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% to 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 August 2009 (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 70 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

Key points

- Core symptoms of ADHD are inattention, hyperactivity, and impulsiveness, although other conditions frequently co-exist 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 that must be evident in more than one setting.

  Formal diagnostic criteria are most applicable to boys aged 6 to 12 years, and most research data relate to this group. Pre-school 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 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 omega-3 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 to 12 years, and most research data relate to this group. Pre-school 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 to 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] For pre-school children there is still a paucity of evidence of efficacy and safety of medical treatments and role of behavioural interventions. [5]

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% to 5%, [1] but other estimates vary from 1.7% to 16.0%. [6] [7] 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 co-exists 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%). [8] 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's syndrome in 7%. [9]

AETIOLOGY/ RISK FACTORS

The underlying causes of ADHD are not known. [8] There is some evidence that there is a genetic component: twin studies suggest an average heritability of 76%. [10] However, a high heritability does not exclude the important role of environment acting through gene–environment interactions. [11] [12] [13] [14] [15] 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. [16]

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. [7] 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, [17] and of antisocial personality disorder. [18]

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 **Symptom severity:** 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 August 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2009, Embase 1980 to August 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 2 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). 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 of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals 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. In the first question on the effects of pharmacological treatments, we searched for the effects of listed pharmacological treatments alone. However, we also searched for three combinations of drugs, namely, methylphenidate plus clonidine, dexamfetamine sulphate plus clonidine, and atomoxetine plus methylphenidate, and reported any studies that we found. Where we have included a systematic review, we have only reported comparisons for which the identified review found RCTs. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we also did a specific harms search and searched for prospective/retrospective cohort studies reporting on atomoxetine and growth. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US FDA and the UK MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 32). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

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

OPTION ATOMOXETINE

Symptom severity
Compared with placebo Atomoxetine seems to be more effective than placebo at improving ADHD symptoms as rated by clinician, parent, or teacher in children and adolescents (moderate-quality evidence).

Compared with methylphenidate We don't know whether atomoxetine is more effective than methylphenidate at improving response rates in children and adolescents aged 6 to 16 years (low-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 to 12 years as assessed using the Academic Performance Rating Scale (low-quality evidence).

Note
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 32 .

Benefits: **Atomoxetine versus placebo:**
We found one systematic review [19] and 4 subsequent RCTs (see comment). [20] [21] [22] [23]

The systematic review (search date 1985–2006, 9 RCTs, 1826 people) included RCTs that compared atomoxetine versus placebo in children and adolescents, included RCTs using any dose of atomoxetine (single doses or different doses) versus placebo, reported validated outcome measures, and reported data on all on adverse effects, withdrawals, or dropouts. [19] The review found 7 RCTs in people with ADHD with or without oppositional defiant disorder, and all but one RCT was double blinded. The quality of included RCTs was assessed by Jadad score ([score 0–5] Jadad score 5, 3 RCTs; score 4, 3 RCTs; score 3, 1 RCT). The review calculated SMDs because different dosages of medications were used in the RCTs, which might have altered the observed variability of the treatment response. The review found that atomoxetine significantly improved symptoms as measured by ADHD Rating Scale-IV (ADHD-RS-IV) total score compared with placebo (7 RCTs, 1615 people; SMD –0.64, 95% CI –0.76 to –0.52; P <0.05). It also found that, compared with placebo, atomoxetine significantly improved symptoms as rated by teacher (CTRS-R:S ADHD index: 3 RCTs, 738 people; SMD –0.34, 95% CI –0.63 to –0.05; P <0.05; significant heterogeneity among RCTs), parent (CPRS-R:S ADHD index, 6 RCTs, 1695 people; SMD –0.62, 95% CI –0.84 to –0.38; P <0.05; significant heterogeneity among RCTs), and clinician (CGI-S, 5 RCTs, 1165 people; SMD –0.64, 95% CI –0.83 to –0.45; P <0.05). [19] The review did not comment on the reasons for heterogeneity in two of the analyses. It found that atomoxetine significantly improved quality of life scores compared with placebo (CHQ psychological summary score, 3 RCTs, 863 people; SMD 0.47, 95% CI 0.25 to 0.69; P <0.05).

The review also included two further RCTs in which all included people had ADHD and oppositional defiant disorder. A subgroup analysis of these RCTs found similar results to the overall analysis with atomoxetine being significantly superior for symptoms to placebo (2 RCTs, 213 people: ADHD-RS-IV total score; SMD –0.7, 95% CI –0.95 to –0.44; CPRS-R:S ADHD index, –0.75, 95% CI –1.0 to –0.48; CPRS-R:S oppositional, –0.42, 95% CI –0.70 to –0.14; CGI-S, –0.60, 95% CI –0.85 to –0.35). The review reported that high baseline ADHD symptoms were associated with greater reduction of symptoms, whereas male sex, oppositional defiant disorder, and ADHD hyperactive/impulsive subtype were associated with smaller reductions. [19]

One included RCT (153 children aged 8–12 years) found no significant difference in academic productivity at 7 weeks between atomoxetine and placebo, as assessed using the Academic Performance Rating Scale (mean change from baseline: +4.8 with atomoxetine *v* +2.2 with placebo; mean difference –2.6, 95% CI –0.6 to +6.5; P = 0.106). [24] An extension of this RCT assessed the effects of atomoxetine on associated functional impairments at school. [25] 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 CHQ; mean change in score from baseline: 7.1 with atomoxetine *v* 3.7 with placebo; P = 0.073). The RCTs included in the review used varying doses of atomoxetine (from low to high doses; see comment). The review analysed for publication bias and reported that it found evidence of publication bias using one test (Eggar's test, P = 0.04), but not another (Begg's test, P = 0.28).

The first subsequent RCT (226 children aged 6–12 years, DSM-IV criteria, comorbid oppositional defiant disorder) found no significant difference between atomoxetine and placebo in oppositional defiant disorder symptoms as assessed by the investigator-rated ODD subscale of the SNAP-IV scale at 8 weeks (SNAP-IV ODD total score, mean change: –3.7 with atomoxetine *v* –2.9 with placebo; P = 0.25). [20] However, it found that atomoxetine was significantly better than placebo at improving general ADHD symptoms at 8 weeks (CGI-I, P = 0.037; CGI-S, P = 0.013; CGI-P total, P = 0.02). [20]

The second subsequent RCT (176 children and adolescents aged 8–17 years, DSM-IV criteria for ADHD and comorbid anxiety disorder) compared atomoxetine versus placebo for 12 weeks and reported on primary outcomes of parent-rated symptoms (as measured by ADHD-RS-IV-PI) and the Paediatric Anxiety Rating Scale (PARS). [21] However, in its primary analysis the RCT excluded 43/176 (24%) participants from the analysis as they had responded to a 2-week placebo lead-in period, and these results were based on 113/176 (64%) people initially randomised. We have not reported these results further. The RCT reported that it had performed an analysis on all randomised participants. It found that atomoxetine significantly improved outcomes compared with placebo (ADHD-RS-IV-PI total score, mean change from baseline: –9.0 with atomoxetine *v* –0.7 with placebo; P <0.001; PARS, mean change from baseline: –4.5 with atomoxetine *v* –2.4 with placebo; P <0.01). The total number of people in this analysis was not reported, and results were based on the last observation carried forward (further details not reported). [21]

The third subsequent three-armed RCT found that atomoxetine (222 people) significantly increased the proportion of people with response compared with placebo (74 people) at 6 weeks (response defined as a decrease from baseline of 40% or more in the total investigator administered and rated ADHD Rating Scale score: 45% with atomoxetine *v* 24% with placebo; P = 0.003; absolute numbers not reported). [22] It also found that atomoxetine significantly improved other outcome

measures compared with placebo at 6 weeks (measured by difference in mean change: CGI ADHD severity index, 282 people in analysis; CPRS, 274 people in analysis; CHQ psychological summary score, 257 people in analysis; all reported as significant difference; P value not reported). [22] For full description of this RCT, please see atomoxetine versus methylphenidate below.

