamine compared with methylphenidate/dexamfetamine* Adding clonidine to methylphenidate/dexamfetamine regimens may be more effective at improving response rates for conduct symptoms, but not hyperactivity, in children with comorbid oppositional defiant disorder or conduct disorder (very low-quality evidence).

*Compared with clonidine plus methylphenidate* Clonidine plus methylphenidate may be no more effective at reducing severity of ADHD symptoms in children aged 7–14 years with comorbid chronic tic disorders, and may increase the risk of bradycardia (very low-quality evidence).

**Note**
Clonidine has not been as extensively studied as drugs that are considered first-line treatments, and evidence of effectiveness is limited. Most evidence points towards a degree of effectiveness.

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Clonidine versus placebo:**
We found one systematic review (search date 1999, 6 RCTs, 143 children, average age 10.6 years, mean dose of clonidine 0.18 mg/day, average length of treatment 10.9 weeks). [49] The review identified 11 studies, eight of which were RCTs. The review carried out a meta-analysis of six studies considered to have sufficiently strong methodology. These studies included children with comorbid conditions, such as autism, tics, or conduct disorder, and were not all RCTs. The review found that clonidine was significantly more effective than placebo at improving combined rating scores (overall effect size of 0.58 [measure of effect size not stated], 95% CI 0.27 to 0.89). One of the six RCTs included in the meta-analysis of clonidine versus placebo was a comparison of clonidine versus methylphenidate [50] rather than versus placebo (24 boys aged 6–16 years), and the rating scales of the clinical features of ADHD completed by parents, teachers, and clinicians were combined in the systematic review. The review did not carry out a sensitivity analysis to determine if removal of these data would change the effect size. The review noted larger effect sizes in smaller and lower-quality studies. Inclusion of the RCT comparing clonidine versus methylphenidate [50] in the systematic review creates difficulties in using that review to indicate the effects of clonidine versus placebo. The RCT had a larger effect size than most other included studies, and it is likely to have inflated the final result of the meta-analysis. [50] The results used by the systematic review for that RCT were not described in the original RCT report, and may have been a less reliable comparison of baseline and end-of-study measures rather than a rigorous comparison of randomly allocated groups. We found one subsequent RCT (136 children aged 7–14 years with comorbid chronic tic disorders) comparing clonidine, either alone or in combination with methylphenidate, versus placebo. [38] The RCT found that clonidine (average dose of 0.25 mg a day) significantly improved severity of ADHD symptoms at 16 weeks compared with placebo, as assessed by the Conners Abbreviated Symptom Questionnaire for Teachers (treatment effect size of 3.3 [positive value for treatment effect indicates a beneficial effect], 95% CI –0.2 to +6.8; P = 0.02). Children already having non-pharmacological treatment for ADHD continued this treatment in addition to pharmacological treatment. There was no subgroup analysis for children on combined drug plus psychological treatments.

**Clonidine alone versus methylphenidate alone:**
One RCT (136 children aged 7–14 years with comorbid chronic tic disorders) compared clonidine (average dose of 0.25 mg a day) versus methylphenidate (average dose of 25.7 mg a day). [38] The RCT found no significant difference in change of severity of ADHD symptoms between clonidine alone and methylphenidate alone (continuous assessment not reported; reported as not significant; P value not reported). Children already having non-pharmacological treatment for ADHD continued this treatment in addition to pharmacological treatment. There was no subgroup analysis for children on combined drug plus psychological treatments.

**Clonidine plus methylphenidate/dexamfetamine (dexamphetamine) sulphate versus methylphenidate/dexamfetamine sulphate alone:**
One RCT (67 children aged 6–14 years with comorbid oppositional defiant disorder or conduct disorder who were already taking CNS stimulants [41/67 [61%] dexamfetamine; 26/67 [39%] methylphenidate]) compared additional clonidine versus additional placebo. [51] It defined improvement using an unconventionally stringent cut-off (38% reduction from baseline in parent-reported symptoms for conduct and 43% reduction in parent-reported symptoms for hyperactivity, using the Hyperactive Index). At 6 weeks, it found that added clonidine significantly improved response rate for conduct compared with added placebo (21/37 [57%] with added clonidine *v* 6/29 [21%] with added placebo; P less than 0.01). It found no significant difference between treatments in response rate for hyperactivity (13/37 [35%] with added clonidine *v* 5/29 [17%] with added placebo; P less than or equal to 0.16). [51] It also found that, compared with adding placebo, adding clonidine significantly reduced lack of interest in others and lack of talking with others, irritability, proneness to crying, and anxiety (rates not reported, P less than 0.05 for each outcome). Another RCT (136

children aged 7–14 years with comorbid chronic tic disorders) compared methylphenidate (average dose of 25.7 mg/day) versus clonidine plus methylphenidate. [38] The RCT found no significant difference in change of severity of ADHD symptoms between methylphenidate alone and clonidine plus methylphenidate (continuous assessment not reported; reported as not significant: P value not reported). Children already having non-pharmacological treatment for ADHD continued this treatment in addition to pharmacological treatment. There was no subgroup analysis for children on combined drug plus psychological treatments.

**Clonidine alone versus clonidine plus methylphenidate:**
One RCT (136 children aged 7–14 years with comorbid chronic tic disorders) compared clonidine (average dose of 0.25 mg a day) versus clonidine plus methylphenidate (average dose of 25.7 mg/day). [38] The RCT found no significant difference in change of severity of ADHD symptoms between clonidine alone and clonidine plus methylphenidate (continuous assessment not reported; reported as not significant: P value not reported). Children already having non-pharmacological treatment for ADHD continued this treatment in addition to pharmacological treatment. There was no subgroup analysis for children on combined drug plus psychological treatments.

**Harms:**

**Clonidine versus placebo:**
The systematic review [49] included information from 10 studies of harms. Harms were reported as the number of studies that recorded a specific adverse effect or not, rather than the number of children experiencing adverse effects. Not all were high-quality RCTs, and their results are difficult to interpret. In children taking clonidine, nine of 10 studies found sedation in children; six studies found increased irritability. ECGs were recorded in two placebo-controlled RCTs, which found no abnormalities. The subsequent RCT found a similar proportion of people reporting worsening of tics as an adverse effect for clonidine alone and placebo at 16 weeks (9/34 [26%] with clonidine *v* 7/32 [22%] with placebo: significance not assessed: P value not reported). [38] The RCT found higher rates of sedation for clonidine alone compared with placebo (48% with clonidine *v* 6% with placebo: significance not assessed; P value not reported). [38]

**Clonidine alone versus methylphenidate alone:**
One RCT found higher rates of sedation for clonidine alone compared with methylphenidate alone (48% with clonidine *v* 14% with methylphenidate: absolute numbers not reported; significance not assessed; P value not reported. [38]

**Clonidine plus methylphenidate/dexamfetamine (dexamphetamine) sulphate versus methylphenidate/dexamfetamine sulphate alone:**
The RCT (67 children already taking CNS stimulants; 41/67 [61%] dexamfetamine, 26/67 [39%] methylphenidate]) found no significant difference between treatments for insomnia, daydreaming or staring, decreased appetite, sadness, euphoria, nightmares, stomach aches, headaches, nail biting, or tics (data and P values not reported). [51] It found that clonidine significantly increased drowsiness and dizziness compared with placebo during treatment (rates not reported; P less than 0.05), although these symptoms resolved within 6 weeks. The second RCT found a similar proportion of people reporting worsening of tics as an adverse effect for methylphenidate alone at 16 weeks compared with clonidine plus methylphenidate at (8/37 [22%] with clonidine alone *v* 6/33 [18%] with clonidine plus methylphenidate: significance not assessed: P value not reported). [38]

**Clonidine alone versus clonidine plus methylphenidate:**
The RCT found a similar proportion of people reporting worsening of tics as an adverse effect for clonidine plus methylphenidate at 16 weeks compared with clonidine alone (6/33 [18%] with clonidine plus methylphenidate *v* 9/34 [26%] with clonidine alone: significance not assessed: P value not reported). [38]

**Comment:** None.

## OPTION MODAFINIL New

**Symptom severity**
*Compared with placebo* Once-daily modafinil may be more effective at improving ADHD symptoms at 4 weeks as assessed by teacher- and clinician-related versions of the ADHD Rating Scale-IV (ADHD-RS-IV) and the Conners ADHD/DSM-IV rating scale (low-quality evidence).

