

Attention deficit hyperactivity disorder in children

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QUESTIONS

What are the effects of treatments for attention deficit hyperactivity disorder? 2

INTERVENTIONS

TREATMENTS FOR ADHD

○● Likely to be beneficial

Atomoxetine.	2
Dexamfetamine sulphate.	3
Methylphenidate.	4
Methylphenidate plus psychological/behavioural treatment.	6

●● Unknown effectiveness

Clonidine.	7
Psychological/behavioural treatment.	8

Key Points

- Core symptoms of ADHD are inattention, hyperactivity and impulsivity, although other conditions frequently coexist with ADHD, including oppositional defiant disorder, and conduct, anxiety and depressive disorders.
Symptoms must be present for at least 6 months, observed in children before the age of 7 years, and clinically important impairment in social, academic or occupational functioning must be evident in more than one setting.
Prevalence estimates among school children range from 3–5%.
- **Methylphenidate** improves core symptoms and school performance in children with ADHD when used alone, and may be beneficial when added to psychological/behavioural treatment.
Dexamfetamine and **atomoxetine** may also reduce symptoms of ADHD but can cause adverse effects.
We don't know how effective any treatment for ADHD is in the long term.
- CAUTION: Atomoxetine may cause rare but serious liver injury.
- **Clonidine** may improve symptoms of ADHD compared with placebo, but we don't know for sure that it makes a clinically significant difference, and it may cause bradycardia.
- We don't know how effective **psychological/behavioural treatments** are compared with each other or with pharmacological treatments, as few high quality studies have been done.
The combination of **methylphenidate plus behavioural treatment** seems to work better than behavioural treatment alone in reducing core symptoms and improving behaviour in children with ADHD.

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. 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] The World Health Organization's *International statistical classification of diseases and related health problems* (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. The evidence presented in this topic largely relates to children aged 5 years and above. There is a paucity of evidence of efficacy and safety of treatments in pre-school children.

INCIDENCE/ PREVALENCE

Prevalence estimates of ADHD vary according to the diagnostic criteria used and the population sampled. DSM-IV prevalence estimates among school children in the US are 3–5%,^[1] but other estimates vary from 1.7% to 16.0%.^{[4] [5]} No objective test exists to confirm the diagnosis of ADHD, which remains a clinical diagnosis. Other conditions frequently co-exist with ADHD. 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%).^[6]

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AETIOLOGY/ RISK FACTORS The underlying causes of ADHD are not known.^[6] There is limited evidence that it has a genetic component.^[7] ^[8] ^[9] Risk factors also include psychosocial factors.^[10] There is increased risk in boys compared with girls, with ratios varying from 3 : 1^[6] to 4 : 1.^[3]

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.^[5] Changes in diagnostic criteria cause difficulty with interpretation of the few outcome studies that exist. One cohort of boys followed up for an average of 16 years found a ninefold increase in antisocial personality disorder and a fourfold increase in substance misuse disorder.^[7]

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

OUTCOMES Measures of children's behaviour, such as Conners Teacher's Rating Scales ; school performance, such as School Situations Questionnaire ; self rated symptoms; adverse effects.

METHODS *Clinical Evidence* search and appraisal May 2005. We have searched for RCTs comparing each listed intervention versus placebo, no treatment, or each other and have included all studies of sufficient quality.

QUESTION What are the effects of treatments for attention deficit hyperactivity disorder in children?

OPTION ATOMOXETINE

Six RCTs found that atomoxetine reduced symptoms of attention deficit hyperactivity disorder compared with placebo after up to 12 weeks of treatment. The RCTs found that atomoxetine decreased appetite and increased nausea, vomiting, asthenia, dyspepsia, infection, laryngitis and pruritus compared with placebo. In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of psycho-active drugs such as atomoxetine to children and adolescents.