The fourth subsequent RCT (142 adolescents aged 12–18 years, DSM-IV criteria, comorbid major depressive disorder [Children's Depression Rating Scale Revised score; CDRS-R score 40 or more at every visit before randomisation]) compared atomoxetine versus placebo over a 9-week treatment period. [23] The RCT found that atomoxetine significantly improved overall symptoms (as measured by ADHD-RS-IV-Parent:Inv — investigator rated and scored) compared with placebo at 9 weeks (141 people, change from baseline: –13.3 with atomoxetine *v* –5.1 with placebo; P <0.001). The RCT found that atomoxetine significantly increased global treatment response (defined as CGI-I score or CGI-S score of 1 or 2 at the end of treatment) when measured by the CGI-I score but not the CGI-S score (responders measured by CGI-I score: 33/69 [48%] with atomoxetine *v* 12/67 [18%] with placebo; P <0.001; responders measured by CGI-S score: 13/69 [19%] with atomoxetine *v* 7/67 [10%] with placebo; P = 0.23). However, it found no significant difference between groups in depression scores (as measured by CDRS-R) at 9 weeks (141 people, change from baseline: –14.8 with atomoxetine *v* –12.8 with placebo; P = 0.34). [23]

Atomoxetine versus methylphenidate:
We found one systematic review (search date 2005, 4 RCTs, 1481 people) comparing atomoxetine versus methylphenidate [26] and two subsequent RCTs. [27] [22] 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.

The first subsequent RCT (330 children aged 6–16 years) compared atomoxetine once daily (dose 0.8–1.8 mg/kg) versus methylphenidate twice daily (0.2–0.6 mg/kg) over 8 weeks. [27] 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, [28] and caution should be taken when interpreting data from trials in which the dosing of one arm may be suboptimal.

The second subsequent three-armed RCT (516 children and adolescents aged 6–16 years, DSM-IV criteria) compared atomoxetine (222 people), osmotically released methylphenidate (220 people), and placebo (74 people), and reported response after 6 weeks of treatment. [22] We have only reported the atomoxetine versus methylphenidate comparison here. The RCT reported on treatment response (defined as a decrease from baseline of 40% or more in the total investigator administered and rated ADHD Rating Scale score). The RCT found that osmotically released methylphenidate significantly increased the proportion of people with response compared with atomoxetine at 6 weeks (response: 56% with osmotically released methylphenidate *v* 45% with atomoxetine; P = 0.02, 95% CI 2% to 21%; absolute numbers not reported). [22] It also found that osmotically released methylphenidate significantly improved other outcome measures compared with atomoxetine (measured by difference in mean change: CGI ADHD severity index, 424 people, P = 0.004; CPRS, 403 people, P = 0.003; CHQ psychological summary score, 386 people, P = 0.02). [22]

Atomoxetine plus methylphenidate:
We found no systematic review or RCTs.

Harms:

Atomoxetine versus placebo:
The review found that for more commonly occurring adverse effects (affecting at least 2% of people), compared with placebo, atomoxetine significantly increased the proportion of people with appetite decrease, somnolence, abdominal pain, vomiting, dyspepsia, and dizziness (appetite decrease: 111/717 [15%] with atomoxetine *v* 20/484 [4%] with placebo; P <0.05; NNH 8.8, 95% CI 6.9 to 12.3; somnolence: 71/717 [10%] with atomoxetine *v* 23/484 [5%] with placebo; P <0.05; NNH 19.4, 95% CI 12.4 to 44.3; abdominal pain: 103/717 [14%] with atomoxetine *v* 48/484 [10%] with placebo; P <0.05; NNH 22.5, 95% CI 12.3 to 133.5; vomiting: 58/717 [8%] with atomoxetine *v* 23/484 [5%] with placebo; P <0.05; NNH 30.0, 95% CI 16.4 to 171.0; dyspepsia: 16/717 [2%] with atomoxetine *v* 1/484 [0.2%] with placebo; P <0.05; NNH 49.4, 95% CI 31.5 to 115.0; dizziness: 15/717 [2%] with atomoxetine *v* 1/484 [0.2%] with placebo; P <0.05; NNH 53.0, 95% CI 33.2 to 131.2). [19]

The first subsequent RCT found that compared with placebo, atomoxetine significantly increased the risk of decreased appetite (P <0.001), nausea (P = 0.033), and fatigue (P = 0.02). [20] It also found that rates of diastolic blood pressure increase were significantly higher with atomoxetine (increase in 5 mm Hg to above the 95th percentile: 9.7% with atomoxetine *v* 1.6% with placebo;

P = 0.042) as were rates of decrease in weight (decrease of 3.5% from baseline weight: 39% with atomoxetine *v* 2.9% with placebo; P < 0.001). [20] The second subsequent RCT found that atomoxetine significantly increased the proportion of people with decreased appetite compared with placebo (11/77 [14%] with atomoxetine *v* 3/80 [4%] with placebo; P = 0.25). [21] The third subsequent three-armed RCT is reported in the atomoxetine versus methylphenidate section below. [22] The fourth subsequent RCT reported that for adverse effects occurring in 5% or more of people during the 9-week treatment period, that atomoxetine significantly increased the proportion of people with nausea and decreased appetite compared with placebo (nausea: 16/72 [22%] with atomoxetine *v* 3/69 [4%] with placebo; P = 0.002; decreased appetite: 9/72 [13%] with atomoxetine *v* 0/69 [0%] with placebo; P = 0.003). [23] The RCT reported that rates of treatment-emergent mania did not differ significantly between groups at 9 weeks (0% with atomoxetine *v* 1.5% with placebo; P >0.99).

A drug safety alert has been issued on the risk of psychotic or manic symptoms associated with atomoxetine (http://www.mhra.gov.uk). Other advice has highlighted that seizures are a potential risk with atomoxetine, and that there have been reports of QT interval prolongation (http://www.mhra.gov.uk).

Atomoxetine versus methylphenidate:
The first subsequent 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). [27] It also found significantly higher rates of somnolence and dizziness with atomoxetine (somnolence: 43/164 [26%] with atomoxetine *v* 6/166 [4%] with methylphenidate; P <0.001; dizziness: 25/164 [15%] with atomoxetine *v* 12/166 [7%] with methylphenidate; P = 0.024). 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). [27] The second subsequent RCT found that atomoxetine significantly increased the proportion of people with somnolence compared with methylphenidate, but significantly reduced the proportion of people with any report of insomnia (somnolence: 14/221 [6%] with atomoxetine *v* 4/219 [2%] with methylphenidate, P <0.05; insomnia: 15/221 [7%] with atomoxetine *v* 29/219 [13%] with methylphenidate; P <0.05). [22]

Atomoxetine plus methylphenidate:
We found no RCTs.