**Note**
Modafinil has not been as extensively studied as those drugs considered as first-line agents. However, it could potentially be considered for children refractory to other treatments. Modafinil has been associated with psychiatric side-effects, hypersensitivity reactions, and serious rashes.

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Modafinil versus placebo:**
We found one RCT assessing the effects of modafinil compared with placebo on symptoms of ADHD (measured by changes in ADHD rating scale [ADHD-RS-IV]). [52] The RCT (248 children, aged 6–13 years) compared once-daily and divided doses of modafinil versus placebo over 4 weeks. Efficacy was measured as improvement in various scales: teacher- and clinician-related versions of the ADHD-RS-IV and the Conners ADHD/DSM-IV rating scale. The RCT found that, compared with placebo, once-daily modafinil 300 mg significantly improved symptoms of ADHD at 4 weeks (see table 4, p 28 ). For modafinil 200/100 mg and 100/200 mg (divided dose) results varied with the different assessments scales used (see table 4, p 28 ). For modafinil 400 mg (divided dose), results varied with the different assessment scales used (see table 4, p 28 ). [52] All children were given three tablets in the morning and two tablets 4–5 hours later. [52] Each tablet contained either modafinil 100 mg or placebo. Randomisation was stratified by body weight. Children weighing less than 30 kg were randomised with an equal probability of assignment to one of four arms: once-daily modafinil 300 mg; modafinil 100 mg followed by 200 mg; modafinil 200 mg followed by 100 mg modafinil; or placebo. Children weighing 30 kg or more were randomised to the same four arms (probability of assignment to the four arms was the same as for children weighing less than 30 kg), and a fifth arm of modafinil 400 mg (2 x 200 mg divided dose), with twice the probability of assignment to this arm.

**Harms:**

**Modafinil versus placebo:**
The RCT found a significantly higher rate of insomnia in the modafinil 200/100 mg group compared with placebo (7/49 [14%] with modafinil 200/100 mg *v* 1/51 [2%] with placebo; P less than 0.05). [52] The RCT found no significant difference in rate of insomnia between other dosing regimens of modafinil and placebo (reported as not significant; P values not reported). Decreased appetite was more frequently reported in the modafinil groups than in the placebo group, but the between-group differences did not reach statistical significance (reported as not significant; P values not reported).

**Comment:**

The FDA and its Pediatric Advisory Committee reviewed data regarding psychiatric adverse effects for the treatment of ADHD. The report revealed that rare events of toxic psychotic symptoms (specifically involving visual and tactile hallucinations of insects) have been reported for the pharmacological agents examined, which were all the CNS stimulants, atomoxetine, and modafinil. [33] A drug safety alert has been issued on psychiatric adverse effects, hypersensitivity reactions, and serious rashes associated with modafinil. [53]

## OPTION BUPROPION New

**Symptom severity**
*Compared with placebo* We don't know whether bupropion is more effective at improving symptoms of aggression at 28 days, in children aged 6–12, years as assessed by the Aggression subscale of the 10-item Conners Teacher Questionnaire (very low-quality evidence).

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Bupropion versus placebo:**
We found no systematic review. We found two RCTs (3 publications) comparing bupropion 3–6 mg/kg/day (dosage schedule dependent on weight of child) versus placebo. [54] [55] [56] The first RCT (109 children aged 6–12 years) compared bupropion (72 children) versus placebo (37children) for 28 days. [54] It found that bupropion significantly improved symptoms of aggression (last observation carried forward; absolute numbers not reported; P less than 0.027) at 28 days compared with placebo, as assessed by the Aggression subscale of the 10-item Conners Teacher Questionnaire. Using the hyperactivity subscale of the same questionnaire, the RCT found that bupropion significantly improved hyperactivity in the children available for assessment at 28 days compared with placebo (96 children; absolute numbers not reported; P less than 0.01). However, this difference was not significant when analysed using the last observation carried forward (absolute numbers not reported; P less than 0.06). The RCT reported significant improvements in conduct problems and restless/impulsive behaviour on the 93-item Conners Parent Questionnaire at day 28 with bupropion compared with placebo (absolute numbers not reported; reported as significant; P values not reported). The follow-up of children assessed by teachers at 28 days was 75%. The second RCT (2 publications, 30 children aged 6–12 years, 20 children randomised to bupropion and 10 children randomised to placebo) found that, at 28 days, bupropion significantly improved symptom severity and improvement on the Clinical Global Impressions Scale compared with placebo (mean change in CGI score: symptom severity: from 5.26 to 3.53 with bupropion *v* from 5.67 to 4.44 with placebo; P = 0.026: improvement: from 4.00 to 2.89 with bupropion *v* from 4.00 to 3.44 with placebo; P = 0.019). [56] [55] Bupropion also significantly improved hyperactivity symptoms compared with placebo, as assessed by teachers using the 39-item Conners Teacher Questionnaire (mean change in hyperactivity score: from 1.81 to 1.47 with bupropion *v* from 1.88

to 2.03 with placebo; P = 0.001). However, the RCT found no significant difference between groups in parent-assessed restlessness (using the Conners Parent Symptom Questionnaire), or in conduct rated by parents or teachers (mean change in score: parent-rated restlessness: from 1.67 to 1.11 with bupropion *v* from 2.12 to 1.96 with placebo; parent-rated conduct: from 1.31 to 0.87 with bupropion *v* from 1.53 to 0.87 with placebo; teacher-rated conduct: from 1.29 to 1.05 with bupropion *v* from 1.23 to 1.39 with placebo; reported as not significant; P values not reported). [55]

**Harms:**

**Bupropion versus placebo:**
The first RCT reported that four people withdrew because of skin rash with urticaria associated with bupropion use. [54] The RCT found that the most common adverse effects reported in children taking bupropion were nausea and vomiting, and skin rashes, rates of which were higher in the bupropion group compared with the placebo group (nausea and vomiting: 16.7% with bupropion *v* 13.5% with placebo; rash: 16.7% with bupropion *v* 8.1% with placebo; absolute numbers not reported; significance not assessed; P value not reported). The second RCT reported that one child (1/20 [5%]) taking bupropion developed a skin rash and perioral oedema and withdrew from the study. [56] [55] High single doses of bupropion (greater than 400 mg) may induce seizures. [33]

**Comment:** None.

## OPTION OMEGA-3 POLYUNSATURATED FATTY ACID COMPOUNDS (FISH OILS) New

**Symptom severity**
*Compared with placebo* Food supplemented with long-chain omega-3 polyunsaturated fatty acids may be no more effective than foods containing olive oil at improving severity of symptoms of ADHD in children aged 6–12 years (very low-quality evidence).

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Omega-3 versus placebo:**
We found one systematic review (search date not reported), which identified five RCTs (286 people) in children and adolescents with ADHD. [57] The review did not pool data. Four of the RCTs identified by the review did not meet *Clinical Evidence* inclusion criteria and are not discussed further. The RCT (40 children aged 6–12 years) of sufficient quality identified by the review assessed the effects of eating food supplemented with omega-3 polyunsaturated fatty acid-rich fish oil (average intake of 3600 mg docosahexaenoic acid and 700 mg eicosapentaenoic acid a week) compared with eating placebo foods containing olive oil. [58] The RCT measured changes in attention deficit, hyperactivity, and impulsivity as primary outcomes. The RCT found no significant difference between groups at 4 months in severity of symptoms of ADHD (mean change in score from baseline: attention deficit: +1 with DHA *v* 0 with placebo; hyperactivity: 0 with DHA *v* 0 with placebo: impulsivity: 0 with DHA *v* –1 with placebo: between-group differences reported as not significant: P values not reported). The population comprised eight children with suspected, but not confirmed, ADHD and a mixture of children not on medication (34 children) and those taking medication for symptoms of ADHD. The authors reported that exclusion of those taking medication from the analysis did not affect the results.

**Harms:**

**Omega-3 versus placebo:**
The systematic review [57] and the RCT gave no information on adverse effects. [58]

**Comment:** Some RCTs in children with other learning difficulties [59] or developmental coordination disorder, [60] but not ADHD, have reported behavioural improvements with polyunsaturated fatty acid supplements. RCTs in children with ADHD are in progress.

## OPTION HOMEOPATHY New

**Symptom severity**
*Compared with placebo* We don't know whether homeopathic interventions are more effective at improving symptoms of ADHD at 12–18 weeks in children and adolescents aged 6–12 years (very low-quality evidence).