Benefits:

[i] Atomoxetine versus placebo:

We found no systematic review. We found six RCTs. The first three RCTs, (reported in 2 papers) found that atomoxetine significantly reduced symptoms measured by the [Attention Deficit Hyperactivity Disorder Rating Scale \(ADHD-RS\)](#) at doses above 0.5 mg/kg twice daily compared with placebo.^[11] ^[12] In the fourth and fifth RCTs, atomoxetine administered at doses above 0.8 mg/kg once daily also significantly reduced symptoms compared with placebo;^[13] ^[14] (see table 3, p 10). The sixth RCT (416 children aged 6–15 years treated with open label atomoxetine for 12 weeks, then randomised to 9 months' double blind atomoxetine or placebo) found that atomoxetine was more effective than placebo in preventing symptom relapse, defined as a return to 90% of baseline symptom severity ADHD-RS score (proportion relapsing: 65/292 [22.3%] with atomoxetine v 47/124 [37.9%] with placebo; P = 0.002).^[15] However, in view of the relatively low relapse rate of the placebo group, the clinical importance of these findings is unclear.

Atomoxetine versus methylphenidate:

We found no systematic review or RCTs.

Harms:

[i] Atomoxetine versus placebo:

The first RCT found that infection and pruritus increased with higher doses (infection: 1/83 [1.2%] with placebo v 0/44 [0%] with atomoxetine 0.5 mg/kg/day v 5/84 [6.0%] with atomoxetine 1.2 mg/kg/day v 6/83 [7.2%] with atomoxetine 1.8 mg/kg/day; pruritus: 0/83 [0%] with placebo v 0/44 [0%] with atomoxetine 0.5 mg/kg/day v 1/84 [1.2%] with atomoxetine 1.2 mg/kg/day v 5/83 [6.0%] with atomoxetine 1.8 mg/kg/day).^[11] The second and third RCTs were reported together.^[12] They also found that atomoxetine significantly decreased appetite compared with placebo (21.7% with atomoxetine v 7.3% with placebo; P < 0.05).^[12] Further analyses of these two RCTs found no significant difference between treatments for cardiovascular adverse effects (palpitations, tachycardia, murmur, extrasystole, and bradycardia; P > 0.2 for all outcomes).^[16] The fourth RCT found that atomoxetine significantly decreased appetite and significantly increased nausea, vomiting, asthenia, and dyspepsia compared with placebo (decreased appetite: 17/85 [20.0%] with atomoxetine v 5/85 [5.9%] with placebo; P = 0.02; vomiting: 13/85 [15.3%] with atomoxetine v 1/85 [1.2%] with placebo; P = 0.001; nausea: 10/85 [11.8%] with atomoxetine v 2/85 [2.4%] with placebo; P = 0.04; asthenia: 9/85 [10.6%] with atomoxetine v 1/85 [1.2%] with placebo; P = 0.02; dyspepsia: 8/85 [9.4%] with atomoxetine v 0/85 [0%] with placebo; P = 0.007).^[13] The fifth RCT found a significantly higher incidence of appetite reduction, somnolence, and fatigue with atomoxetine compared with placebo (decreased appetite: 23/131 [17.6%] with atomoxetine v 4/63 [6.3%] with placebo;

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somnolence: 19/131 [14.5%] with atomoxetine v 1/63 [1.6%] with placebo; fatigue: 13/131 [9.9%] with atomoxetine v 1/63 [1.6%] with placebo; $P < 0.05$ for all comparisons. ^[14] The sixth RCT reported a significant difference between atomoxetine and placebo in the incidence of gastroenteritis and pharyngitis (each occurred in at least 5% of people; further data not reported; reported as significant). ^[15]

Atomoxetine versus methylphenidate:

We found no RCTs.

Atomoxetine and suicide:

Regulatory authorities in both the UK (Medicines and Healthcare products Regulatory Agency [MHRA]) and USA (Food and Drug Administration [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 precautions that can be taken when it is dispensed (see depression in children and adolescents).

Comment:

Clinical guide:

Atomoxetine is metabolised by the CYP 2D6 system of the liver. People with poor metabolism by this pathway may eliminate this drug more slowly and may be at greater risk of adverse effects.

OPTION

DEXAMFETAMINE SULPHATE

Two systematic reviews and one subsequent RCT found limited evidence that dexamfetamine (dexamphetamine) improved some behavioural outcomes compared with placebo. Another systematic review found insufficient evidence to compare the effects of dexamfetamine versus methylphenidate. One RCT found limited evidence that, in children already taking dexamfetamine or methylphenidate, adding clonidine reduced conduct symptoms of ADHD after 6 weeks compared with adding placebo. Four RCTs found that dexamfetamine reduced appetite, and one RCT found that it increased sleep disturbance, compared with placebo.