Atomoxetine and suicide:
We found one meta-analysis of suicide-related behaviour events in paediatric participants treated with atomoxetine. [29] The meta-analysis reported no search strategy, but included data from 14 paediatric clinical trials conducted by one pharmaceutical company, of which 7 had been published and the remaining data was posted on the pharmaceutical company's website. Twelve trials compared atomoxetine versus placebo, and 5 trials compared atomoxetine versus methylphenidate. The meta-analysis did not report on whether all the trials were randomised. The study reported that no participant committed suicide. The study reported that the frequency of suicidal ideation was 0.4% (5/1357) with atomoxetine compared with 0% (0/851) in the placebo-treated groups (Mantel-Haenszel risk ratio 2.92, 95% CI 0.63 to 13.6; P = 0.172; Mantel-Haenszel incidence difference 0.46, 95% CI 0.09 to 0.83; P = 0.016). It found that the frequency of suicidal behaviour or ideation was 0.4% (6/1357) with atomoxetine compared with 0% (0/851) with placebo (Mantel-Haenszel risk ratio 2.49, 95% CI 0.64 to 9.78; P = 0.190; Mantel-Haenszel incidence difference 0.52, 95% CI 0.12 to 0.91; P = 0.010). The frequency of suicide-related events did not differ between the atomoxetine and methylphenidate-treated groups (no suicidal behaviour events with either treatment; suicidal ideation, 1 participant (0.2%) with atomoxetine *v* 1 participant (0.2%) with methylphenidate; suicidal behaviour or ideation, P = 0.65 or P = 0.55 depending on method of calculation; no absolute numbers reported; P value not reported for suicidal behaviour events or suicidal ideation analysis). The review reported that the number needed to harm (NNH) in paediatric patients for an additional suicide-related event was 227 compared with a number needed to treat (NNT) of 5 to achieve remission of ADHD (defined as 40% reduction in ADHD-RS total score; CI not reported; absolute data not reported). The authors of the meta-analysis note that the post-hoc retrospective analysis had limitations in ascertaining intent. [29]

Regulatory authorities in both the UK (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:
We found one meta-analysis (no search strategy reported), which reported long-term outcomes using pooled data from 6- and 7-year-olds enrolled in clinical trials of 2 or more years' duration. [30] It included 272 children identified in 13 RCTs (7 RCTs double-blinded; 6 RCTs open-label) and reported on growth and weight changes from baseline for the atomoxetine group. It calculated expected growth based on standard growth charts and baseline percentile at time points up to 24 months. It reported baseline to end-point weight and height percentile decreases against predicted values at 24 months (weight: 270 children, –9.3%; height: 251 children, –8.3%). It reported that growth rate differences occurred mostly within the first 18 months, after which the growth velocity seemed to increase. [30]

One review examining the effect of atomoxetine on growth suggests that treatment with atomoxetine for 2 years has a minimal effect on height and weight. [31] Data were pooled from 13 multicentre trials conducted at 90 sites. The review assessed data for patients who had completed 2 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 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 long-term effect on growth after 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.

One further report (1312 people, aged 6–17 years) of the previous study followed up the growth of children with ADHD treated with atomoxetine for up to 5 years. [32] It included data from previous clinical trials of atomoxetine (13 studies, 6 placebo-controlled, 7 open-label) who entered open-label treatment. However, it only included 61 participants who had reached a 5-year time point. Of the remaining participants, 384 (29%) had not reached the 5-year time point and 926 (70%) had discontinued. It calculated expected growth and weight at up to 5 years. For weight, a significant difference was seen with respect to expected weight at 1 month from baseline (P <0.001) with a maximum shortfall seen at 15 months (P <0.001) with no significant difference from expected weight at 36 months (P = 0.12) or 60 months (P = 0.75; results presented graphically). For height, a significant difference was seen with respect to expected height at 12 months from baseline (P = 0.022) with a maximum shortfall seen at 18 months (P <0.001) with no significant difference from expected height at 24 months (P = 0.09) or 60 months (P = 0.51; results presented graphically). The study reported that those participants in the top quartile for body-mass index or weight at baseline, and those in the third quartile for height, showed 5-year decreases from expected values. [32] It should be noted that these results are based on small numbers of participants.

Comment:

Atomoxetine versus placebo:
We found one earlier systematic review (search date 2004) [33] comparing atomoxetine versus placebo, which included 4 RCTs included in the later review. [19] The review assessed the effects of atomoxetine based on categorisation of low/medium dose (<1.5 mg/kg/day) and high dose (at least 1.5 mg/kg/day) of atomoxetine. However, this review did not pool data because of quality and methodological issues (heterogeneity) of included RCTs. [33]

Clinical guide:
Atomoxetine is metabolised by the CYP2D6 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). [34] 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. [34]

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 to 18 years (very low-quality evidence).

For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 32 .

Benefits:

Dexamfetamine (dexamphetamine) sulphate versus placebo:
We found three systematic reviews. [7] [33] [35] 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). [35] 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). [7] 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. [7] 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. [33] The third review (search date 2004) [33] built on three other systematic reviews, one of which was the first review reported above. [35] [36] [37] 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 14 .

Dexamfetamine sulphate versus methylphenidate:
See benefits of methylphenidate, p 9 .

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. [33] The review built on three other systematic reviews. [36] [35] [37] 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. [33] [35] The second review found that dexamfetamine increased anorexia and appetite disturbance in three RCTs (data not pooled; absolute numbers not reported). [7] 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). [33]

The FDA issued an alert that sudden death had been reported with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems (www.fda.gov).

Dexamfetamine sulphate versus dexamfetamine sulphate plus clonidine:
See harms of clonidine, p 14 .

Dexamfetamine sulphate versus methylphenidate:
See harms of methylphenidate, p 9 .

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 and adolescents aged 5 to 18 years (low-quality evidence).

Compared with atomoxetine We don't know whether methylphenidate is more effective than atomoxetine at improving response rates in children and adolescents aged 6 to 16 years (low-quality evidence).

Compared with dexamfetamine We don't know whether methylphenidate is more effective at improving ADHD symptoms in children and adolescents aged 5 to 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 to 14 years with comorbid chronic tic disorders (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 to 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 than methylphenidate alone at improving patient-rated SSRS (Social Skills Rating Scale) at 1 year, but not other parent or teacher rating scales in children aged 7 to 9 years (very low-quality evidence).

Methylphenidate plus clonidine compared with clonidine alone We don't know whether clonidine plus methylphenidate is more effective than clonidine alone at improving symptoms of ADHD in children and adolescents (very low-quality evidence).

Compared with modafinil We don't know whether methylphenidate is more effective than modafinil at improving symptoms of ADHD (as measured by ADHD Rating Scale-IV) in children and adolescents aged 6 to 15 years (low-quality evidence).

School performance
Compared with placebo We don't know whether methylphenidate is more effective than placebo at improving school performance as we found insufficient evidence (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 than methylphenidate alone at improving academic performance scores (Stanford Achievement Tests in total reading, math computation, and listening comprehension) at 1 year in children aged 7 to 9 years (very low-quality evidence).

Note
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 32 .