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Homeopathy versus placebo:**
We found one systematic review (search date 2006, 3 RCTs, 125 children) of the effects of homeopathy on the symptoms of ADHD in children and adolescents. [61] The review did not pool data. One RCT identified by the review did not meet *Clinical Evidence* inclusion criteria, and the results from this study are not discussed further. The two other RCTs identified by the review compared homeopathic remedies versus placebo. The first RCT (crossover design, 62 children

aged 6–16 years) identified by the review found that homeopathic treatment significantly improved symptoms of ADHD at 12 weeks compared with placebo (mean difference between groups in Conners Global Index score at 12 weeks: –1.67, 95% CI –3.316 to –0.016, P = 0.0479). [62] Before randomisation, children participated in an initial phase during which they received an individual homeopathic treatment. Children who reached a predefined level of improvement were enrolled in the crossover phase of the study. There was no wash-out period before crossover, and pre-crossover results were not reported. The second RCT (43 children aged 6–12 years) identified by the review found no significant difference at 18 weeks between homeopathic remedies and placebo in improvement in ADHD symptoms, as assessed by primary outcome measures of the Conners Global Index-Parent-Rated score, and the Conners Global Index-Teacher-Rated score (mean change in Conners Global Index-Parent-Rated score: from 67.88 to 62.65 with homeopathy *v* from 69.88 to 60.88 with placebo; P = 0.70; mean change in Conners Global Index-Teacher-Rated score: from 68.80 to 63.53 with homeopathy *v* from 66.14 to 58.81 with placebo; P = 0.23). [63] Of the 43 children randomised, nine (5 in the homeopathy group and 4 in the placebo group) were taking CNS stimulant medication. Randomisation was stratified by sex and use or non-use of CNS stimulant treatment. The homeopathic remedy prescribed to individual children was not restricted to the treatment initially prescribed, and may have varied through the duration of the study. In total, 41 different active treatments were prescribed.

**Harms:**

**Homeopathy versus placebo:**
One RCT identified by the review reported that four people withdrew from the study (3 from the homeopathy group *v* 1 from the placebo group). [62] Reasons for withdrawal were increasing tics (1 person), behavioural disorders (2 people), and a reactive depression (1 people). The RCT did not specify whether adverse effects were treatment related. The second RCT identified by the review found no adverse effects associated with homeopathic treatment or placebo. [63]

**Comment:** None.

## QUESTION What are the effects of psychological treatments for ADHD in children and adolescents?

## OPTION PSYCHOLOGICAL/BEHAVIOURAL TREATMENT

**Symptom severity**
*Compared with standard care (medication, psychological therapy, or both as provided by the community health provider*) Psychological/behavioural treatments (including intensive behavioural treatments for families) may be no more effective at improving Conners Teacher's Rating scales or parent ratings in children and aged 6–13 years (very low-quality evidence).

*Parent plus teacher training compared with parent training alone* Parent plus teacher training may be more effective at 10 weeks at improving symptoms of ADHD (rated using combined Conners Parent/Teacher Short-Form Questionnaire), but not at improving oppositional index scores in children aged 5–12 years (very low-quality evidence).

*Compared with methylphenidate* We don't know whether psychological/behavioural treatment is more effective at improving ADHD symptoms in children and adolescents aged 5–18 years (very low-quality evidence).

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Psychological/behavioural treatment versus standard care:**
We found two systematic reviews. [21] [64] The first systematic review (search date 1997, [21] 2 RCTs, 50 children aged 6–13 years) found no significant difference between psychological/behavioural treatment and standard care (medication, psychological therapy, or both, as provided by the community health provider) in Conners Teacher's Rating Scales (SMD –0.40 points, 95% CI –1.28 points to +0.48 points) or parent ratings (1 RCT, 26 children, WMD –3.8 points, CI –9.6 points to +2.0 points). The RCTs identified by the systematic review were small, and the clinical importance of these results is unclear. The second systematic review (search date 2004, [64] 1 RCT, 290 children aged 7.0–9.9 years), [64] found insufficient evidence to compare the effects of family therapy versus standard care (medication, psychological therapy, or both, as provided by the community health provider). The RCT identified by the review [44] found no significant difference between intensive behavioural treatments for families for 14 months duration and standard community care (medication, psychological therapy, or both, as provided by the community health provider). [44] In children with comorbid anxiety disorders, the RCT found that intensive behavioural treatment resulted in better clinical outcomes. However, the results of this trial should be interpreted with caution because of weakness in the study design.

**Parent plus teacher training versus parent training alone:**
We found one small RCT (30 children aged 5–12 years). [65] The RCT found that a combination of parent training and teacher education significantly improved symptoms of ADHD (rated using combined Conners Parent/Teacher Short-Form Questionnaire) at 10 weeks compared with parent training alone (24 children assessed; mean change from baseline in ADHD index score: from 137.91 to 116.36 with parent plus teacher training *v* from 143.85 to 136.23 with parent training alone; P less than 0.01). However, the RCT found no significant difference between groups in the oppositional subscale of the combined parent/teacher questionnaire (mean change from baseline in oppositional index score: from 130.91 to 121.09 with parent plus teacher training *v* from 133.23 to 122.46 with parent training alone; reported as not significant; P value not reported). The method of randomisation and level of blinding of the study were not clear. The parent training programme comprised once-weekly 2-hour sessions for 10 weeks. During the first four sessions, parents were provided with general information on ADHD, parenting stress, effective communication, and developing children's self-esteem. The next four sessions (weeks 5–8) concentrated on informing parents about how to use behavioural management strategies effectively, including ignoring, natural consequences, and chart systems. The final two sessions involved presentations by guest speakers, who covered pharmacological treatment of ADHD, and education. Teachers involved in the combined programme were provided with a written information/educational pack about ADHD. Teachers were updated weekly on the issues and behavioural-management strategies covered in the group parent-training sessions, and advised on how to integrate the behavioural management strategies in the classroom.

**Psychological/behavioural treatment versus methylphenidate:**
See benefits of methylphenidate, p 6 .

**Psychological/behavioural treatment versus dexamfetamine:**
See benefits of dexamfetamine, p 6 .

**Psychological/behavioural treatment versus psychological/behavioural treatment plus methylphenidate:**
See benefits of methylphenidate plus psychological/behavioural treatment, p 17 .

**Psychological/behavioural treatment versus psychological/behavioural treatment plus dexamfetamine:**
See benefits of dexamfetamine plus psychological/behavioural treatment, p 18 .

**Harms:**

**Psychological/behavioural treatment versus standard care:**
The systematic reviews gave no information on adverse effects. [21] [64]

**Parent plus teacher training versus parent training alone:**
The RCT gave no information on adverse effects. [65]

**Psychological/behavioural treatment versus methylphenidate:**
See harms of methylphenidate, p 6 .

**Psychological/behavioural treatment versus dexamfetamine:**
See harms of dexamfetamine, p 6 .

**Psychological/behavioural treatment versus psychological/behavioural treatment plus methylphenidate:**
See harms of methylphenidate plus psychological/behavioural treatment, p 17 .

**Psychological/behavioural treatment versus psychological/behavioural treatment plus dexamfetamine:**
See harms of dexamfetamine plus psychological/behavioural treatment, p 18 .

**Comment:**

**Psychological/behavioural treatment versus standard care:**
Children in the trials had different comorbid diagnoses, presentations, and clinical needs. Secondary analysis of one RCT [44] suggests a possible small benefit with intensive behavioural treatment compared with standard community care (34% of children improved with intensive behavioural treatment *v* 25% improved with standard community care). [35] However, caution should be exercised in interpreting the results of secondary analysis, as they are more susceptible to bias than the primary outcome analyses.

**QUESTION** What are the effects of combination treatments for ADHD in children and adolescents?

**OPTION** METHYLPHENIDATE PLUS PSYCHOLOGICAL/BEHAVIOURAL TREATMENT

**Symptom severity**

*Compared with control/placebo* Methylphenidate plus psychological/behavioural treatment may be more effective at improving parent ratings (Conners Parent's Rating Scale) of ADHD disorders in children aged 5–13 years, but not teacher ratings (Conners Teacher's Rating scales) (very low-quality evidence).

*Compared with methylphenidate alone* Methylphenidate plus multimodal psychological treatment (including parent training and counselling, social-skills training, psychological therapy and academic assistance) may be more effective at improving patient-rated SSRS (Social Skills Rating Scale) at 1 year in children aged 7–9 years, but not other parent or teacher rating scales (very low-quality evidence).