Benefits:

Dexamfetamine [dexamphetamine] sulphate versus placebo:

We found two systematic reviews ^[5] ^[17] and one subsequent RCT. ^[18] The first systematic 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](#) compared with placebo at up to 21 days (WMD –4.8 points, 95% CI –6.4 points to –2.9 points). ^[17] The second systematic review (search date 1997, 3 RCTs, 150 children aged 6–16 years, dexamfetamine 5–20 mg/day) only evaluated longer term studies (> 12 weeks). ^[5] It found some evidence of positive outcomes (including improved concentration and hyperactivity) with dexamfetamine compared with placebo. However, some methodological problems were identified with the RCTs in this review. ^[5] The subsequent RCT (crossover design, 35 children aged 6–12 years) found significant improvement with slow release formulation of dexamfetamine compared with placebo on two rating scales (including the hyperactivity index of the Conners Teacher's Rating Scale; $P < 0.001$). ^[18]

Dexamfetamine sulphate versus dexamfetamine sulphate plus clonidine:

[See benefits of clonidine, p 7](#) .

Dexamfetamine sulphate versus methylphenidate:

[See benefits of methylphenidate, p 4](#) .

Harms:

Dexamfetamine sulphate versus placebo:

Two RCTs identified by the first systematic review reported people withdrawing from the trial because of adverse events. ^[17] The second systematic review found that dexamfetamine significantly increased anorexia and appetite disturbance in three RCTs. ^[5] The subsequent RCT reported decreased appetite, weight loss, and sleep disturbance in children taking dexamfetamine. ^[18]

Dexamfetamine sulphate versus dexamfetamine sulphate plus clonidine:

[See harms of clonidine, p 7](#) .

Dexamfetamine sulphate versus methylphenidate:

[See harms of methylphenidate, p 4](#) .

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Comment: See benefits of methylphenidate for the principal outcome measures, p 4 .

OPTION METHYLPHENIDATE

One systematic review and subsequent RCTs found that methylphenidate reduced core symptoms of attention deficit hyperactivity disorder in the short term compared with placebo, but disturbed sleep and appetite. Two RCTs found limited evidence that once daily dosing was as efficient as conventional three times a day dosing. The review found inconclusive evidence comparing the effects of methylphenidate and dexamfetamine (dexamphetamine). It found limited evidence that methylphenidate improved symptoms in the medium term compared with psychological/behavioural treatment, but the clinical importance of these findings is unclear. One small RCT provided insufficient evidence to compare clonidine alone, methylphenidate alone, and methylphenidate plus clonidine. A second RCT found limited evidence that, in children already taking dexamfetamine (dexamphetamine) or methylphenidate, added clonidine reduced conduct symptoms of ADHD compared with added placebo after 6 weeks. A second systematic review found limited evidence that high dose methylphenidate was no more effective than low dose methylphenidate plus psychological/behavioural treatment.

Benefits: We found one systematic review (search date 2000) ^[19] and four subsequent RCTs examining effects on symptoms. ^[20] ^[21] ^[22] ^[23] Most studies were conducted in the USA, used a diagnosis of attention deficit disorder (DSM-III) or attention deficit hyperactivity disorder (ADHD; DSM-III-R or DSM-IV), and included children aged 5–18 years, mostly recruited from psychiatric and other hospital outpatient clinics. In addition, one systematic review (search date not reported) that found no RCTs about effects on later substance abuse. ^[24]

Methylphenidate versus placebo:

We found one systematic review that did not pool results from 13 rigorously selected short term RCTs (1177 children aged 5–18 years). ^[19] Ten RCTs found that methylphenidate (dose range 0.56–0.72 mg/kg/day or 5–35 mg/day for trials reporting in those units) 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 2, p 11](#)). 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 first subsequent RCT (parallel design, 276 children aged 6–12 years with ADHD but excluding children with Tourette's syndrome, ongoing seizure disorder, or psychotic disorder, and girls who had reached menarche) compared sustained release (once daily dosing) and conventional (3 times/day dosing) formulations of methylphenidate versus placebo. ^[20] The RCT found that methylphenidate significantly improved attention and behaviour at school compared with placebo (measured using mean teacher rated [Abbreviated Inattention/Overactivity with Aggression \(IOWA\) Conners I/O rating scale](#) ; ([see table 2, p 11](#)) throughout the 4 week period of the study. It found no significant difference between sustained release and conventional formulations of methylphenidate. The second subsequent RCT (crossover design, 68 children aged 6–12 years) found similar benefit for sustained (once daily dosing) release methylphenidate compared with placebo, and broad equivalence compared with conventional (3 times/day dosing) formulations of methylphenidate ([see table 2, p 11](#)). ^[21] Two other subsequent 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 at improving symptoms scores compared with placebo (both measured by the IOWA Connors rating) ([see table 2, p 11](#)). ^[22] ^[23]