Benefits: We found two systematic reviews (search date 2000 [37] and 2004 [33]) 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 4 additional [38] [39] [40] [41] and 6 subsequent RCTs [42] [43] [44] [45] [46] [22] examining effects of methylphenidate on symptoms of ADHD. We found one further subsequent RCT, which reported on co-existing oppositional defiant disorder/conduct disorder (ODD/CD) symptoms as well as ADHD symptoms, [47] and one report on harms. [48] 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 to 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. [36] [35] [37] 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. [49]

Methylphenidate versus placebo:
The first systematic review (search date 2000) found 13 rigorously selected short-term RCTs (1177 children and adolescents aged 5–18 years). [37] 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 <0.05) compared with placebo. This improvement was non-significant in three small RCTs (99 children) (see table 1, p 27 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 9 RCTs subsequent to the search date of the first review. [33] The review reported 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 1, p 27). 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 1, p 27). [38] 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 1, p 27). [39] [40] 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. [41] 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 1, p 27).

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 1, p 27). [42]

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 mg and 40 mg] and modified-release tablets [methylphenidate 18 mg and 36 mg]) versus each other and placebo. [43] 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 1, p 27). 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.

The third, fourth, and fifth subsequent RCTs compared a methylphenidate transdermal system of administration versus placebo. [44] [45] [46] In the third subsequent RCT (crossover design, 80 children aged 6–12 years), children with ADHD first entered an open-label dose-optimisation phase, which took place over 5 weeks. [45] 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 1, p 27). Patches were applied in the morning and worn for 9 hours. The method of randomisation in this RCT was unclear, and pre-crossover results were not reported.

The fourth subsequent 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. [44] 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 1, p 27). Counsellor-rated

improvement of symptoms was significant for methylphenidate 0.9 mg/h 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.

The fifth subsequent RCT (children aged 6–12 years, DSM-IV-TR criteria) compared methylphenidate transdermal system patch (100 children), osmotic release oral system methylphenidate capsules (94 children), and placebo (88 children). [46] Participants entered a 5-week lead-in dose optimisation phase and a 2-week dose maintenance phase. The RCT found that both methylphenidate preparations significantly improved symptoms measured by the ADHD Rating Scale-IV (ADHD-RS-IV) mean total score (the primary outcome measure) compared with placebo, and also found a significant improvement with both methylphenidate preparations compared with placebo when assessed by other secondary symptom measures (see table 1, p 27). [46]

The sixth subsequent three-armed RCT found that osmotically released methylphenidate significantly increased the proportion of people with response compared with placebo at 6 weeks (response defined as a decrease from baseline of 40% or more in the total investigator administered and rated ADHD Rating Scale score) and also significantly improved other outcome measures compared with placebo (see table 1, p 27). [22] For a full description of this RCT, see methylphenidate versus atomoxetine in option on atomoxetine, p 3 .

The seventh subsequent RCT examined the effects of methylphenidate on co-existing ODD/CD symptoms as well as ADHD symptoms. [47] The RCT (85 people with ADHD and ODD/CD, 6–16 years, DSM-IV criteria) reported on ADHD symptoms as measured by the ADHD Symptom Checklist (FBB-HKS) and ODD/CD symptoms as measured by the ODD/CD Symptom Checklist (FBB-SSV). The RCT found that methylphenidate significantly improved ODD/CD symptoms compared with placebo over 4 weeks measured by FBB-HKS total score (see table 1, p 27). The RCT did not report a between-group analysis for ADHD Symptom Checklist (FBB-HKS) scores. [47]

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

Methylphenidate alone versus dexamfetamine (dexamphetamine) sulphate alone:
The first systematic review [37] identified 4 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. [33] 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 1, p 27). 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 14 .

Methylphenidate alone versus methylphenidate plus clonidine:
See benefits of clonidine, p 14 .

Methylphenidate plus clonidine versus clonidine alone:
See benefits of clonidine, p 14 .

Methylphenidate versus modafinil:
See benefits of modafinil, p 16 .

Methylphenidate versus psychological/behavioural treatment:
We found two systematic reviews (search dates 2000 [37] and 2004 [33]). Two RCTs were identified by both reviews. The first review identified 4 RCTs comparing methylphenidate versus psychological/behavioural treatment. Two of the RCTs reported Conners' Teacher's Rating Scale scores (see table 1, p 27). 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 4 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). [50] 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. [50] Subsequent secondary analysis suggested that 56% of children taking a pharmacological treatment improved compared with 34% in the intensive behavioural management group. [51] There is also a suggestion that children with comorbid behaviour problems (ODD/CD) 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. [52] 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. [53] 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 pre-school children.

The second review identified 6 RCTs (174 children aged 5–13 years) comparing methylphenidate versus psychological/behavioural treatment. [33] Inconsistent reporting of outcomes precluded pooling of data. The remaining 4 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 21 .

Harms:

The first systematic review did not combine results on harms because of heterogeneity and incomplete data reporting. [37] 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. [33] 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 2, p 31). The second review found no differences in adverse effects between low-dose methylphenidate and placebo. [33] 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 [38] and one subsequent RCT [42] reported similar adverse effects. Two other additional RCTs gave no information on adverse effects. [39] [40] 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 [21.6%] with methylphenidate *v* 7/32 [21.9%] with placebo; significance not assessed; P value not reported). [41] 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). [41]

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). [43] Two 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). [44] [45] No severe adverse effects were reported in either RCT. Another subsequent RCT reported that the most commonly reported adverse effects were decreased appetite, nausea, vomiting, and insomnia, but did not report a statistical analysis between groups. [46] Overall, participants with at least one adverse effect during the study were 74/98 (75%) children with methylphenidate transdermal system, 63/91 (69%) children with osmotic release oral system, and 49/85 (57%) children with placebo (statistical analysis between groups not reported). The seventh subsequent RCT did not report on harms. [47] We found no good evidence about the effects of methylphenidate on growth rates in children. We found one report of a study in pre-school children (183 children, aged 3–5 years), which compared methylphenidate versus placebo and included a 1-week open-label lead-in period (183 children), a 5-week placebo-controlled double-blind titration phase (165 children), a 5-week double-blind parallel phase (114 children), and 10 months of open-label maintenance (140 children), and reported on adverse effects. [48] It found that overall, 21/183 (11%) children discontinued study treatment because of adverse effects. During the titration phase,

the RCT reported that decreased appetite, trouble sleeping, and weight loss were significantly increased with methylphenidate compared with placebo (appetite, P <0.003; trouble sleeping, P <0.03; weight loss, P <0.05; results presented graphically). The RCT reported that overall, 30% of parents spontaneously reported moderate to severe adverse effects in all study phases after baseline, the most common being crabby/irritability, emotional outbursts, difficulty falling asleep, repetitive behaviours and thoughts, and decreased appetite, which differed from the pattern seen in school-age children. [48]

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

Methylphenidate alone versus dexamfetamine alone:
Of the 4 RCTs identified by the first systematic review, [37] 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. [33]

Methylphenidate alone versus clonidine alone:
See harms of clonidine, p 14 .

Methylphenidate alone versus methylphenidate plus clonidine:
See harms of clonidine, p 14 .

Methylphenidate plus clonidine versus clonidine alone:
See harms of clonidine, p 14 .

Methylphenidate versus modafinil:
See harms of modafinil, p 16 .

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). [50] 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 one) could have resulted from non-medication factors.