*Compared with psychological/behavioural treatments alone* Methylphenidate plus behavioural treatments may be more effective at improving ADHD behaviours and symptoms in children aged 5–18 years, but not social skills or measures of parent-child relationships (very low-quality evidence).

**School performance**

*Compared with methylphenidate alone* Methylphenidate plus multimodal psychological treatment (including parent training and counselling, social-skills training, psychological therapy and academic assistance) may be no more effective at improving academic performance scores (Stanford Achievement Tests in total reading, math computation, and listening comprehension) at 1 year in children aged 7–9 years (very low-quality evidence).

*Compared with psychological/behavioural treatments alone* Methylphenidate plus behavioural treatments may be more effective at improving measures of academic behaviours in children aged 5–18 years (very low-quality evidence).

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Methylphenidate plus psychological/behavioural treatment versus control/placebo:**
We found two systematic reviews (search date 1997, [21] and search date 2004 [18] ). The first review ( 3 RCTs, 35 children aged 5–13 years) found that the combination of methylphenidate plus psychological/behavioural treatments significantly improved parent ratings of ADHD compared with placebo or control (Conners Parent's Rating Scale; WMD –7.3, 95% CI –12.3 to –2.4), but not teacher ratings of ADHD (Conners Teacher's Rating Scale; WMD +3.8 points, 95% CI –2.0 points to +9.6 points). [21] The clinical importance of these findings is unclear. [21] The second review incorporated studies from and built on three other systematic reviews, one of which was the identified review with the earlier search date. [20] [21] [34] The review identified three RCTs (93 children aged 5–13 years) but reported that unclear presenting of statistical results and non-reporting of direct statistical comparisons precluded pooling of data. [18] One RCT was identified by both reviews. The remaining two RCTs identified by the second review do not meet *Clinical Evidence* inclusion criteria and are not discussed further.

**Methylphenidate plus psychological/behavioural treatment versus methylphenidate alone:**
We found one RCT (103 children aged 7–9 years who had exhibited symptom improvement in a 5-week open-label trial of methylphenidate) with different outcomes reported in three publications. [66] [67] [68] The RCTs compared methylphenidate plus multimodal psychosocial treatment (including parent training and counselling, social skills training, psychological therapy, and academic assistance) versus methylphenidate plus attention-control treatment and versus methylphenidate alone over a period of 1 year. Outcomes investigated were change in symptoms of ADHD, [66] academic achievement and emotional status, [67] and social functioning. [68] Measures of outcome included the teacher-related and parent-related Conners Rating Scale, the School Situations Questionnaire, DSM-III-R checklist for ADHD, ODD, and conduct disorder symptoms, and Social Skills Rating Scale (SSRS). The RCT assessing social functioning found a significant improvement in parent-rated SSRS with methylphenidate plus attention control at 1 year compared with methylphenidate alone (see table 2, p 24 ). [68] However, no other significant differences between combination treatment and methylphenidate alone in any parent or teacher rating scales at 1 year were reported for the individual outcomes of interest (see table 2, p 24 ; reported as not significant: no P values reported). [66] [67] [68] Follow-up 12 months after treatment found no additional improvements in any outcomes assessed, but any improvement that had occurred during the 1-year treatment period was maintained. [66] [67] [68] The method of randomisation was unclear, and the average dose of methylphenidate given was not reported.

**Methylphenidate plus psychological/behavioural treatment versus psychological/behavioural treatments alone:**
We found two systematic reviews (search dates 2000, [34] and 2004 [18]). The review with the later search date [18] incorporated studies from and built on three other systematic reviews, one of which was the identified review with the earlier search date. [20] [21] [34] The review [18] searched for studies on methylphenidate from 1999 onwards to update the findings of the identified systematic review with the earlier search date. [34] Quality and methodological issues precluded meta-analysis in the second review. The first review (search date 2000, 11 RCTs, 428 children aged 5–18 years) found that methylphenidate plus behavioural treatments significantly improved ADHD behaviours, symptoms, and measures of academic achievement compared with behavioural treatments alone (absolute numbers not reported; reported as significant; P value not reported). [34] The review found no significant difference in social skills or in measures of the relationship between parents and children (absolute numbers not reported; reported as not significant; P value not reported). [34] The second review (search date 2004, 11 RCTs, 457 children aged 5–18 years) identified one RCT subsequent to the search date of the first systematic review. [18] This RCT does not meet *Clinical Evidence* inclusion criteria for this comparison and is not discussed further. The review reported that methylphenidate plus psychological treatment improved symptoms of ADHD compared with psychological treatment alone. The reviews separately assessed one RCT (see comment), [44] which did not meet *Clinical Evidence* inclusion criteria. The RCT found that methylphenidate plus intensive behavioural treatment significantly improved three out of five measures of ADHD core symptoms, one out of three measures of aggression/oppositional behaviour, one out of three measures of anxiety depression, and one out of three measures of academic achievement, compared with intensive behavioural treatment alone. [44]

**Harms:**

**Methylphenidate plus psychological/behavioural treatment versus control/placebo:**
The systematic reviews gave no information on adverse effects (see harms of methylphenidate, p 6). [21] [18]

**Methylphenidate plus psychological/behavioural treatment versus methylphenidate alone:**
The RCTs gave no information on adverse effects (see harms of methylphenidate, p 6). [68] [66] [67]

**Methylphenidate plus psychological/behavioural treatment versus psychological/behavioural treatments alone:**
The systematic reviews gave no information on adverse effects (see harms of methylphenidate, p 6). [21] [18]

**Comment:**

The MTA Cooperative Group Multimodal Treatment Study RCT [44] is the largest and most methodologically rigorous study of ADHD treatments, with high standards for reporting and follow-up of nearly all children. [47] The results of a secondary analysis of this RCT [45] suggest that children with ADHD and comorbid anxiety respond equally well to medication management or intensive behavioural treatment; [46] but secondary analysis indicated that combined medication management plus intensive behavioural treatment was better than medication management alone. [46] Results of a 3-year follow-up study found no differences between treatment groups in any outcomes (based on results from 84% of the children initially participating in the study), [69] which seemed to be attributable to changes within each group when families and individuals were free to choose their own treatments. The proportion of those in behavioural management taking medication increased (14% to 45%), whereas the proportion of those in combination treatment decreased (from 91% to 71%). The study suggests that there is an age-related decline in ADHD symptoms; but changes in medication use and management intensity or other factors affect longer-term outcome of treatment. A secondary analysis identified three subgroups after analysis of different trajectories. [70] One subgroup (34%) showed an initial small improvement followed by gradual improvement over time, the second subgroup (52%) showed an initial large improvement that was maintained for 3 years (over-representation of cases treated with the medical algorithm), and the third subgroup (14%) showed an initial large improvement followed by subsequent deterioration (this group was identified as having high initial symptom scores and baseline aggression, lower IQs, lower social skills, and other risk factors).

## OPTION DEXAMFETAMINE SULPHATE PLUS PSYCHOLOGICAL TREATMENT New

**Symptom severity**
*Compared with psychological treatments* Slow-release dexamfetamine plus psychological treatment may be more effective at improving rating scales (including the hyperactivity index of the Conners Teacher's Rating Scale) in children aged 6–12 years (low-quality evidence).

**Note**

We found no clinically important results about the effects of dexamfetamine sulphate plus psychological treatment versus placebo.

**For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 29 .**

**Benefits:**

**Dexamfetamine sulphate plus psychological treatments versus placebo:**
We found one systematic review (search date 2004, 1 RCT, 34 children aged 4–6 years) comparing dexamfetamine versus psychological treatments. [18] The review incorporated studies from and built on the two identified systematic reviews and another review with the same search date. [20] [21] [34] The review searched for studies on dexamfetamine from 1997 onwards. The RCT identified by the review did not meet *Clinical Evidence* inclusion criteria and is not discussed further. [18]

**Dexamfetamine sulphate plus psychological treatments versus psychological treatments alone:**
We found one systematic review (search date 2004, 4 RCTs, 138 children aged 4–12 years) comparing dexamfetamine plus psychological treatments versus psychological treatments alone. [18] The review incorporated studies from and built on the two identified systematic reviews and another review with the same search date. [20] [21] [34] The review searched for studies on dexamfetamine from 1997 onwards. Inconsistent reporting of outcomes precluded pooling of data. Three RCTs identified by the review did not meet *Clinical Evidence* inclusion criteria and are not discussed further. The fourth RCT identified by the review (crossover design, 35 children aged 6–12 years) found a significant improvement on two rating scales (including the hyperactivity index of the Conners Teacher's Rating Scale) with slow-release formulation of dexamfetamine plus psychological treatment compared with placebo plus psychological treatment (absolute numbers not reported; P less than 0.001). [71]

**Harms:**

**Dexamfetamine sulphate plus psychological treatments versus placebo:**
The review gave no information on adverse effects for this specific comparison (see harms of dexamfetamine, p 6 ). [18]

**Dexamfetamine sulphate plus psychological treatments versus psychological treatments alone:**
The RCT gave no information on adverse effects (see harms of dexamfetamine, p 6 ). [71]

**Comment:**

None.