Methylphenidate versus clonidine:

[See benefits of clonidine., p 7](#)

Methylphenidate versus dexamfetamine (dexamphetamine):

The systematic review ^[19] identified four poorly reported crossover RCTs (224 children aged 5–18 years) comparing methylphenidate (dose range 0.6–4.5 mg/kg/day or 20 mg/day for trials reporting in those units) versus dexamfetamine (dose range 0.39–2.6 mg/kg/day or 10 mg/day for trials reporting in those units) but, because of heterogeneity, could not pool their results. Three RCTs (99 children aged 5–12 years) found no significant difference between methylphenidate and dexamfetamine in [core symptoms](#) score ([see table 2, p 11](#)). The other RCT found improvement with methylphenidate compared with dexamfetamine for teacher reported, but not parent reported, outcomes. No firm conclusions can be drawn from these studies.

Methylphenidate versus methylphenidate plus clonidine:

[See benefits of clonidine, p 7](#) .

Methylphenidate versus methylphenidate plus psychological/behavioural treatment:

[See benefits of methylphenidate plus psychological/behavioural treatment, p 6](#) .

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Methylphenidate versus psychological/behavioural treatment:

We found one systematic review (search date 2000) that identified four RCTs comparing methylphenidate versus [psychological/behavioural treatment](#).^[19] Three of the RCTs (192 children aged 5–12 years) were poorly reported and compared a variety of psychological/behavioural treatments (individual [cognitive training](#) over 12 weeks; parent and teacher training; behaviour treatment for 8 weeks) versus methylphenidate (5–60 mg/day). Overall, these three RCTs found limited evidence that, in the medium term (12–52 weeks), methylphenidate improved symptoms compared with psychological/behavioural treatment. The fourth RCT (579 children aged 7–10 years) compared four treatment arms: medication treatment (144 children, double blind titration of methylphenidate dose, switched to alternative medication, such as dextroamphetamine (dextroamphetamine), pemoline, or imipramine, after 28 days if response unsatisfactory, mean initial dose 30.5 mg/day); intensive behavioural management; medication plus intensive behavioural management; and standard community care (treatments by community providers).^[25] A total of 74% of the children in the medication group 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, of the symptoms of ADHD compared with intensive behavioural management. This RCT is the largest and most rigorous currently available RCT of ADHD treatments.^[25] Subsequent secondary analysis suggested that 56% of the children taking medication improved compared with 34% in the intensive behavioural management group.^[26] There is also a suggestion that children with comorbid behaviour problems ([oppositional defiant disorder](#) / [conduct disorder](#)) show 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.^[27] 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.^[28] 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.^[17]

Methylphenidate/dexamfetamine sulphate plus clonidine versus placebo:

[See benefits of clonidine plus methylphenidate/dexamfetamine sulphate, p 7](#) .

Harms:

The systematic review did not combine results on harms because of heterogeneity and incomplete data reporting.^[19] It presented the number of RCTs that had found significant results, but did not report the number of adverse events.

Methylphenidate versus placebo:

The following symptoms were found by at least one RCT included in the systematic review to be significantly more common in children receiving methylphenidate than placebo: sleep disorders, anorexia or appetite disturbance, headache, motor tics, irritability, and abdominal pain ([see table 1, p 12](#)). Two of the subsequent RCTs^[20] ^[21] reported similar adverse effects. The fourth and fifth subsequent RCTs did not report on adverse effects.^[22] ^[23] We found no good evidence about the effects of methylphenidate on growth rates in children.

Methylphenidate versus clonidine:

[See harms of clonidine, p 7](#) .

Methylphenidate versus dexamfetamine:

Out of the four RCTs identified by the systematic review, two RCTs reported no significant difference with methylphenidate and dexamfetamine for anorexia or appetite disturbance and one RCT reported no significant difference in motor tics, abdominal pain, and irritability.