Methylphenidate alone versus methylphenidate plus psychological/behavioural treatment:
See harms of methylphenidate plus psychological treatment, p 21 .

Comment:

Systematic review of RCTs and other controlled studies examining wider cognitive effects of immediate-release methylphenidate is beset with methodological difficulty. We found one overview of placebo-controlled studies, which reported that 63.5% of the studies reported improvement in some aspect of cognitive function such as planning/flexibility, attention/vigilance, and inhibitory control. [54]

Clinical guide:
A review of methylphenidate and its isomers has suggested that the largest transdermal system patch size of 37.5 cm² delivers approximately 30 mg of methylphenidate through the skin over a 9-hour period. [55] 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. [34] 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, [34] as 0.2 for methylphenidate, 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 to 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 to 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 to 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 We don't know whether clonidine alone is more effective than clonidine plus methylphenidate at improving symptoms of ADHD in children and adolescents (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 32 .

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). [57] The review identified 11 studies, 8 of which were RCTs. The review carried out a meta-analysis of 6 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 6 RCTs included in the meta-analysis of clonidine versus placebo was a comparison of clonidine versus methylphenidate [58] 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 [58] 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. [58] 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. [41] The RCT found that clonidine (average dose of 0.25 mg/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/day) versus methylphenidate (average dose of 25.7 mg/day). [41] 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. [59] 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 <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). [59] 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 <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. [41] 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/day) versus clonidine plus methylphenidate (average dose of 25.7 mg/day). [41] 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. We found one further RCT (122 children, aged 7–12 years, DSM-IV criteria), which compared clonidine alone, methylphenidate alone, methylphenidate plus clonidine, and placebo. [60] Children with a family history of a long QT syndrome, cardiomyopathy, or premature sudden death were excluded. Although the RCT performed an intention-to-treat (ITT) analysis using the last observation carried forward (LOCF), only 10/30 (33%) participants with placebo and 18/29 (62%) participants with methylphenidate alone completed the trial. We have not reported these results further. Of those assigned to the clonidine or clonidine plus methylphenidate groups, 50/63 (79%) completed the trial. The RCT found that clonidine plus methylphenidate significantly improved outcome measured by Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher) score at 16 weeks compared with clonidine alone (mean change –3.4, 95% CI –6.4 to –0.4; P = 0.03; ITT analysis with LOCF adjusted for treatment centre and baseline values). However, the RCT did not report an analysis for clonidine plus methylphenidate versus clonidine alone for outcomes measured by Conners' ASQ-Parent score. It found no significant difference between clonidine and clonidine plus methylphenidate for outcomes measured by Children's Global Assessment Scale (CGAS; mean change –0.9, 95% CI –6.2 to +4.4; P = 0.73; ITT analysis with LOCF adjusted for treatment centre and baseline values). [60]

Harms:

Clonidine versus placebo:
The systematic review [57] 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, 9 of 10 studies found sedation in children; 6 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). [41] 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). [41]

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). [41]

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). [59] It found that clonidine significantly increased drowsiness and dizziness compared with placebo during treatment (rates not reported; P <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 (8/37 [22%] with clonidine alone *v* 6/33 [18%] with clonidine plus methylphenidate: significance not assessed: P value not reported). [41]

Clonidine alone versus clonidine plus methylphenidate:
The first 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). [41] The second RCT reported that one severe adverse event occurred in the clonidine plus methylphenidate group. [60] This was a long QTc interval/left ventricular hypertrophy observed on the ECG, but with no clinical symptoms and a normal echocardiogram. There was a further follow-up report of this RCT on harms. [61] The RCT that compared clonidine alone, methylphenidate alone, methylphenidate plus clonidine, and placebo, did not report statistical analysis between individual groups, but combined groups in the analysis. The RCT found that clonidine (clonidine-alone group and clonidine plus methylphenidate groups combined) significantly increased the proportion of people with bradycardia (heart rate less than 60 bpm), nervousness, somnolence, and fatigue compared with no clonidine (placebo group and methylphenidate-only groups combined) at 16 weeks (bradycardia: 17.5% with clonidine groups *v* 3.4% without clonidine groups; P = 0.02; nervousness: 31.7% with clonidine groups *v* 15.3% without clonidine groups; P = 0.04; somnolence: 38.1% with clonidine groups *v* 6.8% without clonidine groups; P <0.0001; lethargy: 19.0% with clonidine groups *v* 5.1% without clonidine groups; P = 0.03). [61]

Comment: None.

OPTION MODAFINIL

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).

Compared with methylphenidate We don't know whether modafinil is more effective than methylphenidate at improving symptoms of ADHD (as measured by ADHD-RS-IV) in children and adolescents aged 6 to 15 years (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 adverse effects, hypersensitivity reactions, and serious rashes.

For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 32 .

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-IV [ADHD-RS-IV]). [62] 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 3, p 31). For modafinil 200/100 mg and 100/200 mg (divided dose), results varied with the different assessments scales used (see table 3, p 31). For modafinil 400 mg (divided dose), results varied with the different assessment scales used (see table 3, p 31). [62] All children were given three tablets in the morning and two tablets 4 to 5 hours later. [62] 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 4 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 4 arms (probability of assignment to the 4 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.

Modafinil versus methylphenidate:
We found one RCT (60 children, aged 6–15 years, DSM-IV-TR diagnostic criteria), which compared modafinil versus methylphenidate for 6 weeks. [56] Outcomes were assessed using the Parent and Teacher ADHD-RS-IV. The RCT found no significant difference between groups in outcomes at 6 weeks although both groups improved from baseline (baseline to end point; Parent ADHD-RS-IV: –24.4 with modafinil *v* –22.7 with methylphenidate; P = 0.94; Teacher ADHD-RS-IV: –20.5 with modafinil *v* –21.3 with methylphenidate; P = 0.87; results presented graphically). The RCT did not report on other outcome measures. [56]

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 <0.05). [62] 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).

Modafinil versus methylphenidate:
The RCT found that decreased appetite and difficulty falling asleep occurred significantly more frequently with methylphenidate compared with modafinil (decreased appetite: 18 events with modafinil *v* 26 events with methylphenidate; P = 0.03; difficulty falling asleep: 2 events with modafinil *v* 8 events with methylphenidate; P = 0.05). [56]

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. [34] A drug safety alert has been issued on psychiatric adverse effects, hypersensitivity reactions, and serious rashes associated with modafinil. [63]

OPTION BUPROPION

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 to 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 32 .

Benefits:

Bupropion versus placebo:
We found no systematic review. We found two RCTs (3 publications) comparing bupropion 3 mg/kg/day to 6 mg/kg/day (dosage schedule dependent on weight of child) versus placebo. [64] [65] [66] The first RCT (109 children aged 6–12 years) compared bupropion (72 children) versus placebo (37 children) for 28 days. [64] It found that bupropion significantly improved symptoms of aggression (last observation carried forward; absolute numbers not reported; P <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 <0.01). However, this difference was not significant when analysed using the last observation carried forward (absolute numbers not reported; P <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 (CGI) 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). [65] [66] 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). [65]

Harms:

Bupropion versus placebo:
The first RCT reported that 4 people withdrew because of skin rash with urticaria associated with bupropion use. [64] 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. [65] [66] High single doses of bupropion (greater than 400 mg) may induce seizures. [34]

The FDA issued an alert in 2009 highlighting the risk of serious neuropsychiatric symptoms, which was based on postmarketing reports including those with a temporal relationship between the use of bupropion and suicidal events and the occurrence of suicidal ideation in people using bupropion as a smoking cessation aid (www.fda.gov). Some of these cases may have been confounded by symptoms typically seen in people who have stopped smoking and are experiencing withdrawal symptoms.