## GLOSSARY

**Anxiety disorder** A range of conditions with features including apprehension, motor tension, and autonomic overactivity.
**Behavioural treatment** Treatment using insights from learning theory to achieve specific changes in behaviour. It is usually highly structured. It can be used with either children with attention deficit hyperactivity disorder or their parents/carers.
**Cognitive training** Brief structured treatment aimed at changing dysfunctional beliefs.
**Conduct disorder** Conduct disorders include a repetitive pattern of antisocial, aggressive, or defiant conduct that violate age appropriate social expectations. [2]
**Conners Teacher's Rating Scales** Widely used rating scales for assessment of symptoms of attention deficit hyperactivity disorder used extensively in both clinical work and epidemiological studies. There are parent and teacher questionnaires containing 10 items that can be used for children aged 3–17 years.
**Core symptoms** Inattention, hyperactivity, and impulsivity are commonly known as the core symptoms of attention deficit hyperactivity disorder. [6]
**Depressive disorder** Characterised by persistent low mood, loss of interest and enjoyment, and reduced energy.
**Oppositional defiant disorder** The presence of markedly defiant, disobedient, provocative behaviour, but without the severely dissocial or aggressive acts seen in conduct disorder. [2]
**Psychological/behavioural treatments** Includes any of the following methods: contingency management methods (e.g. behaviour modification); cognitive behavioural therapy; individual psychotherapy; parent training or education; teacher training and education; parent and family counselling/therapy; social skills training; and electroencephalogram, biofeedback, or relaxation treatment.
**ADHD-RS (ADHD Rating Scale)** an 18-point rating scale based on the 18 DSM-IV diagnostic criteria, which include a subjective assessment of inattention, hyperactivity, and impulsivity.
**Low-quality evidence** 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.
**Moderate-quality evidence** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**School Situations Questionnaire** A teacher-completed questionnaire that measures the pervasiveness of child behaviour problems across 12 school situations. [72]
**Very low-quality evidence** Any estimate of effect is very uncertain.

## SUBSTANTIVE CHANGES

**Modafinil** One RCT added; [52] benefits and harms data added; categorised as Likely to be beneficial. The RCT found that, compared with placebo, once-daily modafinil 300 mg and modafinil 200/100 mg (divided dose) improved symptoms of ADHD at 4 weeks (assessed using various scales). The RCT found no significant difference in changes in ADHD symptoms between modafinil 100/200 mg and placebo on any assessment scale.

**Bupropion** Two RCTs (three publications) added; [54] [56] [55] benefits and harms data enhanced; categorised as Unknown effectiveness. Both RCTs found that bupropion improved symptoms of ADHD at 28 days compared with placebo. [54] [56] [55] However, absolute numbers were not available for all comparisons and the second RCT was small in size. [56] [55]

**Omega-3 polyunsaturated fatty acid compounds** One systematic review [57] and one RCT added; [58] benefits and harms data added; categorised as Unknown effectiveness. The review [57] identified one RCT of sufficient quality that assessed the effects of taking food supplemented with omega-3 polyunsaturated fatty acid-rich fish oil compared with eating placebo foods containing olive oil. [58] The RCT found no significant difference in severity of symptoms of ADHD between groups at 4 months.

**Homeopathy** One systematic review [61] and two RCTs added; [62] [63] benefits and harms data added; categorised as Unknown effectiveness. One RCT identified by the review found that homeopathic treatment improved symptoms of ADHD at 12 weeks compared with placebo (mean difference between groups in Conners Global Index score at 12 weeks. [62] The second RCT identified by the review found no significant difference at 18 weeks in improvement in ADHD symptoms between homeopathic remedies and placebo. [63]

**Dexamfetamine sulphate plus psychological treatment** One systematic review [18] and one RCT added; [71] benefits and harms data added; categorised as Unknown effectiveness. The review identified no RCTs of sufficient quality comparing dexamfetamine plus psychological treatment versus placebo. One RCT identified by the review found that slow-release formulation of dexamfetamine plus psychological treatment improved symptoms of ADHD compared with placebo plus psychological treatment. [71]

**Atomoxetine** Two systematic reviews [18] [28] and two RCTs added; [19] [29] benefits and harms data enhanced; categorisation unchanged (Likely to be beneficial). One review and one RCT found that atomoxetine improved symptoms of ADHD compared with placebo. [18] [19] The second review identified no RCTs that met our inclusion criteria. [28] The second RCT found no significant difference between atomoxetine and methylphenidate in response rate at 8 weeks. [29]

**Dexamfetamine sulphate** One systematic review added; [18] benefits and harms data enhanced; categorisation unchanged (Likely to be beneficial). The review found that, for medium-dose dexamfetamine (10–20 mg/day), results for hyperactivity varied with assessment scale used, but that high-dose dexamfetamine (more than 20 mg/day) seemed to improve hyperactivity compared with placebo.

**Methylphenidate** One systematic review [18] and six RCTs added; [38] [39] [40] [41] [42] [29] benefits and harms data enhanced; categorisation unchanged (Likely to be beneficial). The review found variable results on the effects of methylphenidate on the symptoms of ADHD compared with placebo. [18] One RCT found that methylphenidate improved severity of ADHD symptoms at 16 weeks compared with placebo. [38] Two RCTs found that transdermal methylphenidate improved symptoms of ADHD compared with placebo at 12 hours. [41] [42] One subsequent RCT found that both extended-release and immediate-release formulations of methylphenidate improved symptoms of ADHD compared with placebo. [39] One RCT found improvements in attention at 12 hours and in attempts at and correct completion of mathematical problems at 8 hours for extended- and modified-release formulations of methylphenidate compared with placebo. [40] One RCT comparing atomoxetine versus methylphenidate found no significant difference between treatments in response rate at 8 weeks. [29]

**Methylphenidate plus psychological/behavioural treatment** One systematic review added; [18] benefits data enhanced; categorisation unchanged (Likely to be beneficial). The review reported that methylphenidate plus psychological treatment improved symptoms of ADHD compared with psychological treatment alone.

**Clonidine** One RCT added; [38] benefits and harms data enhanced; categorisation changed (from Unknown effectiveness to Likely to be beneficial). The RCT found that clonidine improved severity of ADHD symptoms at 16 weeks compared with placebo. [38] The RCT found no significant difference in change of severity of ADHD symptoms between clonidine alone and methylphenidate alone.

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**TABLE 1** **Placebo-controlled RCTs of atomoxetine (see text, p 3 ).** [19] [22] [23] [24] [25]

| Ref | Intervention and population | Mean difference (95% CI) in ADHD-RS score between treatment and placebo |
|---|---|---|
| [22] | 0.5, 1.2, 1.8 mg/kg ATX twice daily *v* placebo<br>Duration: 8 weeks, 297 children and adolescents aged 8–18 years | –4.1 (–9.0 to +0.8) with 0.5 mg/kg *v* –7.8 (–11.6 to –4.0) with 1.2 mg/kg *v* –7.7 (–11.6 to –3.8) with 1.8 mg/kg |
| [23] | ATX 1.5 mg/kg twice daily *v* placebo<br>Duration: 12 weeks, 147 children and adolescents aged 7–13 years | –10.1 (–14.5 to –5.7) |
| [23] | ATX 1.5 mg/kg twice daily *v* placebo<br>Duration: 12 weeks, 147 children and adolescents aged 7–13 years | –8.5 (–13.0 to –4.0) |
| [24] | ATX 1.0 mg/kg once daily *v* placebo<br>Duration: 6 weeks, 171 children and adolescents aged 6–16 years | –7.8 (–11.2 to –4.4) |
| [25] | ATX 0.8–1.2 mg/kg/day once daily *v* placebo<br>Duration: 8 weeks, 197 children and adolescents aged 6–12 years | –9.7 (–13.8 to –5.9) |
| [19] | ATX 0.8-1.8 mg/kg/day once daily *v* placebo<br>Duration: 7 weeks, 153 children and adolescents aged 8–12 years<br>Ratio of randomisation was 2:1 (ATX: placebo)<br>Mean dose of ATX at study end of 1.33 mg/kg/day | *Mean change in Teacher-rated ADHD-RS-IV (change from baseline):* –14.5 with ATX *v* –7.2 with placebo; Mean difference, –7.3, 95% CI –10.8 to –2.8; P = 0.001<br>*Mean change in clinician-rated CGI severity score (change from baseline):* –1.5 with ATX *v* –0.7 with placebo; Mean difference –0.8, 95% CI –1.1 to –0.3; P = 0.001<br>*Mean change in Conners Parent Rating Scale-Revised ADHD index (change from baseline):* –12.1 with ATX *v* –4.1 with placebo; Mean difference –8.0, 95% CI –11.4 to –4.4; P less than 0.001<br>*Mean change in Academic Performance Rating Scale (change from baseline):* +4.8 with ATX *v* +2.2 with placebo; Mean difference –2.6, 95% CI –0.6 to +6.5; P = 0.106 |