Methylphenidate versus methylphenidate plus clonidine:

[See harms of clonidine, p 7](#) .

Methylphenidate versus methylphenidate plus psychological/behavioural treatment:

[See harms of methylphenidate plus psychological/behavioural treatment, p 6](#) .

Methylphenidate versus psychological/behavioural treatment:

The one large RCT comparing medication with intensive [behavioural treatment](#) found that, of the children receiving either medication management or medication plus intensive behavioural treatment, 50% reported mild adverse effects, 11% had moderate adverse effects, and 3% experienced severe adverse effects.^[25] The study did not report on adverse effects of non-drug intervention but did comment that 6/11 reported severe adverse effects (depression, worrying, or irritability, with some children reporting more than 1) could have resulted from non-medication factors.

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Methylphenidate/dexamfetamine sulphate plus clonidine versus placebo:

See [harms of clonidine, p 7](#) .

Comment: **Conners Teacher's Rating Scale:**

The abbreviated Conners Teacher's Rating Scale has been used widely in treatment studies and has been researched, validated, and standardised to measure treatment effects in ADHD. ^[29] However, the clinical importance of the effect of methylphenidate compared with placebo on the abbreviated Conners Teacher's Rating Scale remains unclear.

OPTION

METHYLPHENIDATE PLUS PSYCHOLOGICAL/BEHAVIOURAL TREATMENT

One systematic review found inconsistent results for methylphenidate plus psychological/behavioural treatment compared with placebo in children with attention deficit hyperactivity disorder. A second systematic review found that methylphenidate plus psychological/behavioural treatment improved ADHD symptoms compared with psychological/behavioural treatments alone. A third systematic review found limited evidence that low dose methylphenidate plus psychological/behavioural treatment was as effective as high dose methylphenidate alone.

Benefits: **Methylphenidate plus psychological/behavioural treatment versus control/placebo:**

We found one systematic review (search date 1997, 3 RCTs, 35 children aged 5–13 years). ^[17] It found that the combination of methylphenidate plus [psychological/behavioural treatments](#) significantly improved parent ratings of attention deficit hyperactivity disorder (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, 95% CI -2.0 to +9.6). The clinical importance of these findings is unclear. ^[17]

Methylphenidate plus psychological/behavioural treatment versus methylphenidate alone:

One systematic review (search date 2004, 1 RCT, 32 children with ADHD, mean age 8.27 years) found no significant difference between methylphenidate plus parent behavioural training plus child self control instruction compared with methylphenidate alone in teacher ratings of ADHD (mean score, [Conners Teacher's Rating Scale](#) : 17.77 with combination treatment v 19.75 with methylphenidate alone; WMD -1.98 95% CI -6.01 to +2.05). ^[30] It found limited evidence that low dose (0.4 mg/kg) methylphenidate plus psychological/behavioural treatment was as effective as high dose (0.8 mg/kg) methylphenidate alone. ^[30]

Methylphenidate plus psychological/behavioural treatment versus psychological/behavioural treatments alone:

We found one systematic review (search date 2000, 11 RCTs, 428 children aged 5–18 years). ^[19] It found that methylphenidate plus [behavioural treatments](#) significantly improved ADHD behaviours, symptoms, and measures of academic achievement compared with behavioural treatments alone. No significant difference was found in social skills or in measures of the relationship between parents and children. ^[19] The review separately assessed one RCT, ^[25] which 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. ^[25]

Harms: **Methylphenidate plus psychological/behavioural treatment versus control/placebo:**

The systematic review did not report on adverse effects. ^[17]

Methylphenidate plus psychological/behavioural treatment versus methylphenidate alone:

The systematic review did not report on adverse effects. ^[30]

Methylphenidate plus psychological/behavioural treatment versus psychological/behavioural treatments alone:

The RCT identified by the systematic review did not report on adverse effects. See [harms of methylphenidate, p 4](#) . ^[19]

Comment: The MTA Cooperative Group Multimodal Treatment Study RCT ^[25] is the largest and most methodologically rigorous study of ADHD treatments, with high standards for reporting and follow up of nearly all children ([see comment of methylphenidate, p 4](#)). ^[28] The results of a secondary analysis of this RCT ^[26] suggest that children with ADHD and comorbid anxiety respond equally well to medication management or intensive behavioural treatment ([see comment about secondary analysis under methylphenidate, p 4](#)); ^[27] but secondary analysis indicated that combined medication management plus intensive behavioural treatment was better than medication management alone. ^[27]

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OPTION

CLONIDINE

Limited evidence from one systematic review suggested that clonidine reduced core attention deficit hyperactivity disorder symptoms compared with placebo, but the clinical importance of these findings is unclear. One small RCT provided insufficient evidence to compare clonidine alone, methylphenidate alone, and clonidine plus methylphenidate and found limited evidence that clonidine and clonidine plus methylphenidate increased the risk of bradycardia. A second RCT found limited evidence that, in children already taking dexamfetamine (dexamphetamine) or methylphenidate, added clonidine reduced conduct symptoms of ADHD compared with added placebo after 6 weeks.

Benefits:

Clonidine versus placebo:

We found one systematic review (search date 1999, 6 RCTs, 143 children, mean age 11 years, dose of clonidine 0.1–0.24 mg/day for 4–12 weeks).^[31] The review found that clonidine was more effective than placebo at improving combined rating scores (effect size 0.58, 95% CI 0.27 to 0.89). The clinical importance of this result is unclear, and the results should be treated with caution. One of the six RCTs included in the meta-analysis comparing clonidine versus placebo conducted by the review was a comparison of clonidine versus methylphenidate,^[32] rather than versus placebo, and the rating scales of the clinical features of attention deficit hyperactivity disorder completed by parents, teachers, and clinicians were combined in the systematic review. The review noted larger effect sizes in smaller and lower quality studies. Inclusion of the RCT comparing clonidine versus methylphenidate^[32] 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.^[32] 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 the study measures rather than a rigorous comparison of randomly allocated groups.

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 psychostimulants [41/67 [61%] dexamfetamine; 26/67 [39%] methylphenidate]) compared additional clonidine versus additional placebo.^[33] 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. It found no significant difference between treatments in response rate for hyperactivity (conduct response: 21/37 [57%] with added clonidine v 6/29 [21%] with added placebo; $P < 0.01$; hyperactive index response: 13/37 [35%] with added clonidine v 5/29 [17%] with added placebo; P less than or equal to 0.16).^[33] It also found that, adding clonidine significantly reduced lack of interest in others and lack of talking with others; irritability, proneness to crying, and anxiety compared with adding placebo (rates not reported, $P < 0.05$ for each outcome).

Clonidine alone versus methylphenidate alone versus clonidine plus methylphenidate:

One small RCT (3 groups of 8 boys aged 6–16 years with ADHD and either comorbid [oppositional defiant disorder](#) or [conduct disorder](#)) compared three interventions: clonidine (mean dose 0.17 mg/day), methylphenidate (mean dose 35 mg/day), and clonidine plus methylphenidate.^[32] Most outcomes were not significantly different among the three groups. However, clonidine was significantly less effective than methylphenidate at improving the teacher reported score ([School Situations Questionnaire](#); $P < 0.0003$). The clinical importance of this isolated result is unclear.

Harms:

Clonidine versus placebo:

The systematic review^[31] included information from 10 studies of harms. Harms were reported as the number of studies that recorded a specific adverse effect or not rather than the number of children experiencing adverse effects. Not all were high quality RCTs, and their results are difficult to interpret. In children taking clonidine, nine of 10 studies found sedation in children; six studies found increased irritability. Electrocardiographs were recorded in two placebo controlled RCTs, which found no abnormalities.

Clonidine plus methylphenidate/dexamfetamine (dexamphetamine) sulphate versus methylphenidate/dexamfetamine sulphate alone:

The RCT (67 children already taking psychostimulants; 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).^[33] 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.

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Clonidine versus clonidine plus methylphenidate:

The RCT (24 boys) found that 2/8 [25%] boys on clonidine and 4/8 [50%] boys on clonidine plus methylphenidate developed bradycardia. ^[32]

Comment: None.

OPTION PSYCHOLOGICAL/BEHAVIOURAL TREATMENT

One systematic review of two small RCTs provided insufficient evidence to assess the effects of psychological/behavioural treatment compared with standard care. One systematic review of one large RCT found no significant difference between family therapy and standard care in behaviour rating scales. One systematic review found limited evidence that psychological/behavioural treatment was less effective at improving symptoms in the medium term compared with methylphenidate, but the clinical importance of these findings is unclear.

Benefits: [i] Psychological/behavioural treatment versus standard care:

We found two systematic reviews. The first systematic review (search date 1997; ^[17] 2 RCTs, 50 children aged 6–13 years) found no significant difference between [psychological/behavioural treatment](#) and standard care (medication, psychotherapy, or both, as provided by the community health provider) in Conners Teacher's Rating Scales (SMD –0.40 points, 95% CI –1.28 points to +0.48 points) or parent ratings (1 RCT, 26 children, WMD –3.8 points, CI –9.6 points to +2.0 points). The RCTs identified by the systematic review were small and the clinical importance of these results is unclear. The second systematic review (search date 2004; ^[30] 1 RCT, 290 children aged 7.0–9.9 years), ^[30] found insufficient evidence to compare the effects of family therapy versus standard care (medication, psychotherapy, or both, as provided by the community health provider). The RCT identified by the review, ^[25] found no significant difference between intensive [behavioural treatments](#) for families for 14 months duration and standard community care (medication, psychotherapy, or both, as provided by the community health provider). ^[25] In children with comorbid [anxiety disorders](#), the RCT found that intensive behavioural treatment resulted in better clinical outcomes. The results of this trial should be interpreted with caution, because of weakness in the study design.

Psychological/behavioural treatment versus methylphenidate:

[See benefits of methylphenidate, p 4](#) .

Psychological/behavioural treatment versus psychological/behavioural treatment plus methylphenidate:

[See benefits of methylphenidate plus psychological/behavioural treatment, p 6](#) .

Harms: Psychological/behavioural treatment versus standard care:

The systematic reviews did not make any comment about adverse effects. ^[17] ^[30]

Psychological/behavioural treatment versus methylphenidate:

[See harms of methylphenidate, p 4](#) .

Psychological/behavioural treatment versus psychological/behavioural treatment plus methylphenidate:

[See harms of methylphenidate plus psychological/behavioural treatment, p 6](#) .

Comment: Psychological/behavioural treatment versus standard care:

Children in the trials had different comorbid diagnoses, presentations, and clinical needs. Secondary analysis of one RCT ^[25] suggests 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). ^[21] However, caution should be exercised in interpreting the results of secondary analysis as they are more susceptible to bias than the primary outcome analyses.

GLOSSARY

Abbreviated Inattention/Overactivity with Aggression (IOWA) Conners I/O rating scale Consists of 10 items scored on a 4 point scale (from 0 = “not at all” to 3 = “very much”), divided into 2 subsets of 5 items: Inattention/Overactivity (I/O) and Oppositional/Defiance (O/D).

ADHD-RS (ADHD Rating Scale) an 18 point rating scale that is based on the 18 DSM-IV diagnostic criteria, which include a subjective assessment of inattention, hyperactivity, and impulsivity.

Anxiety disorder A range of conditions with features including apprehension, motor tension, and autonomic overactivity.

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Behavioural treatment Treatment using insights from learning theory to achieve specific changes in behaviour. It is usually highly structured. It can be used with either children with attention deficit hyperactivity disorder or their parents/carers.

Cognitive training Brief structured treatment aimed at changing dysfunctional beliefs.

Conduct disorder Conduct disorders include a repetitive pattern of antisocial, aggressive, or defiant conduct that violate age appropriate social expectations.^[2]

Conners Teacher's Rating Scales Widely used rating scales for assessment of symptoms of attention deficit hyperactivity disorder used extensively in both clinical work and epidemiological studies. There are parent and teacher questionnaires containing 10 items that can be used for children aged 3–17 years.

Core symptoms Inattention, hyperactivity, and impulsivity are commonly known as the core symptoms of attention deficit hyperactivity disorder.^[5]

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 dissociative or aggressive acts seen in conduct disorder.^[2]

Psychological/behavioural treatments Includes any of the following methods: contingency management methods (e.g. behaviour modification); cognitive behavioural therapy; individual psychotherapy; parent training or education; teacher training and education; parent and family counselling/therapy; social skills training; and electroencephalogram, biofeedback, or relaxation treatment.

School Situations Questionnaire A teacher completed questionnaire that measures the pervasiveness of child behaviour problems across 12 school situations.^[34]

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TABLE 1 Placebo controlled RCTs of atomoxetine (see text, p 2). ^[11] ^[12] ^[13]

Ref	Population and intervention	Mean difference (95% CI) in ADHD-RS score between treatment and placebo
[11]	0.5, 1.2, 1.8 mg/kg ATX twice daily v placebo Duration: 8 weeks 297 people aged 8–18 years	–4.1 (–9.0 to +0.8) with 0.5 mg/kg v –7.8 (–11.6 to –4.0) with 1.2 mg/kg v –7.7 (–11.6 to –3.8) with 1.8 mg/kg
[12]	ATX 1.5 mg/kg twice daily v placebo Duration: 12 weeks 147 people aged 7–13 years	–10.1 (–14.5 to –5.7)
[12]	ATX 1.5 mg/kg twice daily v placebo Duration: 12 weeks 147 people aged 7–13 years	–8.5 (–13.0 to –4.0)
[13]	ATX 1.0 mg/kg once daily v placebo Duration: 6 weeks 171 people aged 6–16 years	–7.8 (–11.2 to –4.4)
[14]	ATX 0.8 – 1.2 mg/kg/day once daily v placebo Duration: 8 weeks 197 people aged 6–12 years	–9.7 (–13.8 to –5.9)

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

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TABLE 2 Methylphenidate studies (see text, p 4). [19] [20] [21] [22] [23]

Ref	Intervention	Outcome		
[19]	MPH v placebo 13 RCTs	Core symptoms score:		
		<i>Study author (year)</i>	<i>MPH (mean) v placebo (mean)</i>	<i>SMD (95% CI)</i>
		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)
		Hoepfner (1997)	8.20 v 13.54	-0.68 (-1.08 to -0.28)
		Manos (1999)	56.12 v 64.38	-0.60 (-1.03 to -0.16)
		Zeiner (1999)	8.83 v 14.69	-0.92 (-1.40 to -0.43)
		Pliszka (2000)	12.80 v 15.40	-0.32 (-0.96 to +0.32)
	MPH v dexamphetamine 3 RCTs	Core symptoms score:		
		<i>Study author (year)</i>	<i>MPH (mean) v dexamphetamine (mean)</i>	<i>SMD (95% CI)</i>
		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:		
		<i>Study author (year)</i>	<i>MPH (mean) v TCAs (mean)</i>	<i>SMD (95% CI)</i>
		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:		
		<i>Study author (year)</i>	<i>MPH (mean) v psychological/behavioural treatments (mean)</i>	<i>SMD (95% CI)</i>
		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)
	MPH plus psychological/behavioural treatments 2 RCTs	Conners Teacher's Rating Scale score:		
		<i>Study author (year)</i>	<i>MPH (mean) v MPH + psychological/behavioural treatments (mean)</i>	<i>SMD (95% CI)</i>
		Brown (1985)	15.10 v 15.00	+0.02 (-0.85 to +0.90)
		Klein (1997)	0.21 v 1.20	-1.35 (-1.93 to -0.78)
[20]	IR-MPH 3 times/day v SR-MPH once daily v placebo	Inattention/overactivity score (from baseline to end of study): From 9.74 to 5.98 with SR-MPH v from 9.94 to 6.35 with IR-MPH v from 10.28 to 9.77 with placebo Oppositional/defiant score (from baseline to end of study): From 4.34 to 2.74 with SR-MPH v from 3.83 to 2.50 with IR-MPH v from 5.44 to 5.21 with placebo P < 0.001 for both interventions v placebo for all outcomes		
[21]	IR-MPH 3 times/day v SR-MPH once daily v placebo	Inattention/overactivity score (at end of study): 5.00 with MPH 3 times/day v 4.69 with MPH once daily v 10.34 with placebo		

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Ref	Intervention	Outcome
		Oppositional/defiant score (at end of study): 1.99 with MPH 3 times/day v 1.81 with MPH once daily v 5.09 with placebo Abbreviated Conners score (at end of study): 7.94 with MPH 3 times/day v 7.82 with MPH once daily v 16.40 with placebo
[22]	MPH 10, 20, or 30 mg 3 times/day 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
[23]	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

IR, immediate release; MPH, methylphenidate; Ref, reference; SMD, standardised mean difference; SR, sustained release; TCA, tricyclic antidepressant.

TABLE 3 The number of RCTs reporting significant adverse effects with methylphenidate versus placebo (see text, p 4).^[11] 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%)