Comment:

None.

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

Symptom severity
Compared with placebo We don't know whether food supplemented with long-chain omega-3 polyunsaturated fatty acids is more effective than foods containing olive oil at improving severity of symptoms of ADHD at 4 months in children aged 6 to 12 years (very low-quality evidence).

For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 32 .

Benefits:

Omega-3 versus placebo:
We found two systematic reviews (search date not reported for either review), [67] [68] which identified one RCT of sufficient quality. [69] The RCT (40 children aged 6–12 years) 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 [DHA] and 700 mg eicosapentaenoic acid a week) compared with eating placebo foods containing olive oil. [69] 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 8 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 reviews [67] [68] and the RCT [69] gave no information on adverse effects.

Comment:

Some RCTs in children with other learning difficulties [70] or developmental coordination disorder, [71] but not ADHD, have reported behavioural improvements with polyunsaturated fatty acid supplements. RCTs in children with ADHD are in progress.

This option only reports on RCTs in which omega 3 has been given as the sole intervention (i.e., without other interventions such as omega 6 or other fatty acids/supplements).

OPTION HOMEOPATHY

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

For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 32 .

Benefits:

Homeopathy versus placebo:
We found one systematic review (search date 2006), which compared the effects of homeopathy on the symptoms of ADHD in children and adolescents. [72] The review included 4 RCTs. One RCT was quasi-randomised (alternate allocation) and we have not reported this further.

The first included crossover RCT (62 children aged 7–15 years, mean age 10 years) used individualised homeopathic medicines, and the children were seen once by the homeopathic physician and the regimen was adjusted by parents at 4-weekly intervals. However, the trial was preceded by a screening phase in which 83 children were given homeopathic medicines, and only those who had improved (50% on Conners' Global Index) were entered into the trial. An indefinite number of follow-ups was allowed at this stage until a successful response was achieved. The 62 children in the RCT then received either the successful therapy or placebo. Pre-crossover results were not reported. [72]

The second included RCT (43 children, mean age 9 years) used individualised homeopathic medicines (using the Bombay or Sankaran methods) without restrictions for a total of 18 weeks, with the option to vary the potency and frequency at 6 weeks and 12 weeks of follow-up. In this RCT, 9 children (5 active group; 4 placebo group) were also taking stimulant medication. [72]

The third included RCT (20 children aged 7–10 years) compared a commercially sold homeopathic combination (including selenium and potassium phosphate) for 8 weeks. There was no clinical consultation as a standard preparation was used. In this RCT, half the participants (10 children) were already taking methylphenidate, and were equally distributed in the two groups. The review found no significant difference between homeopathy and placebo in parent or teacher-rated global scores as measured by Conners' Global Index scores (CGI-P [parent rated]: 2 RCTs, 105 people; mean difference –1.56, 95% CI –3.18 to +0.06; P = 0.059; CGI-T [teacher rated]: 1 RCT, 43 people; SMD +0.41, 95% CI –0.20 to +1.01; P = 0.19). It found no significant difference between groups in core symptoms as measured using the parent-rated ADHD index component of the Conners' Parent Rating Scale Revised Short (CPRS) and Conners' Rating Scale (CRS) scores (ADHD Index [parent rated]: 2 RCTs, 63 people; SMD +0.06, 95% CI –0.43 to +0.56; P = 0.8). [72]

The review noted that significant clinical heterogeneity existed as to how the homeopathic treatment was administered in the three RCTs. The review concluded that there was insufficient evidence to draw robust conclusions about the effectiveness of any particular form of homeopathy from the three small RCTs. [72]

Harms:

Homeopathy versus placebo:
One RCT identified by the review reported that 4 people withdrew from the study (3 from the homeopathy group *v* 1 from the placebo group). [73] 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. [74] The review noted that there was a lack of data collected regarding safety issues. [72]

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 We don't know whether psychological/behavioural treatments (including intensive behavioural treatments for families) are more effective than standard care alone at improving ADHD symptoms in children and adolescents (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 to 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 to 18 years (very low-quality evidence).

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

Compared with psychological/behavioural treatments plus dexamfetamine Psychological treatment alone may be less effective than slow-release dexamfetamine plus psychological treatment at improving rating scales (including the hyperactivity index of the Conners' Teacher's Rating Scale) in children aged 6 to 12 years; however, evidence was weak (low-quality evidence).

School performance
Compared with psychological/behavioural treatments plus methylphenidate Behavioural treatments may be less effective than methylphenidate plus behavioural treatments at improving measures of academic behaviours in children aged 5 to 18 years (very low-quality evidence).

For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 32 .

Benefits:

Psychological/behavioural treatment versus standard care:
We found two systematic reviews. [35] [75] The first systematic review (search date 1997, [35] 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, 95% 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, [75] 1 RCT, 290 children aged 7.0–9.9 years), [75] 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 [50] 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). [50] 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. One subsequent RCT (94 children, aged 4–12 years, DSM-IV criteria) compared behavioural parent training (twelve 120-minute sessions in a group format) plus routine clinical care (including medication where appropriate) versus routine clinical care alone. [76] The RCT found that behavioural parent training plus routine care significantly improved behavioural symptoms and internalising symptoms at 25 weeks, but found no significant difference between groups in ADHD symptoms (behavioural symptoms measured by target behaviours and CBCL externalising: P = 0.017, multivariate analysis; internalising symptoms measured by CBCL internalising: P = 0.42, multivariate analysis; ADHD symptoms measured by ADHD index of the CPRS-R:S: P = 0.161, multivariate analysis). In subgroup analysis, the review found similar effects in children taking, or not taking, existing drug medication. The RCT reported that significantly more children received polypharmaceutical treatment at the end of the intervention in the routine case group compared with the behavioural parent training group (P = 0.026). [76]

Parent plus teacher training versus parent training alone:
We found one small RCT (30 children aged 5–12 years). [77] 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 <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 4 sessions, parents were provided with general information on ADHD, parenting stress, effective communication, and developing children's self-esteem. The next 4 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 9 .

Psychological/behavioural treatment versus dexamfetamine (dexamphetamine):
See benefits of dexamfetamine, p 8 .

Psychological/behavioural treatment versus psychological/behavioural treatment plus methylphenidate:
See benefits of methylphenidate plus psychological/behavioural treatment, p 21 .

Psychological/behavioural treatment versus psychological/behavioural treatment plus dexamfetamine:
See benefits of dexamfetamine plus psychological/behavioural treatment, p 23 .

Harms:

Psychological/behavioural treatment versus standard care:
The systematic reviews [35] [75] and subsequent RCT [76] gave no information on adverse effects.

Parent plus teacher training versus parent training alone:
The RCT gave no information on adverse effects. [77]

Psychological/behavioural treatment versus methylphenidate:
See harms of methylphenidate, p 9 .

Psychological/behavioural treatment versus dexamfetamine:
See harms of dexamfetamine, p 8 .

Psychological/behavioural treatment versus psychological/behavioural treatment plus methylphenidate:
See harms of methylphenidate plus psychological/behavioural treatment, p 21 .