ADHD-RS, Attention Deficit Hyperactivity Disorder Rating Scale; ATX, atomoxetine.

**TABLE 2** **RCTs of methylphenidate: effects as assessed by various symptom scales (see text, p 6 ).**

| Ref | Intervention | | Outcome | |
|---|---|---|---|---|
| [34] | MPH *v* placebo 13 RCTs | | **Core symptoms score:** | |
| | | *Study author (year)* | *MPH (mean) v placebo (mean)* | *SMD (95% CI)* |
| | | Brown (1988) | 17.33 *v* 24.50 | –2.09 (–3.17 to –1.01) |
| | | McBride (1988) | 9.56 *v* 16.42 | –1.06 (–1.42 to –0.69) |
| | | Rapport (1989) | 6.53 *v* 13.27 | –1.26 (–1.72 to –0.81) |
| | | Fischer (1991) | 8.40 *v* 13.70 | –0.76 (–0.98 to –0.53) |
| | | Fitzpatrick (1992) | 7.30 *v* 13.60 | –0.85 (–1.51 to –0.18) |
| | | DuPaul (1993) | 7.16 *v* 15.84 | –1.70 (–2.29 to –1.12) |
| | | Klorman (1994) | 6.50 *v* 14.00 | –1.45 (–1.80 to –1.09) |
| | | Buitelaar (1996) | 18.00 *v* 22.00 | –0.59 (–1.47 to +0.29) |
| | | Lufi (1997) | 30.85 *v* 32.60 | –0.12 (–0.74 to +0.50) |
| | | Hoeppner (1997) | 8.20 *v* 13.54 | –0.68 (–1.08 to –0.28) |
| | | Manos (1999) | 56.12 *v* 64.38 | –0.60 (–1.03 to –0.16) |
| | | Zeiner (1999) | 8.83 *v* 14.69 | –0.92 (–1.40 to –0.43) |
| | | Pliszka (2000) | 12.80 *v* 15.40 | –0.32 (–0.96 to +0.32) |
| | MPH *v* dexamphetamine 3 RCTs | | **Core symptoms score:** | |
| | | *Study author (year)* | *MPH (mean) v dexamphetamine (mean)* | *SMD (95% CI)* |
| | | Arnold (1978) | 73.55 *v* 70.26 | 0.53 (0.01 to 1.06) |
| | | Efron (1997) | 56.14 *v* 58.76 | –0.25 (–0.50 to 0) |
| | | Pelham (1990) | 2.30 *v* 1.70 | +0.34 (–0.25 to +0.94) |
| | MPH *v* TCAs 1 study | | **Core symptoms score:** | |
| | | *Study author (year)* | *MPH (mean) v TCAs (mean)* | *SMD (95% CI)* |
| | | Quinn (1975) | 8.30 *v* 8.07 | +0.05 (–0.41 to +0.50) |
| | MPH *v* psychological/behavioural treatments 2 RCTs | | **Conners Teacher's Rating Scale score:** | |
| | | *Study author (year)* | *MPH (mean) v psychological/behavioural treatments (mean)* | *SMD (95% CI)* |
| | | Brown (1985) | 15.0 *v* 15.7 | –0.22 (–1.10 to +0.66) |
| | | Klein (1997) | 1.2 *v* 2.10 | –0.93 (–1.48 to –0.39) |

| Ref | Intervention | | Outcome | |
|---|---|---|---|---|
| [18] (we have reported RCTs identified 2000–2004) | MPH (more than 30 mg/day) *v* placebo | Wolraich (2001) [73] | **Mean SNAP-IV hyperactivity/impulsivity (teacher-rated) score:** 0.93 with MPH *v* 1.57 with placebo | Mean difference –1.26 (–1.44 to –1.08) |
| | | | **Mean SNAP-IV hyperactivity/impulsivity (parent-rated) score:** 1.10 with MPH *v* 1.83 with placebo | Mean difference –0.58 (–0.73 to –0.43) |
| | ER-MPH (20–40 mg/day) *v* placebo | Wolraich (2001) [73] | **Mean SNAP-IV hyperactivity/impulsivity (teacher-rated) score:** 0.96 with ER-MPH *v* 1.57 with placebo | Mean difference –1.21 (–1.40 to –1.02) |
| | | | **Mean SNAP-IV hyperactivity/impulsivity (parent-rated) score:** 1.11 with ER-MPH *v* 1.83 with placebo | Mean difference –0.75 (–0.89 to –0.61) |
| [35] | IR-MPH 3 times/day *v* ER-MPH once daily *v* placebo | | **Inattention/overactivity score (at end of study):** | |
| | | | 5.00 with MPH 3 times daily *v* 4.69 with MPH once daily *v* 10.34 with placebo | Difference between placebo and active treatments reported as significant, P value not reported |
| | | | **Oppositional/defiant score (at end of study):** | |
| | | | 1.99 with MPH 3 times daily *v* 1.81 with MPH once daily *v* 5.09 with placebo | Difference between placebo and active treatments reported as significant, P value not reported |
| | | | **Abbreviated Conners score (at end of study):** | |
| | | | 7.94 with MPH 3 times/day *v* 7.82 with MPH once daily *v* 16.40 with placebo | Difference between placebo and active treatments reported as significant, P value not reported |
| [36] | MPH 10, 20, or 30 mg 3 times daily *v* placebo | | **Inattention/overactivity score:**<br>2.7 with 10 mg *v* 1.7 with 20 mg *v* 1.2 with 30 mg *v* 4.4 with placebo | |
| | | | **Oppositional/defiant score:**<br>1.3 with 10 mg *v* 0.9 with 20 mg *v* 0.6 with 30 mg *v* 2.5 with placebo<br>P less than 0.05 for all doses *v* placebo for all outcomes | |
| [38] | MPH *v* placebo | | Treatment effect 3.3, 95% CI -0.2 to 6.8, P = 0.02 (positive value for treatment effect indicates a beneficial effect) | |
| [37] | MPH 0.3 mg/kg 2 times/day *v* placebo | | **Inattention/overactivity score:**<br>0.5 with MPH *v* 1.9 with placebo<br>1.8 with MPH *v* 3.5 with placebo<br>P less than 0.001 for MPH *v* placebo for both outcomes | |
| | | | **Oppositional/defiant score:**<br>0.5 with MPH *v* 1.9 with placebo P less than 0.01 | |
| [39] | IR-MPH 2 times daily *v* ER-MPH once daily *v* placebo | | **Inattention/overactivity score of teacher-related Conners Rating Scale at 3 weeks (mean score adjusted for baseline; baseline scores not reported):** | |
| | | | 4.5 with ER-MPH *v* 7.7 with placebo | AR −3.1, 95% CI −4.26 to −2.00, P less than 0.001 |
| | | | 4.3 with IR-MPH *v* 7.7 with placebo | AR −3.4, 95% CI −4.53 to −2.26, P less than 0.001 |
| | | | **Inattention/overactivity score of parent-related Conners Rating Scale at 3 weeks (mean score adjusted for baseline; baseline scores not reported):** | |
| | | | 6.4 with ER-MPH *v* 8.1 with placebo | AR −1.7, 95% CI −2.78 to −0.54, P = 0.004 |