Psychological/behavioural treatment versus psychological/behavioural treatment plus dexamfetamine:
See harms of dexamfetamine plus psychological/behavioural treatment, p 23 .

Comment:

Psychological/behavioural treatment versus standard care:
Children in the trials had different comorbid diagnoses, presentations, and clinical needs. Secondary analysis of one RCT [50] 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). [38] 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 to 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 than methylphenidate alone at improving patient-rated Social Skills Rating Scale (SSRS) at 1 year in children aged 7 to 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 to 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 than methylphenidate alone at improving academic performance scores (Stanford Achievement Tests in total reading, math computation, and listening comprehension) at 1 year in children aged 7 to 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 to 18 years (very low-quality evidence).

For GRADE evaluation of interventions for ADHD in children and adolescents, see table, p 32 .

Benefits:

Methylphenidate plus psychological/behavioural treatment versus control/placebo:
We found two systematic reviews (search date 1997 [35] and search date 2004 [33]). 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). [35] The clinical importance of these findings is unclear. [35] 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. [35] [36] [37] 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. [33] One RCT was identified by both reviews. The remaining two RCTs identified by the second review did 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 shown symptom improvement in a 5-week open-label trial of methylphenidate) with different outcomes reported in three publications. [78] [79] [80] 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, [78] academic achievement and emotional status, [79] and social functioning. [80] Measures of outcome included the teacher-related and parent-related Conners' Rating Scale, the School Situations Questionnaire, DSM-III-R checklist for ADHD, oppositional defiant disorder (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 1, p 27). [80] 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 1, p 27 ; reported as not significant; no P values reported). [78] [79] [80] 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. [78] [79] [80] 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 [37] and 2004 [33]). The review with the later search date [33] incorporated studies from and built on three other systematic reviews, one of which was the identified review with the earlier search date. [35] [36] [37] The review [33] searched for studies on methylphenidate from 1999 onwards to update the findings of the identified systematic review with the earlier search date. [37] 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). [37] 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). [37] 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. [33] 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), [50] 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. [50]

Harms:

Methylphenidate plus psychological/behavioural treatment versus control/placebo:
The systematic reviews gave no information on adverse effects (see harms of methylphenidate, p 9). [35] [33]

Methylphenidate plus psychological/behavioural treatment versus methylphenidate alone:
The RCTs gave no information on adverse effects (see harms of methylphenidate, p 9). [80] [78] [79]

Methylphenidate plus psychological/behavioural treatment versus psychological/behavioural treatments alone:
The systematic reviews gave no information on adverse effects (see harms of methylphenidate, p 9). [35] [33]

Comment: The MTA Cooperative Group Multimodal Treatment Study RCT [50] is the largest and most methodologically rigorous study of ADHD treatments, with high standards for reporting and follow-up of nearly all children. [53] The results of a secondary analysis of this RCT [51] suggest that children with ADHD and comorbid anxiety respond equally well to medication management or intensive behavioural treatment; [52] but secondary analysis indicated that combined medication management plus intensive behavioural treatment was better than medication management alone. [52] 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), [81] 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 (from 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. [82] 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). Further long-term follow-up at 8 years concludes that the type of early intervention does not predict functioning 6 to 8 years later. [83] Rather, that early symptom trajectory regardless of treatment type is prognostic, implying that children with sociodemographic and behavioural advantage, with the best response to any treatment, will have the best long-term prognosis. [83]

OPTION DEXAMFETAMINE SULPHATE PLUS PSYCHOLOGICAL TREATMENT

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 to 12 years; however, evidence was weak (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 32 .

Benefits: **Dexamfetamine (dexamphetamine) 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. [33] The review incorporated studies from and built on the two identified systematic reviews and another review with the same search date. [35] [36] [37] 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. [33]

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. [33] The review incorporated studies from and built on the two identified systematic reviews and another review with the same search date. [36] [35] [37] 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 <0.001). [84]

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 8). [33]

Dexamfetamine sulphate plus psychological treatments versus psychological treatments alone:
The RCT gave no information on adverse effects (see harms of dexamfetamine, p 8). [84]

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.

Core symptoms Inattention, hyperactivity, and impulsivity are commonly known as the core symptoms of attention deficit hyperactivity disorder. [7]

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]

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 to 17 years.

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.

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.

School Situations Questionnaire A teacher-completed questionnaire that measures the pervasiveness of child behaviour problems across 12 school situations. [85]

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Atomoxetine New evidence added. [19] [20] [21] [22] [23] [29] [30] [32] Categorisation unchanged (Likely to be beneficial).

Clonidine New evidence added. [60] [61] Categorisation unchanged (Likely to be beneficial).

Homeopathy New evidence added. [72] Categorisation unchanged (Unknown effectiveness) as there remains insufficient RCT evidence to judge effects of this intervention.

Methylphenidate New evidence added. [22] [46] [47] [48] [54] [56] Categorisation unchanged (Likely to be beneficial).

Methylphenidate plus psychological/behavioural treatment New evidence added. [83] Categorisation unchanged (Likely to be beneficial).

Modafinil New evidence added. [56] Categorisation unchanged (Likely to be beneficial).

Omega-3 polyunsaturated fatty acid compounds (fish oils) New evidence added. [68] Categorisation unchanged (Unknown effectiveness) as there remains insufficient RCT evidence to judge effects of this intervention.

Psychological/behavioural treatment New evidence added. [76] Categorisation unchanged (Unknown effectiveness) as there remains insufficient RCT evidence to judge effects of this intervention.

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TABLE 1 **RCTs of methylphenidate: effects as assessed by various symptom scales (see text, p 9).**

Ref	Intervention			Outcome	
[37]	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* dexamfetamine 3 RCTs		**Core symptoms score:**		
		Study author (year)	*MPH (mean) v dexamfetamine (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)*

Ref	Intervention		Outcome	
		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)
[33] (we have reported RCTs identified 2000–2004)	MPH (more than 30 mg/day) *v* placebo	Wolraich (2001) [86]	**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) [86]	**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)
[38]	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 daily *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
[39]	MPH 10, 20, or 30 mg 3 times daily *v* placebo		**Inattention/overactivity score:** 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: 1.3 with 10 mg *v* 0.9 with 20 mg *v* 0.6 with 30 mg *v* 2.5 with placebo P <0.05 for all doses *v* placebo for all outcomes	
[41]	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)	
[40]	MPH 0.3 mg/kg 2 times/day *v* placebo		**Inattention/overactivity score:** 0.5 with MPH *v* 1.9 with placebo 1.8 with MPH *v* 3.5 with placebo P <0.001 for MPH *v* placebo for both outcomes	
			Oppositional/defiant score: 0.5 with MPH *v* 1.9 with placebo P <0.01	
[42]	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 <0.001
			4.3 with IR-MPH *v* 7.7 with placebo	AR −3.4, 95% CI −4.53 to −2.26; P <0.001

Ref	Intervention	Outcome	
		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
		5.1 with IR-MPH *v* 8.1 with placebo	AR −3.0, 95% CI −4.09 to −1.85; P <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 <0.001
		2.3 with IR-MPH *v* 4.6 with placebo	AR −2.3, 95% CI −3.36 to −1.38; P <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 <0.001
[43]	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 pre-dose 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 <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 <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 <0.05 for all methylphenidate formulations versus placebo
[45]	MPH *v* placebo	**SKAMP rating of deportment at 12 hours:**;	
		Data presented graphically	P <0.01 for methylphenidate versus placebo
[44]	MPH 0.45 mg/hour *v* MPH 0.9 mg/hour *v* MPH 1.8 mg/hour *v* placebo	**Abbreviated teacher-related Conners' Rating (mean score; baseline scores not reported):**	
		3.9 with MPH 0.45 mg/hour *v* 2.3 with MPH 0.9 mg/hour *v* 2.8 with MPH 1.8 mg/hour *v* 5.7 with placebo	P <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/hour *v* 2.7 with MPH 0.9 mg/hour *v* 2.3 with MPH 1.8 mg/hour *v* 5.5 with placebo	P <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/hour *v* 5.2 with MPH 0.9 mg/hour *v* 5.1 with MPH 1.8 mg/hour *v* 6.9 with placebo	P <0.05 for MPH 0.9 mg/hour and MPH 1.8 mg/hour *v* placebo: P value for MPH 0.45 mg/hour *v* placebo not reported

Ref	Intervention	Outcome
[78] [79] [80]	MPH plus multimodal psychosocial treatment *v* MPH plus attention-control treatment *v* MPH alone	**ADHD symptoms:** [78] Between-group differences on all scales reported to be not significant (unless P value reported), P values not reported *for MPH plus attention-control *v* methylphenidate alone: P <0.05 *change in CPRS at 1 year:* 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 *change in HSQ (situations component) at 1 year:* 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 *change in HSQ (severity component) at 1 year:* 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 *change in CTRS (hyperactivity) at 1 year:* 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 *change in SSQ (situations component) at 1 year:* 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 *change in HSQ (severity component) at 1 year:* 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 **Academic achievement:** [79] *change in Stanford Achievement Test (total reading) scored at 1 year:* 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 *change in Stanford Achievement Test (math computation) scored at 1 year:* 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 *change in Stanford Achievement Test (listening comprehension) scored at 1 year:* 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 **Social functioning:** [80] *change in parent-rated SSRS at 1 year:* 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* *change in child-rated SSRS at 1 year:* 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
[46]	MPH transdermal system patch (100 children) *v* osmotic release oral system MPH capsules (94 children) *v* placebo (88 children)	**Symptoms measured by ADHD-RS-IV mean total score:** 270 children, baseline to study end point: MPH transdermal system *v* placebo, difference −13.9, 95% CI −18.1 to −9.7; P <0.001; osmotic release oral system *v* placebo, difference −11.3, 95% CI −15.5 to −7.0; P <0.0001. **Other measures:** 270 children, baseline to study end point: MPH transdermal system *v* placebo, CTRS-R [teacher rated], difference −10.1, 95% CI −15.0 to −5.3; P <0.0001, CPRS-R at 3 p.m. [parent rated], difference −12.4, 95% CI −18.5 to −6.1; P = 0.0001; osmotic release oral system *v* placebo, CTRS-R [teacher rated], difference −12.4, 95% CI −17.3 to −7.5; P <0.0001, CPRS-R at 3 p.m. [parent rated], difference −7.0, 95% CI −13.2 to −0.7; P = 0.03. All the above results in favour of MPH
[22]	Osmotically released MPH *v* placebo	**Response (defined as a decrease from baseline of 40% or more in the total investigator administered and rated ADHD Rating Scale score) at 6 weeks:** 56% with osmotically released MPH *v* 24% with placebo; P <0.001; absolute numbers not reported. **Other outcomes** *v* placebo at 6 weeks: difference in mean change: CGI ADHD severity index, 279 people in analysis; CPRS, 261 people in analysis; CHQ psychological summary score, 257 people in analysis; all reported as significant difference between groups, P value not reported

Ref	Intervention	Outcome
[47]	MPH *v* placebo	The RCT found that methylphenidate significantly improved oppositional defiant disorder/conduct disorder symptoms compared with placebo over 4 weeks (FBB-HKS total score: teacher-rated, P <0.0001; parent-rated: P = 0.0008; calculated by ANOVA)

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

TABLE 2 **The number of RCTs reporting significant adverse effects with methylphenidate versus placebo (see text, p 9). [87] 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 3 **RCTs assessing the effects of modafinil (see text).**

Reference	Population	Intervention/comparison	Significance
[62]	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 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?									
9 (at least 2461) [19] [20] [21] [22] [23]	Symptom severity	Atomoxetine *v* placebo	4	0	−1	0	0	Moderate	Consistency point deducted for statistical heterogeneity among RCTs
1 (153) [24] [25]	School performance	Atomoxetine *v* placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (772) [27] [22]	Symptom severity	Atomoxetine *v* methylphenidate	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for suboptimal dosing of comparator in 1 RCT
12 (336) [35] [7] [33]	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 16 RCTs (at least 1787 people) [33] [37] [38] [39] [40] [41] [43] [42] [44] [45] [46] [22] [47]	Symptom severity	Methylphenidate *v* placebo	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for weak methods
1 (53) [43]	School performance	Methylphenidate *v* placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
4 (224) [37]	Symptom severity	Methylphenidate *v* dexamfetamine sulphate	4	−1	−2	0	0	Very low	Quality point deducted for incomplete and poor reporting of results. Consistency points deducted for heterogeneity between RCTs and for conflicting results
13 (at least 753 people) [50] [53] [33]	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) [41] [57] [58]	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) [41]	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) [59] [41]	Symptom severity	Clonidine plus methylphenidate/dexamfetamine *v* methylphenidate/dexamfetamine	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and stringent definition of improvement in 1 RCT. Directness point deducted for inclusion of other interventions
2 (258) [41] [60]	Symptom severity	Clonidine *v* clonidine plus methylphenidate	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods. Directness point deducted for inclusion of co-interventions

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 (248) [62]	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
1 (60) [56]	Symptom severity	Modafinil v methylphenidate	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of comparators (only one outcome measure reported)
2 RCTs in 3 publications (140) [64] [65] [66]	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) [69]	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 point deducted for inclusion of children with suspected but not confirmed ADHD
3 (125) [72]	Symptom severity	Homeopathy *v* placebo	4	−1	0	−2	0	Very low	Quality point deducted for sparse data. Directness points deducted for clinical heterogeneity between regimens used and exclusion of homeopathy non-responders in 1 RCT
What are the effects of psychological treatments for ADHD in children?									
4 (460) [35] [75] [50] [76]	Symptom severity	Psychological/behavioural treatment *v* standard care	4	−2	0	−2	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) [77]	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) [35]	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) [78] [79] [80]	Symptom severity	Methylphenidate plus psychological/behavioural treatment *v* methylphenidate alone	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about method of randomisation. Directness point deducted for unclear intervention (not reporting doses used)
1 RCT in 3 publications (103) [78] [79] [80]	School performance	Methylphenidate plus psychological/behavioural treatment *v* methylphenidate alone	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about method of randomisation. Directness point deducted for unclear intervention (not reporting doses used)
At least 11 RCTs (at least 428 children) [37] [50]	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

Important outcomes	Symptom severity, school performance, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 11 RCTs (at least 428 children) [37] [50]	School performance	Methylphenidate plus psychological/behavioural treatment *v* psychological/behavioural treatments alone	4	−2	−1	0	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
1 (35) [84]	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.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.