| Ref | Intervention | Outcome | |
|---|---|---|---|
| | | 5.1 with IR-MPH *v* 8.1 with placebo | AR −3.0, 95% CI −4.09 to −1.85, P = 0.004, P less than 0.001 |
| | | **Oppositional/defiant score of teacher-related Conners Rating Scale at 3 weeks (mean score adjusted for baseline; baseline scores not reported):** | |
| | | 2.1 with ER-MPH *v* 4.6 with placebo | AR −2.5, 95% CI −3.47 to −1.48, P less than 0.001 |
| | | 2.3 with IR-MPH *v* 4.6 with placebo | AR −2.3, 95% CI −3.36 to −1.38, P less than 0.001 |
| | | **Oppositional/defiant score of parent-related Conners Rating Scale at 3 weeks (mean score adjusted for baseline; baseline scores not reported):** | |
| | | 5.3 with ER-MPH *v* 6.9 with placebo | AR −1.6, 95% CI −2.74 to −0.44, P = 0.007 |
| | | 4.6 with IR-MPH *v* 6.9 with placebo | AR −2.3, 95% CI −3.46 to −1.16, P less than 0.001 |
| [40] | ER-MPH 20 mg *v* ER-MPH 40 mg *v* MR-MPH 18 mg *v* MR-MPH 36 mg *v* placebo | **SKAMP rating of attention (change from predose to 12 hours after treatment):** | |
| | | From 1.99 to 2.13 with ER-MPH 20 mg *v* from 2.18 to 1.89 with ER-MPH 40 mg *v* from 2.01 to 1.73 with MR-EPH 18 mg *v* from 2.05 to 1.53 with MR-MPH 36 mg *v* from 1.59 to 2.22 with placebo | P less than 0.05 for all methylphenidate formulations versus placebo |
| | | **Mathematical testing — attempted (change from predose to 8 hours):** | |
| | | From 69.6 to 78.0 with ER-MPH 20 mg *v* from 68.0 to 98.3 with ER-MPH 40 mg *v* from 65.8 to 77.7 with MR-EPH 18 mg *v* from 60.8 to 78.6 with MR-MPH 36 mg *v* from 65.7 to 57.9 with placebo | P less than 0.05 for all methylphenidate formulations versus placebo |
| | | **Mathematical testing — correct (change from predose to 8 hours):** | |
| | | From 63.1 to 68.6 with ER-MPH 20 mg *v* from 59.1 to 84.4 with ER-MPH 40 mg *v* from 60.5 to 68.9 with MR-EPH 18 mg *v* from 53.8 to 69.7 with MR-MPH 36 mg *v* from 59.1 to 48.0 with placebo | P less than 0.05 for all methylphenidate formulations versus placebo |
| [42] | MPH *v* placebo | **SKAMP rating of deportment at 12 hours:**; | |
| | | Data presented graphically | P less than 0.01 for methylphenidate versus placebo |
| [41] | MPH 0.45 mg/h *v* MPH 0.9 mg/h *v* MPH 1.8 mg/h *v* placebo | **Abbreviated teacher-related Conners Rating (mean score; baseline scores not reported):** | |
| | | 3.9 with MPH 0.45 mg/h *v* 2.3 with MPH 0.9 mg/h *v* 2.8 with MPH 1.8 mg/h *v* 5.7 with placebo | P less than 0.05 for all doses of methylphenidate *v* placebo |
| | | **Abbreviated parent-related Conners Rating Scale (mean score adjusted for baseline; baseline scores not reported):** | |
| | | 3.4 with MPH 0.45 mg/h *v* 2.7 with MPH 0.9 mg/h *v* 2.3 with MPH 1.8 mg/h *v* 5.5 with placebo | P less than 0.05 for all doses of methylphenidate *v* placebo |
| | | **Abbreviated counsellor-related Conners Rating Scale (mean score adjusted for baseline; baseline scores not reported):** | |
| | | 5.8 with MPH 0.45 mg/h *v* 5.2 with MPH 0.9 mg/h *v* 5.1 with MPH 1.8 mg/h *v* 6.9 with placebo | P less than 0.05 for MPH 0.9 mg/h and MPH 1.8 mg/h *v* placebo: P value for MPH 0.45 mg/h *v* placebo not reported |

| Ref | Intervention | Outcome |
|---|---|---|
| [66] [67] [68] | MPH plus multimodal psychosocial treatment *v* MPH plus attention control treatment *v* MPH alone | **ADHD symptoms:** [66]<br>Between-group differences on all scales reported to be not significant (unless P value reported), P values not reported<br>*for MPH plus attention control *v* methylphenidate alone: P less than 0.05<br>*change in CPRS at 1 year:*<br>from 1.9 to 1.2 with MPH plus multimodal psychosocial treatment *v* from 1.9 to 1.0 with MPH plus attention control treatment *v* from 1.9 to 1.1 with MPH alone<br>*change in HSQ (situations component) at 1 year :*<br>from 13.1 to 11.3 with MPH plus multimodal psychosocial treatment *v* from 12.6 to 11.1 with MPH plus attention-control treatment *v* from 12.9 to 9.9 with MPH alone<br>*change in HSQ (severity component) at 1 year:*<br>from 3.8 to 2.4 with MPH plus multimodal psychosocial treatment *v* from 3.7 to 2.4 with MPH plus attention control treatment *v* from 3.6 to 2.3 with MPH alone<br>*change in CTRS (hyperactivity) at 1 year:*<br>from 2.5 to 0.9 with MPH plus multimodal psychosocial treatment *v* from 2.3 to 0.9 with MPH plus attention control treatment *v* from 2.4 to 1.2 with MPH alone<br>*change in SSQ (situations component) at 1 year:*<br>from 9.5 to 6.1 with MPH plus multimodal psychosocial treatment *v* from 10.1 to 5.5 with MPH plus attention-control treatment *v* from 9.2 to 4.6 with MPH alone<br>*change in HSQ (severity component) at 1 year:*<br>from 5.5 to 2.2 with MPH plus multimodal psychosocial treatment *v* from 5.7 to 1.7 with MPH plus attention-control treatment *v* from 5.5 to 1.7 with MPH alone<br>**Academic achievement:** [67]<br>*change in Stanford Achievement Test (total reading) scored at 1 year:*<br>from 576.6 to 623.3 with MPH plus multimodal psychosocial treatment *v* from 555.3 to 609.5 with MPH plus attention-control treatment *v* from 572.0 to 625.3 with MPH alone<br>*change in Stanford Achievement Test (math computation) scored at 1 year:*<br>from 568.9 to 623.6 with MPH plus multimodal psychosocial treatment *v* from 556.7 to 615.7 with MPH plus attention-control treatment *v* from 567.2 to 617.2 with MPH alone<br>*change in Stanford Achievement Test (listening comprehension) scored at 1 year:*<br>from 591.9 to 611.4 with MPH plus multimodal psychosocial treatment *v* from 575.6 to 616.7 with MPH plus attention-control treatment *v* from 598.7 to 630.7 with MPH alone<br>**Social functioning:** [68]<br>*change in parent-rated SSRS at 1 year:*<br>from 75.7 to 87.5 with MPH plus multimodal psychosocial treatment *v* from 75.7 to 88.0 with MPH plus attention-control treatment *v* from 78.1 to 78.5 with MPH alone*<br>*change in child-rated SSRS at 1 year:*<br>from 96.3 to 108.0 with MPH plus multimodal psychosocial treatment *v* from 103.7 to 111.9 with MPH plus attention-control treatment *v* from 102.2 to 111.6 with MPH alone |

ER, extended release; IR, immediate release; MPH, methylphenidate; MR, modified release; Ref, reference; SMD, standardised mean difference; TCA, tricyclic antidepressant.

**TABLE 3** **The number of RCTs reporting significant adverse effects with methylphenidate versus placebo (see text, p 6 ). [22] Published with permission ©NICE 2000.**

| Adverse effect | Number of trials reporting adverse effect |
|---|---|
| Anorexia or appetite disturbance | 7/12 (58%) |
| Motor tics | 1/2 (50%) |
| Irritability | 2/9 (22%) |
| Sleep disorder | 4/20 (20%) |
| Abdominal pain | 2/10 (20%) |
| Headache | 2/10 (20%) |

**TABLE 4** **RCTs assessing the effects of modafinil (see text, p ? ).**

| Reference | Population | Intervention/comparison | Significance |
|---|---|---|---|
| [52] | 248 children, aged 6–13 years | Modafinil 300 mg *v* placebo | ADHD-RS-IV (teacher-related) total score: mean changes from baseline represented graphically; P = 0.006 |
| | Modafinil 300 mg, 50 children; modafinil 100/200 mg, 48 children; modafinil 200/100 mg, 49 children; modafinil 200/200 mg, 50 children; placebo, 51 children | | ADHD-RS-IV (clinician-related): mean changes from baseline represented graphically; P = 0.006 |
| | | | Conners ADHD/DSM-IV scale (total score): mean changes from baseline represented graphically; P = 0.01 |
| | | Modafinil 100/200 mg *v* placebo | Conners ADHD/DSM-IV scale (total score): mean changes from baseline represented graphically; P = 0.01<br>No significant difference compared with placebo on teacher- or clinician-related version ADHD-RS-IV, mean changes from baseline presented graphically: reported as not significant; P values not reported |
| | | Modafinil 200/100 mg *v* placebo | ADHD-RS-IV (teacher-related) total score: mean changes from baseline represented graphically; P = 0.03 |
| | | | ADHD-RS-IV (clinician-related): mean changes from baseline represented graphically; reported as not significant; P value not reported |
| | | | Conners ADHD rating scale ADHD index: mean changes from baseline represented graphically reported as not significant; P value not reported |
| | | Modafinil 200/200 mg *v* placebo | ADHD-RS-IV (teacher-related): mean changes from baseline represented graphically; reported as not significant; P value not reported |
| | | | ADHD-RS-IV (clinician-related): mean changes from baseline represented graphically; P = 0.01 |

**TABLE** GRADE evaluation of interventions for ADHD in children and adolescents

| Important outcomes | Symptom severity, school performance, adverse effects | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of studies (participants)** | **Outcome** | **Comparison** | **Type of evidence** | **Quality** | **Consistency** | **Directness** | **Effect size** | **GRADE** | **Comment** |
| What are the effects of pharmacological treatments for ADHD in children? | | | | | | | | | |
| 6 (1381) [22] [23] [24] [25] [26] [19] | Symptom severity | Atomoxetine *v* placebo | 4 | −1 | 0 | 0 | 0 | Moderate | Quality point deducted for incomplete reporting of results |
| 1 (153) [19] [27] | School performance | Atomoxetine *v* placebo | 4 | −2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |
| 1 (326) [29] | Symptom severity | Atomoxetine *v* methylphenidate | 4 | 0 | 0 | −1 | 0 | Moderate | Directness point deducted for suboptimal dosing of comparator |
| 12 (336) [21] [6] [18] | Symptom severity | Dexamfetamine sulphate *v* placebo | 4 | −2 | −1 | 0 | 0 | Very low | Quality points deducted for incomplete reporting of results and for methodological problems in one SR. Consistency point deducted for assessing outcomes using different assessment scales and for different treatment durations |
| at least 13 RCTs (at least 1177 people) [18] [34] [35] [36] [37] [38] [40] [39] [41] [42] | Symptom severity | Methylphenidate *v* placebo | 4 | −2 | 0 | 0 | 0 | Low | Quality points deducted for incomplete reporting of results and for methodological issues |
| 1 (53) [40] | School performance | Methylphenidate *v* placebo | 4 | −2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |
| 4 (224) [34] | Symptom severity | Methylphenidate *v* dexamfetamine sulphate | 4 | −1 | −2 | 0 | 0 | Very low | Quality point deducted for incomplete and poor reporting of results. Consistency point deducted for heterogeneity between RCTs and for conflicting results |
| 13 (at least 753 people) [44] [47] [18] | Symptom severity | Methylphenidate *v* psychological/behavioural treatment | 4 | −3 | 0 | −2 | 0 | Very low | Quality points deducted for incomplete, poor reporting of results, and for methodological flaws. Directness points deducted for no direct measurements of response and for excluding participant responses |
| 7 (279) [38] [49] [50] | Symptom severity | Clonidine *v* placebo | 4 | −3 | 0 | −1 | 0 | Very low | Quality points deducted for incomplete reporting of results and methodological weaknesses. Directness point deducted for inclusion of non-placebo trials |
| 1 (136) [38] | Symptom severity | Clonidine *v* methylphenidate | 4 | −2 | 0 | −1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of other interventions |
| 2 (203) [51] [38] | Symptom severity | Clonidine plus methylphenidate/dexamfetamine *v* methylphenidate/dexamfetamine | 4 | −2 | 0 | −1 | 0 | Very low | Quality points deducted for incomplete reporting of results. Directness point deducted for inclusion of other interventions |
| 1 (136) [38] | Symptom severity | Clonidine *v* clonidine plus methylphenidate | 4 | −2 | 0 | −1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of other interventions |
| 1 (248) [52] | Symptom severity | Modafinil *v* placebo | 4 | −1 | −1 | 0 | 0 | Low | Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results |

| Important outcomes | Symptom severity, school performance, adverse effects | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of studies (participants)** | **Outcome** | **Comparison** | **Type of evidence** | **Quality** | **Consistency** | **Directness** | **Effect size** | **GRADE** | **Comment** |
| 2 RCTs in 3 publications (140) [54] [55] [56] | Symptom severity | Bupropion *v* placebo | 4 | −2 | −1 | 0 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results |
| 1 (40) [57] [58] | Symptom severity | Omega-3 *v* placebo | 4 | −2 | 0 | −1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness points deducted for inclusion of children with suspected but not confirmed ADHD |
| 2 (105) [62] [63] | Symptom severity | Homeopathy *v* placebo | 4 | −2 | −1 | −1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for variation in treatments used |
| What are the effects of psychological treatments for ADHD in children? | | | | | | | | | |
| 3 (366) [21] [64] [44] | Symptom severity | Psychological/behavioural treatment *v* standard care | 4 | −2 | 0 | −1 | 0 | Very low | Quality points deducted for incomplete reporting of results and for methodological weaknesses. Directness points deducted for uncertainty about clinical relevance of outcomes measured in 2 RCTs and for different disease severities |
| 1 (24) [65] | Symptom severity | Parent plus teacher training *v* parent training alone | 4 | −3 | −1 | 0 | 0 | Very low | Quality points deducted for sparse data, incomplete reporting of results and for uncertainty about blinding and randomisation. Consistency point deducted for lack of consistent beneficial effects |
| What are the effects of combination treatments for ADHD in children? | | | | | | | | | |
| 3 (35) [21] | Symptom severity | Methylphenidate plus psychological/behavioural treatment *v* control | 4 | −2 | −1 | −1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for lack of consistent beneficial effects. Directness point deducted for uncertainty about clinical relevance of outcomes assessed |
| 1 RCT in 3 publications (103) [66] [67] [68] | Symptom severity | Methylphenidate plus psychological/behavioural treatment *v* methylphenidate alone | 4 | −3 | −1 | −1 | 0 | Very low | Quality points deducted for sparse data, incomplete reporting of results and uncertainty about method of randomisation. Consistency point deducted for lack of consistent beneficial effects. Directness point deducted for not reporting doses used |
| 1 RCT in 3 publications (103) [66] [67] [68] | School performance | Methylphenidate plus psychological/behavioural treatment *v* methylphenidate alone | 4 | −3 | −1 | −1 | 0 | Very low | Quality points deducted for sparse data, incomplete reporting of results and uncertainty about method of randomisation. Directness point deducted for not reporting doses used |
| At least 11 RCTs (at least 428 children) [34] [44] | Symptom severity | Methylphenidate plus psychological/behavioural treatment *v* psychological/behavioural treatments alone | 4 | −2 | 0 | −1 | 0 | Very low | Quality points deducted for incomplete reporting of results and for no direct comparison between groups. Consistency point deducted for lack of consistent beneficial effects |
| At least 11 RCTs (at least 428 children) [34] [44] | School performance | Methylphenidate plus psychological/behavioural treatment *v* psychological/behavioural treatments alone | 4 | −2 | −1 | −1 | 0 | Very low | Quality points deducted for incomplete reporting of results and for no direct comparison between groups. Consistency point deducted for lack of consistent beneficial effects |

| Important outcomes | Symptom severity, school performance, adverse effects | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of studies (participants)** | **Outcome** | **Comparison** | **Type of evidence** | **Quality** | **Consistency** | **Directness** | **Effect size** | **GRADE** | **Comment** |
| 1 (35) [71] | Symptom severity | Dexamfetamine sulphate plus psychological treatments *v* psychological treatments alone | 4 | −2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio