Attention deficit hyperactivity disorder

Evidence Update July 2013

A summary of selected new evidence relevant to NICE clinical guideline 72 ‘Diagnosis and management of ADHD in children, young people and adults’ (2008)

Evidence Update 45
Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the NICE Evidence Services topic page for attention deficit disorder.

**Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.**

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Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

1. **Attention deficit hyperactivity disorder.** NICE clinical guideline 72 (2008)

A search was conducted for new evidence from 19 May 2011 to 22 February 2013 (with a supplementary search up to 21 March 2013). A total of 8187 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 19 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. The following guidance is also of relevance to UK attention deficit hyperactivity disorder (ADHD) practice, however the Evidence Update does not discuss any potential effect the new evidence may have upon the recommendations:

1. **Antisocial behaviour and conduct disorders in children and young people.** NICE clinical guideline 158 (2013)

Quality standards

- **Attention deficit hyperactivity disorder.** NICE quality standard 39 (2013)

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

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1 NICE-accredited guidance is denoted by the Accreditation Mark 🟢
# Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG’s opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

**Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.**

<table>
<thead>
<tr>
<th>Key point</th>
<th>Potential impact on guidance</th>
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<tr>
<td><strong>Prerequisites of treatment and care for all people with attention deficit hyperactivity disorder (ADHD)</strong></td>
<td></td>
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<tr>
<td>• Treatment of ADHD may have long-term benefits on a wide range of outcome measures, although normal function is rarely achieved.</td>
<td>✓</td>
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<tr>
<td>• Perceptions of stigma among young people with ADHD may be associated with reduced uptake of mental health services.</td>
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<td><strong>Diagnosis of ADHD</strong></td>
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<tr>
<td>• People with ADHD may have significant reduction in grey matter volume in the basal ganglia, although ageing and stimulant drug treatment may be associated with brain structure that approaches normal.</td>
<td>✓</td>
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<tr>
<td><strong>Post-diagnostic advice</strong></td>
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<tr>
<td>• Some children with ADHD may respond to dietary intervention or elimination of food additives or colourings, although effect sizes are small and further research is needed.</td>
<td>✓</td>
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<tr>
<td>• Dietary fatty acid supplementation may reduce ADHD symptoms in some children and young people and further research is needed.</td>
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<td><strong>Treatment for children and young people</strong></td>
<td></td>
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<tr>
<td>• Parental training may bring some benefits for parents, but appears to have little impact on ADHD symptoms and behaviour outside the home, although further research is needed.</td>
<td>✓</td>
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<tr>
<td>• Telephone-based parental training may have benefits over no intervention, although further research is needed to assess delivery of parental training.</td>
<td>✓</td>
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<tr>
<td>• Training in organisational skills may reduce the functional impact of ADHD in school-age children.</td>
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<tr>
<td>• Teacher-led whole-class behavioural interventions that reduce peer devaluation and emphasise social inclusion may benefit children with ADHD.</td>
<td>✓</td>
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<tr>
<td>• Drug treatment of ADHD in school-age children may improve on-task behaviour in the classroom, although the impact on academic attainment is less clear.</td>
<td>✓</td>
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<tr>
<td>• Methylphenidate seems to be effective in children and young people with ADHD and coexisting intellectual disability or substance use disorder.</td>
<td>✓</td>
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</tbody>
</table>
### Key point

<table>
<thead>
<tr>
<th>Potential impact on guidance</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td><strong>A NICE Evidence Summary: New Medicine about lisdexamfetamine dimesylate in children and young people with ADHD has recently been published.</strong></td>
<td>✔️</td>
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### Treatment of adults with ADHD

- ADHD symptoms in adults receiving medication for ADHD may be improved by the addition of cognitive behaviour therapy (CBT).
- Extended-release methylphenidate may reduce ADHD symptoms in imprisoned adults with ADHD and complex comorbidities.

### How to use drugs for the treatment of ADHD

- Despite a small but significant increase in blood pressure and heart rate, the risk of serious cardiovascular adverse events and sudden cardiac death associated with therapeutic doses of drugs for ADHD appears to be low.
1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the ‘key references’ (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Section headings are taken from the guidance.

1.1 Prerequisites of treatment and care for all people with attention deficit hyperactivity disorder (ADHD)

Long term effectiveness of treatment for ADHD

NICE clinical guideline 72 (NICE CG72) notes that people with ADHD require integrated care that addresses a wide range of personal, social, educational and occupational needs. The effectiveness of treatment or non-treatment over the long term was not discussed.

Shaw et al. (2012) conducted a systematic review to assess the effects of treatment and non-treatment on long-term (defined as 2 years or more) outcomes of ADHD. Studies were included only if ADHD was the primary disorder and reported life-consequence outcomes. Studies included untreated ADHD (that is, naturalistic examination of ADHD course compared with baseline or non-ADHD controls) or ADHD treated with drug or non-drug therapy (compared with ADHD natural course, pretreatment baseline or control participants without ADHD).

The review included longitudinal studies with prospective follow-up or retrospective measures of at least 2 years, cross-sectional studies comparing 2 ages differing by at least 2 years, and single cross-sectional studies of participants aged at least 10 years. Meta-analyses, case studies and literature reviews were not included. A total of 351 studies were included in the review (number of participants not reported).

Some studies reported more than one outcome result. Outcome measures were compiled into 9 major groups: drug misuse or addictive behaviour (160 results reported), academic (119 results), antisocial behaviour (104 results), social function (98 results), occupation (45 results), self-esteem (44 results), driving (30 results), service use (26 results) and obesity (10 results). Analysis was based on whether the outcome was statistically significantly different, or presented by study authors as ‘obviously’ different.

Among studies of participants with untreated ADHD compared with baseline or control participants without ADHD, 89 showed that outcomes were not substantially different from controls (26% of outcome results), compared with 244 studies showing that untreated participants experienced worse long-term outcomes (74% of outcome results).

In 48 studies comparing ADHD treatment with untreated ADHD, 55 of 76 outcomes showed a benefit of treatment (72%). In these studies, treatment was beneficial for 100% of driving and obesity outcomes reported, 90% of self-esteem outcomes, 83% of social function outcomes, 71% of academic outcomes, 67% of drug misuse or addictive behaviour outcomes, 50% of antisocial behaviour and service use outcomes, and 33% of occupation outcomes. Treatment of ADHD did not generally result in normal function (42 studies, 76 outcomes; 58 worse outcomes in 35 studies, 18 comparable outcomes in 16 studies).

Limitations of the review included the potential for bias arising from search constraints and changes in diagnostic criteria over time. With heterogeneity of study design and outcomes measured, meta-analysis was not possible. Despite these limitations, the evidence indicates
that treatment of ADHD may have long-term benefits on a wide range of outcome measures, although normal function is rarely achieved. As such, this evidence provides context that is consistent with NICE CG72.

**Key reference**

**Impact of perceptions about ADHD on treatment uptake**

NICE CG72 notes that many people with ADHD, and their parents or carers, experience stigma and other difficulties because of the symptoms and impairment associated with ADHD and current practice within healthcare and education.

Bussing et al. (2011) used data from a US longitudinal cohort study to assess the views of parents and young people with ADHD, and how these views affect use of mental health services. Screening within a school district between 1998 and 2006 identified children and young people at high risk of ADHD, who subsequently underwent diagnostic assessment for ADHD, oppositional defiant disorder and conduct disorder. The cohort was followed at intervals. The analysis reported by Bussing et al. (2011) was based on information collected during the fourth follow-up interviews with the cohort, a mean of 6.8 years after screening.

Of 372 eligible young people, 192 agreed to participate, but 24 young people considered not likely to need ADHD treatment were excluded from the analysis. The analysis reported information from 168 young people (mean age 15 years, 53% female). Additionally, 35% were African American, 58% qualified for free or reduced cost lunch and 61% met full Diagnostic and Statistical Manual of Mental Disorders (DSM) 4th edition criteria for ADHD during diagnostic interviews.

Parents and young people used validated scales to assess ADHD symptoms and attitude towards drug treatment and counselling. Parents used a validated questionnaire to assess the strain of caring for their child with ADHD and the young people completed the ADHD Stigma Questionnaire. Information on the use of mental health services was collected for the 12 months before the study, with longitudinal data from previous interviews used to provide information on earlier service use. The analysis assessed the independent predictors of past year mental health service use.

Most young people (n=133, 79%) had received some mental health intervention, although this use occurred during the last year in a smaller proportion (n=71, 42%). Sociodemographic characteristics, including gender and race, showed no association with treatment received by the young people. Use of mental health services during the previous year significantly reduced with increasing perceptions of stigma of ADHD among the young people (odds ratio [OR]=0.2, 95% confidence interval [CI] 0.10 to 0.59, p=0.0015).

Past-year use of mental health services significantly increased with:

- increased functional impairment reported by young people (OR=1.1, 95% CI 1.02 to 1.13, p=0.0081)
- increasing parental perception of inattention in the young person (OR=1.2, 95% CI 1.05 to 1.31, p=0.0060)
- parents’ positive attitude to drug treatment (OR=3.8, 95% CI 1.62 to 8.71, p=0.0020).

Limitations of the study included the small sample size recruited from a single US regional population (which may not be representative of the UK ADHD population) and loss to follow-up. This evidence, demonstrating the influence of perceptions of stigma on treatment use, is consistent with the importance placed on sensitivity to stigma of ADHD in NICE CG72.
1.2 Identification, pre-diagnostic intervention in the community and referral to secondary services

No new key evidence was found for this section.

1.3 Diagnosis of ADHD

Brain structure in ADHD

**NICE CG72** recommends full clinical and psychosocial assessment of the person as part of diagnosis of ADHD, but does not mention assessment of brain structure.

**Nakao et al. (2011)** conducted a meta-analysis to examine brain structural abnormalities in children, young people and adults with ADHD, compared with healthy people. The impact of age and stimulant treatment was also assessed. Voxel-based morphometric studies to measure grey matter volume were included (14 studies: 5 with adults, 9 with children or young people). These studies included 378 patients with ADHD (176 adults and 202 children or young people) and 344 healthy participants (146 adults and 198 children or young people).

Patients with ADHD (n=191, 6 paediatric studies and 1 adult study) had significantly smaller global grey matter volume compared with healthy participants (n=179, p=0.008). Information from all studies was available to investigate regional differences in grey matter volume, with the most prominent and replicable structural abnormalities in ADHD found in the basal ganglia. Patients with ADHD showed significantly reduced grey matter volume in the right lentiform nucleus (p<0.001) but significantly increased volume in the left posterior cingulated cortex (p<0.001) compared with healthy participants.

Information on both increasing age and medication use was available from all studies and showed that both resulted in more normal grey matter volume in patients with ADHD. Increasing age was significantly (p≤0.001) and independently correlated with increased grey matter volume in the right putamen. Stimulant use was significantly (p≤0.001) and independently correlated with increased grey matter volume in the right caudate nucleus.

Limitations of the analysis included the use of summarised data, different statistical thresholds, difficulty controlling for false negative results, difficulty detecting spatially complex differences, lack of information about ADHD symptom severity, and assessment of stimulant effects by the percentage of recipients rather than subtler measures such as dose level. In addition, some studies reported grey matter density rather than volume.

Despite these limitations, the analysis provides information on the structural brain abnormalities in people with ADHD. It also suggests that the normal course of development with age and stimulant drug treatment may each be associated with brain structures appearing more normal. However, further studies are needed, so this evidence is unlikely to have an impact on **NICE CG72**.

**Key reference**

1.4 **Post-diagnostic advice**

**Dietary elimination of food additives and colourings**

NICE CG72 recommends that healthcare professionals should stress the value of a balanced diet, good nutrition and regular exercise for children, young people and adults with ADHD. The elimination of artificial colouring and additives from the diet is not recommended as a generally applicable treatment for children and young people with ADHD.

Clinical assessment of ADHD in children and young people should include asking about food or drinks that appear to influence hyperactive behaviour. If there is a link, healthcare professionals should advise parents or carers to keep a diary of food and drinks taken and ADHD behaviour. If the diary supports a relationship between specific foods and drinks and behaviour, then referral to a dietitian should be offered. Further management (for example, specific dietary elimination) should be jointly undertaken by the dietitian, mental health specialists or paediatrician, and the parent or carer and child or young person.

The role of diet and food colouring in ADHD and its symptoms was investigated in a meta-analysis by Nigg et al. (2012). Analysis first involved grouping outcomes in studies according to rater (for example, parents), choosing the most psychometrically well-established measure reported (for example, Conners Rating Scale for parents [CRS-P] or teachers [CRS-T]). Further analyses were restricted to studies with objective verification of blinding, and to studies considered to be high quality (that is, reporting measures with published reliability and validity data). Correction was also made for publication bias.

The literature review identified 6 studies of restriction diets that used either a placebo-controlled challenge or crossover design (n=195 children). The dietary restriction included elimination of synthetic food colours or other additives. After sensitivity analysis resulting in removal of 1 study with weak blinding, the response rate to dietary restriction was 33% (95% CI 19 to 52%, n=164) with an effect size of 0.29 (95% CI 0.07 to 0.53, p=0.014).

A total of 25 studies were identified that included a restriction diet to eliminate synthetic food additives and colourings, followed by challenges with food or drink containing one or more additive or colouring. Analysis of studies with parental reports showed an effect size of 0.18 (95% CI 0.08 to 0.24, p=0.0007; 20 studies, n=794), but the result became non-significant after correction for possible publication bias. Analysis of studies with teacher or observer ratings showed no significant effect of additives or colourings on behaviour (effect size=0.07, 95% CI −0.03 to 0.18, p=0.14; 10 studies, n=323).

Restriction of the data to high quality studies of colour additives gave a significant impact (effect size=0.22, 95% CI 0.10 to 0.41, p=0.030). A significant effect of food additives or colouring was shown in studies of psychometric tests of attention (effect size=0.27, 95% CI 0.07 to 0.47, p=0.007; 6 studies, n=154). This result remained significant after correction for possible publication bias.

Limitations of the analysis included lack of clarity regarding study selection, data extraction and quality assessment used. Methodological limitations were reported for several of the included studies.

Sonuga-Barke et al. (2013) conducted a systematic review and meta-analysis of non-drug interventions for ADHD in children and young people (3–18 years), based on randomised controlled trials (RCTs) of dietary and psychological treatments. The outcome measure was change in total ADHD symptom severity, measured using ADHD-specific symptoms scales or ADHD-related dimensions of general questionnaires. Analysis was based on the most proximal assessment (that is, report by a rater closest to the therapeutic setting such as a parent) and by ‘probably blinded assessment’ (that is, made by an individual likely to be blind to treatment allocation).
Of the 54 studies (n=3154) included, 7 (n=407) evaluated food antigen-specific and general restrictive diets. A significant effect was noted (standardised mean difference [SMD]=1.48, 95% CI 0.35 to 2.61, p=0.01) with proximal assessment. No significant difference was seen when the analysis was restricted to the 5 studies with probably blinded assessments. The review included 8 studies (n=294) that excluded synthetic food colourings. A significant impact was found with both proximal assessment (SMD=0.32, 95% CI 0.06 to 0.58, p=0.02) and probably blinded assessment (SMD=0.42, 95% CI 0.13 to 0.70, p=0.004).

General limitations of the analysis of non-drug interventions included methodological variations, differences in reported study quality, range of control conditions, and lack of information about ADHD severity. The authors noted that participants in studies eliminating food or synthetic food additives or colourings were often preselected to be responders before entering the controlled phase of the trial, so the effects seen may be restricted to individuals with suspected food sensitivities.

Taken together, these studies suggest that some children with ADHD may respond to dietary interventions or removal of food colourings. Effect sizes, however, are not large and their cost-effectiveness is not clear. These findings are consistent with NICE CG72. Further research may clarify the value of restricting colourings generally, and identify specific colourings that may affect ADHD symptoms.

Key references

Dietary fatty acid supplementation
NICE CG72 states that dietary fatty acid supplementation is not recommended for the treatment of ADHD in children and young people.

A Cochrane review by Gillies et al. (2012) assessed the effect on ADHD symptoms of polyunsaturated fatty acids (PUFA) compared with other forms of treatment or placebo in children and adolescents. A total of 13 studies (n=1011, age 6–18 years) were included in the review. Studies (8 parallel design, 5 crossover design) ranged in size from 18–147 participants and evaluated omega 3 PUFA, omega 6 PUFA or both, compared with placebo or other comparator. Supplements were given for 4–16 weeks. The primary outcome was change in ADHD symptoms measured by validated scales. Secondary outcomes (including severity or incidence of depressive symptoms, anxiety symptoms and behavioural problems) were analysed separately by rater (parent, teacher, clinician and patient).

Supplementation with combined omega 3 and omega 6 PUFA showed a significantly increased likelihood of symptomatic improvement compared with placebo (risk ratio [RR]=2.19, 95% CI 1.04 to 4.62, p=0.039; 2 studies, n=97). However, there were no statistically significant differences for all other comparisons.

Limitations of the analysis included methodological shortcomings in many of the included studies, with lack of clarity over randomisation, treatment allocation, blinding and risk of bias. A major difficulty with some studies of omega 3 PUFA supplementation is masking of the distinctive smell and taste of fish oil. The authors concluded that, overall, there is little evidence that PUFA supplementation provides any benefit for the symptoms of ADHD in children and adolescents.
As noted above (see ‘Dietary elimination of food additives and colourings’), Sonuga-Barke et al. (2013) conducted a systematic review and meta-analysis of non-drug interventions for ADHD in children and young people (3–18 years), based on RCTs of dietary and psychological treatments. A total of 11 placebo-controlled trials (n=890) examined free fatty acid supplementation with omega 3 (5 studies), omega 6 (2 studies) or both omega 3 and omega 6 (4 studies). Treatment effects were significant both for proximal assessment (SMD=0.21, 95% CI 0.05 to 0.36, p=0.007) and for probably blinded assessment (SMD=0.16, 95% CI 0.01 to 0.31, p=0.04). The authors noted a similar effect size of PUFA supplementation to that reported by Gillies et al. (2012), despite differences in the inclusion criteria, number of studies and statistical models used.

The review by Sonuga-Barke et al. (2013) included a single centre RCT conducted in Israel by Manor et al. (2012). This 15-week double-blind, placebo-controlled trial of omega 3 PUFA in 200 children aged 6–13 years measured ADHD by CRS-T (the primary outcome), CRS-P, Strengths and Difficulties Questionnaire and Child Health Questionnaire.

Omega 3 supplementation resulted in a significant reduction in the CRS-P ‘global: restless/impulsive’ score (−5.19 SD 9.93) compared with placebo (−1.71 SD 11.14, p=0.047). The ‘emotional impact on parent’ score of the Child Health Questionnaire had a significantly greater change from baseline (9.45 SD 21.17) compared with placebo (0.72 SD 20.77, p=0.022). No significant differences between omega 3 supplementation and placebo were seen for any other CRS-P or Child Health Questionnaire score, or any CRS-T score.

Limitations of this study included factors that may have influenced the sensitivity of the primary efficacy measure such as the high number of children per class in Israel (up to 42 children), lack of training for Israeli teachers in identifying and managing ADHD, lack of active teacher involvement, and unexpected replacement of reporting teachers during the study. Furthermore, most CRS-T subscale median values were within the normal range (<63) at baseline, despite a diagnosis of ADHD and parental scale ratings indicating abnormality. In this exploratory study, the subgroup analysis was conducted post-hoc, rather than with a predefined cohort.

Despite the caution needed when interpreting the clinical significance of small effects, overall the evidence suggests that PUFA supplementation may reduce ADHD symptoms in some children and young people. These findings add to the evidence base for NICE CG72, although further research is needed.

**Key references**

Gillies D, Sinn JKH, Lad SS et al. (2012) Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database of Systematic Reviews issue 10: CD007986


### 1.5 Treatment for children and young people

**Parent training interventions**

As first-line treatment, NICE CG72 recommends parent-training/educational programmes for parents or carers of pre-school children, and (group-based) for parents of children and young people of school age with ADHD and moderate impairment.

**Effectiveness**

A Cochrane review by Zwi et al. (2011) evaluated the effectiveness of parent training interventions in reducing ADHD symptoms and associated problems in children and young
people (5–18 years). RCTs comparing parent training with no treatment, a waiting list or treatment as usual were included if ADHD was the main focus of the trial, participants were aged over 5 years and had a clinical diagnosis made by a specialist using standard diagnostic criteria, and at least 1 child outcome was reported. A total of 5 studies were included (284 participants), all comparing parent training with usual treatment.

Meta-analysis for child externalising behaviour (a measure of rule breaking, oppositional behaviour and aggression) found no significant effect of parent training (SMD = −0.32, 95% CI −0.83 to 0.18, p=0.21; 3 studies, n=190). Meta-analysis for child internalising behaviour (for example, withdrawal and anxiety) found a significant effect of parent training (SMD=−0.48, 95% CI −0.84 to −0.13, p=0.0074; 2 studies, n=142). Meta-analysis of parenting skill changes following parent training found a significant change in parental perception of child behaviour, assessed using the Parenting Stress Index (mean difference [MD]=−10.52, 95% CI −20.55 to −0.48, p=0.04).

The analysis was limited by the poor methodological quality of the included studies, with risk of bias in the results. Data concerning ADHD-specific behaviour changes were ambiguous and important outcomes (for example, school achievement) were not reported. The authors concluded that this evidence was not strong enough to form a basis for clinical practice guidelines, with further research needed.

As noted above (see ‘Dietary elimination of food additives and colourings’), Sonuga-Barke et al. (2013) conducted a systematic review and meta-analysis of non-drug interventions for ADHD in children and young people (3–18 years), based on RCTs of dietary and psychological treatments. Of the 54 studies included (n=3154), 15 (n=1041) focused on behavioural interventions that included parent training (8 studies), combination of parent and child training (4 studies), combination of parent, child and teacher training (2 studies) and child training only (1 study, n=18). The intervention was significant when all studies were included in the meta-analysis (SMD=0.40, 95% CI 0.20 to 0.60, p=0.0001), but not when the analysis was restricted to the 7 studies with probably blinded assessments. Limitations with regard to behavioural interventions included considerable differences in the intensity and duration of therapy.

Together, this evidence suggests that parental training may bring some benefits for parents, but appears to have little impact on ADHD symptoms and behaviour outside the home, although further research is needed. The evidence is unlikely to have an impact on NICE CG72.

**Key reference**

Zwi M, Jones H, Thorgaard C et al. (2011) Parent training interventions for attention deficit hyperactivity disorder (ADHD) in children aged 5 to 18 years. Cochrane Database of Systematic Reviews issue 12: CD003018

**Telephone delivery**

McGrath et al. (2011) conducted 3 separate RCTs in single Canadian centres to assess telephone delivery of parent training or usual care for the parents of children with ADHD (n=72, aged 8–12 years), oppositional defiant disorder or anxiety. Children included had 6-month symptom duration and mild or moderate impairment in 2 or more domains of the Schedule for Affective Disorders and Schizophrenia (K-SADS-PL). Exclusion criteria included a co-intervention within 6 months, complex comorbidity, evidence of immediate danger to self or others, and serious cognitive delay.

The intervention received by parents of children with ADHD was provided through handbooks, videos and 12 weekly 40-minute telephone sessions from a coach, which involved skill material review, skill modelling using role playing and verbal examples, problem solving and skill implementation. Follow-up booster calls were made 2 and 4 months after treatment completion. The control group (usual care) did not receive any materials or coaching.
sessions, and were contacted only to complete the follow-up assessments. The primary outcome was diagnosis (successful treatment was defined as no diagnosis) based on a structured interview, K-SADS-PL (primary and comorbid diagnoses) and validated supplemental measurements conducted by telephone.

Although there was no significant treatment effect among children with ADHD when assessed 120 days after the intervention, significantly more were defined as successful than with usual care when assessed after 240 days (OR=2.18, 95% CI 1.06 to 7.33, p=0.03) and 365 days (OR=2.74, 95% CI 1.06 to 7.15, p=0.04).

Limitations included the risk of bias from unblinded reporting of outcomes by parents, and the lack of control for the attention given to the intervention group. The study may not be directly applicable to the UK setting so is unlikely to have an impact on NICE CG72, however the evidence suggests that telephone-based parent training shows benefits over no intervention. Further research is indicated because telephone or internet based interventions may increase access (offering convenience and potentially reducing drop-out) and allow more cost-effective delivery.

Key reference

Other psychological interventions
NICE CG72 advises that group psychological treatment (cognitive behaviour therapy and/or social skills training) may be appropriate for younger school-age children with ADHD. Particular emphasis should be given to targeting a range of areas, including social skills with peers, problem-solving, self-control, listening skills and dealing with and expressing feelings. For older age groups, individual psychological treatment may be more acceptable if group behavioural or psychological approaches have not been effective or have been refused.

Organisational skills training
Abikoff et al. (2013) conducted an RCT to compare the efficacy of 2 behavioural interventions to improve organisation, time management and planning difficulties in 158 children (aged 8–11 years) with ADHD treated at centres in the USA. The study also included a control group assigned to a waiting list. The primary outcome measures were the total score on the Children’s Organizational Skills Scale measured by teachers (COSS-T) and by parents (COSS-P) on completion of treatment. Other outcomes included organisational skills measured 1 month after completion of treatment, academic performance and proficiency, homework behaviours, family functioning, attitude towards school and teachers and global improvement, all measured using published scales.

Both interventions comprised 20 1-hour therapy sessions, held in the clinic twice a week over a 10–12 week period. Delivery was by psychologists (n=14) who provided both interventions. One intervention (Organisational Skills Training [OST]) is based on the assumption that children with ADHD lack organisational skills so this intervention took a playful approach to teach children new tools and routines, with prizes for in-session and at-home application of the methods. Session time was spent primarily with the child, with the parent joining for the last 10 minutes. The other intervention, (Parents And Teachers Helping Kids Organize [PATHKO]) is based on a performance deficit model, so motivates children by training teachers and parents to establish specific, individualised goals for children on written charts for daily completion. Session time was spent primarily with the parent, with the child joining for the last 10 minutes.

Compared with the control group, OST significantly improved organisational skills as rated by teachers (effect size=1.18, p<0.001) and by parents (effect size=2.77, p<0.001). Secondary
outcomes also showed significant improvement with OST. Compared with the control group, PATHKO significantly improved organisational skills as rated by teachers (effect size=1.21, p<0.001) and by parents (effect size=2.13, p<0.001). Most secondary outcomes also showed significant improvement with PATHKO, but academic proficiency was not improved. OST resulted in significant improvements in COSS-P total score compared with PATHKO (effect size=0.63, p<0.005). Both treatments showed maintenance of effects at 2-year follow-up.

Limitations of the study included some differences between baseline characteristics of the groups and the risk of rater bias. The population may also not be representative of children with ADHD in the UK.

Langberg et al. (2012) conducted an RCT to evaluate an intervention (Homework, Organization and Planning Skills [HOPS]) delivered by school mental health providers (7 school psychologists and 10 school counsellors) in 5 US school districts compared with a waiting list control group. Teachers and parents assessed the organisational skills in the 47 children (11–14 years) using subscales of COSS-T and COSS-P, respectively. Other outcomes measured included homework completion and management (assessed using the Homework Problems Checklist), school grades at the end of the school year and satisfaction with the intervention.

The HOPS intervention was delivered during the school day to the child in 16 sessions (each of 20 minutes duration) over an 11-week period, and included 2 meetings (each of 1 hour duration) held at school with parent and child. HOPS covered skills and provided tools to improve school materials organisation, homework recording and management, and planning/time management.

Compared with the control group, HOPS resulted in significant improvement on the COSS-P subscales of ‘organised actions’ (effect size=0.88, p=0.006) and ‘task planning’ (effect size=1.05, p<0.001). Parents also rated homework completion as significantly improved (effect size=0.85, p=0.001). Teacher ratings showed no significant improvement with the intervention. However, HOPS participants scored higher school grades than the comparator group for the first and second quarters of the school year during the intervention period (effect size=0.69–0.82, p=0.01–0.03). Most effects of the intervention were maintained 3 months after the end of treatment.

Limitations of the study included lack of blinding, differing therapist attention between groups, self-recruitment of intervention providers and lack of information on randomisation and treatment completion.

The evidence from these two studies is consistent with NICE CG72, indicating the value of organisational skills training to reduce the functional impact of ADHD in school-age children. Further research is needed to evaluate this intervention in the UK.

Key references

Langberg JM, Epstein JN, Becker SP et al. (2012) Evaluation of the homework, organization and planning skills (HOPS) intervention for middle school students with attention deficit hyperactivity disorder as implemented by school mental health providers. School Psychology Review 41: 342–64

Classroom-based behavioural intervention
NICE CG72 advises that teachers who have received training about ADHD and its management should provide behavioural interventions in the classroom to help children and young people with ADHD.
Mikami et al. (2013) conducted a RCT to assess social inclusion of children with ADHD undertaking behavioural management training with and without adjunctive procedures for the peer group. The study evaluated 24 children with ADHD (age 6–10 years) who were attending a US summer day programme with 113 previously unacquainted age- and sex-matched children without ADHD. Participants in the summer school were allocated to a class with children of the same age and gender (average of 3 children with ADHD and 7 children without ADHD in each class). Each class was led by 2 trainee teachers who did not know which children in their class were diagnosed with ADHD. Children remained with their class peer group for all activities.

The control intervention was Contingent Management Training (COMET), a traditional behavioural management treatment to improve socially competent behaviour in children with ADHD using a system of gaining or losing points based on compliance with approved behaviour. The alternative intervention was Making Socially Accepting Inclusive Classrooms (MOSAIC). This intervention used the same behavioural management approach as COMET but emphasised the importance of social inclusion by awarding points for positive peer behaviour and removing points for excluding peers, and avoided public comparison of children’s point totals to minimise social comparison. Trainee teachers were trained to use either COMET or MOSAIC. They used the intervention at all times with the whole class.

Children with ADHD attended the summer school for 4 weeks. They were randomly allocated for 2 weeks to a class taught using either the COMET (n=12) or the MOSAIC approach (n=12), with crossover after 2 weeks to the alternative intervention with a different class of unacquainted peers and teachers. Children without ADHD attended the summer school for 2 weeks. They were randomly allocated to a class taught using either the COMET (n=58) or MOSAIC (n=55) approach.

All children were rated every day by teachers using the Teacher-Child Rating Scale. During lunch and break periods when teachers were absent, children were videotaped by research assistants and negative peer interactions were independently analysed for each child. At the end of each 2-week period, all children nominated an unlimited number of peers who they liked (positive nomination), disliked (negative nomination) and considered friends (friendship nomination). All children also used a 5-point scale to rate how much they liked each peer in the class. A memory book was compiled for each class, with a message from each child to their individual classmates. Outcomes for children with ADHD were compared after the MOSAIC and COMET interventions.

No differences in teacher rating, negative peer interactions and positive nominations were observed between children with ADHD in classes taught using the COMET or MOSAIC intervention. However, when in MOSAIC compared with COMET children with ADHD received significantly:

- fewer negative nominations (effect size=0.23, 95% CI 0.00 to 0.48)
- more reciprocated friendship nominations (effect size=0.34, 95% CI 0.04 to 0.56)
- more favourable ratings from their peers on the 5-point scale (effect size=0.22, 95% CI 0.00 to 0.47)
- more positive memory book messages from peers relative to the same child when in COMET (effect size=0.19, 95% CI 0.00 to 0.45).

Limitations of the study included the downplaying of comparisons in points total during MOSAIC to prevent peers from devaluing those with few points, which could have reduced motivation relative to COMET. The small study size, social and ethnic homogeneity (81% white, university community) and high average intelligence of participants, and the US setting limit the relevance of the study to the UK population of children with ADHD. The evidence is
unlikely to have an impact on NICE CG72. Nevertheless, the evidence suggests the potential value for school-age children with ADHD of teacher-led whole-class behavioural interventions that reduce peer devaluation and emphasise social inclusion.

**Key reference**
Mikami AY, Griggs MS, Lerner MD et al. (2013) A randomized trial of a classroom intervention to increase peers' social inclusion of children with attention-deficit/hyperactivity disorder. Journal of Consulting and Clinical Psychology 81: 100–12

**Drug treatment**
NICE CG72 recommends that drug treatment is not indicated as the first-line treatment for all school-age children and young people with ADHD. It should be reserved for those with severe symptoms and impairment or for those with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment. Where drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the management of ADHD in children and adolescents.

**Effectiveness of drug treatment on school-related outcomes**
Prasad et al. (2013) conducted a systematic review and meta-analysis to assess the effectiveness of drug treatments on academic achievement and on-task behaviour in school-age children with ADHD. Studies were included in the review if they were RCTs that compared drug treatment for ADHD with no drug treatment, baseline or placebo, and reported outcomes of educational achievement and learning ability within a classroom or school environment. Only studies with participants aged 4–16 years and ADHD as the core condition were included. A total of 43 studies (n=2110) were included in the review, with the majority (37 studies) comparing the effects of methylphenidate with placebo.

On-task behaviour was generally measured by the length of time during observed intervals that children spent paying attention to task. Measures of academic performance were more variable, and included seatwork completion or productivity (percentage of the child’s assigned work that they completed) and seatwork accuracy (percentage of a child’s assigned work that they answered correctly). Insufficient information was provided or there were insufficient studies using the same outcome measure for 29 studies that were excluded from the meta-analysis. Analysis of on-task behaviour and academic performance was by individual drug treatment.

Methylphenidate significantly increased on-task behaviour in 17 of the 18 studies assessing this outcome. Pooled analysis of low dose methylphenidate (0.3 mg/kg or 10 mg fixed dose) compared with placebo showed a mean increase in observed on-task behaviour of 9.72% (95% CI 5.69 to 13.76%, p<0.00001; 9 studies). Pooled analysis of high dose methylphenidate (0.6 mg/kg or 17.5–20 mg fixed dose) compared with placebo showed a mean increase in observed on-task behaviour of 14.04% (95% CI 8.63 to 19.44%, p<0.00001; 7 studies). High-dose methylphenidate showed a mean increase in observed on-task behaviour of 2.96% over low-dose methylphenidate (95% CI 1.34 to 4.59%, p=0.0004; 7 studies).

Methylphenidate significantly increased the percentage of seatwork completed in 14 of the 15 studies assessing this outcome. Low dose methylphenidate compared with placebo showed a mean increase in work completed of 11.76% (95% CI 9.63 to 13.90%, p<0.00001; 9 studies). High dose methylphenidate compared with placebo showed a mean increase in work completed of 14.40% (95% CI 10.91 to 17.90%, p<0.00001; 6 studies). However, only 5 of the 14 studies assessing seatwork accuracy showed a significant effect of methylphenidate, with pooled analysis of 8 studies showing no significant effect of low-dose...
methylphenidate (no analysis reported for high dose methylphenidate). Meta-analysis of other measures of academic achievement with methylphenidate treatment was not possible. Of the 11 studies using independent arithmetic tests, 10 reported an increase in questions attempted and 8 reported an increase in correctly answered questions. Of the 10 studies using a variety of academic measures (such as grade averages), 7 reported improvement and 3 reported no significant effect of treatment.

Dexamfetamine was investigated in 5 studies. All reported significant improvement in the amount of academic work completed compared with placebo. Atomoxetine was investigated in 2 studies, with 1 reporting significant improvement in some academic measures, and 1 finding no improvement with treatment.

Limitations of the review include the variable quality of the studies included, the likely clinical heterogeneity, the variability in the duration of treatment and differing outcome definitions. This review adds to the evidence base for NICE CG72 by extending and clarifying the benefits of treatment with methylphenidate and dexamfetamine on school-related outcomes in children with ADHD. Although the evidence suggests that on-task behaviour is improved, the impact on academic attainment is less clear.

Key reference

Methylphenidate in children and young people with ADHD and additional problems
Simonoff et al. (2013) conducted an RCT to investigate the use of methylphenidate compared with placebo in children and young people with severe ADHD and intellectual disability. The 122 participants in the study were recruited through clinical referrals and community screening across the south east of England. Inclusion criteria included age 7–15 years, diagnosis of hyperkinetic disorder, intelligence quotient (IQ) of 30–69, living in a stable situation and regularly attending school. Exclusion criteria included current stimulant use, recent use of neuroleptic medication, epilepsy or psychotic conditions, and household resident with substance abuse disorder.

Children and young people randomised to drug treatment received methylphenidate 3 times daily, at increasing doses of 0.5 mg/kg, 1.0 mg/kg and 1.5 mg/kg, each for at least 1 week. At the end of the titration period, the optimal dose for each participant was determined on the basis of adverse events (assessed by parent, teacher and clinician) and behaviour improvement (assessed by parent and teacher on the Conners’ hyperactivity scale and hyperactivity subscale of the Aberrant Behaviour Checklist). Participants then received the optimal dose for the remainder of the 16-week trial.

Compared with placebo, methylphenidate treatment was associated with significantly increased adverse events of sleep difficulties (p<0.01) and poor appetite (p=0.02) but there were no significant differences in other parent-reported adverse events or in mean changes of blood pressure or heart rate. Methylphenidate treatment significantly improved ratings on the Conners hyperactivity scale given by parents (MD=−1.8, 95% CI −3.4 to −0.2, p=0.03) and teachers (MD=−3.2, 95% CI −4.9 to −1.5, p<0.001). Ratings on the hyperactivity subscale of the aberrant behaviour checklist was also improved with active treatment, as judged by parents (MD=−6.8, 95% CI −10.2 to −3.5, p<0.001) and teachers (MD=−6.7, 95% CI −10.0 to −3.3, p<0.001).

Limitations of the study included the high proportion of participants who did not adhere to drug treatment (n=33, 27%), although this is comparable to adherence rates in general UK healthcare. The study was not powered to detect the impact of treatment on ADHD symptoms and or for any moderating effects or interactions.
Riggs et al. (2011) carried out an RCT to evaluate extended-release methylphenidate compared with placebo in young people with ADHD who were receiving cognitive behaviour therapy (CBT) for substance misuse disorders. Participants (n=303, aged 13–18 years, mean age 16.5 years, 78.9% male, 61.7% white) met diagnostic criteria for ADHD and at least one non-tobacco substance use disorder. Exclusion criteria included psychotic or bipolar disorder, opiate dependence, methamphetamine misuse or dependence, and cardiac or serious medical illness. All participants received CBT throughout the 16-week drug trial.

Randomisation was to placebo or extended-release methylphenidate (starting dose 18 mg once daily with titration to 72 mg once daily or highest dose tolerated). The primary outcome measure was the clinician-administered ADHD Rating Scale. Secondary outcome measures included parent-administered ADHD Rating Scale, Adolescent Relapse Coping Questionnaire, Clinical Global Impression-Improvement (CGI-I) and the Massachusetts General Hospital Liking Scale question on perceived effectiveness of drug treatment. The primary outcome measure for substance misuse was the number of days of use in the past 28 days using standardised procedures.

The primary ADHD outcome measure showed no significant difference between treatment groups. Parent ADHD rating scores were significantly lower with treatment than placebo (MD=6.9, 95% CI 2.9 to 10.9, p<0.001). Compared with placebo, young people reported significantly greater improvement in domains of the Adolescent Relapse Coping Questionnaire (problem solving ability: MD=7, 95% CI 3 to 8, p=0.002; focused coping skills: MD=4, 95% CI 1 to 7, p=0.02) and a significant difference in perceived effectiveness of treatment (p<0.001). No significant differences between treatment groups were noted for CGI-I and substance misuse. The study was not powered to address safety, although there were more adverse events with drug treatment than with placebo (mean 2.4 versus 1.6 per patient, p=0.02).

Limitations of the study included concerns about possible lack of compliance with drug treatment in some participants. This evidence suggests that overall, drug treatment in addition to CBT may not result in improvements in ADHD over those seen with CBT alone, although drug treatment may lead to improvements in problem solving and focused coping skills. Because previous studies on methylphenidate in ADHD may have excluded participants with intellectual disability and substance misuse disorder, these studies add to the evidence base but are unlikely to have an impact on NICE CG72.

Key references


Lisdexamfetamine dimesylate
Lisdexamfetamine dimesylate is a pro-drug of dexamfetamine that is licensed for use in children and young people with ADHD (age 6 years and above) who have not shown adequate clinical response to methylphenidate. Unlike other drug treatments for ADHD, it is readily soluble so provides a liquid formulation, which may be of value for children and young people who are unable to swallow tablets or granules. Lisdexamfetamine dimesylate is not mentioned in NICE CG72.

NICE Evidence Summary: New Medicine 19 'Attention deficit hyperactivity disorder in children and young people: lisdexamfetamine dimesylate’ has recently been published. Although the Evidence Update found new evidence in this area (see the key reference Coghill et al. 2013
below, upon which the Evidence Summary is based), commentary is not provided because the Evidence Summary was recently issued \(^2\) and provides the latest information.

**Key reference**

1.6 **Transition to adult services**
No new key evidence was found for this section.

1.7 **Treatment of adults with ADHD**

**NICE CG72** recommends drug treatment as first-line treatment for adults with ADHD with moderate or severe impairment. Methylphenidate is the first-line drug, with atomoxetine or dexamfetamine tried if it is ineffective or unacceptable. \(^3\) If there is residual impairment despite drug treatment, CBT may be considered. There is potential for misuse and diversion of drug treatments for ADHD in adults in some settings, such as prison, although there is no strong evidence that this is a significant problem. Where there may be concern about the potential for drug misuse and diversion, atomoxetine may be considered the first-line drug treatment for ADHD in adults.

**Addition of CBT to medication for persistent symptoms of ADHD**

**Emilsson et al. (2011)** reported an RCT conducted in Iceland to evaluate the addition of CBT to drug treatment in adults with ADHD. Participants in the study (n=54) were 34 women with mean age 34.1 years and 20 men with mean age 33.5 years. All participants were on stable drug treatment for ADHD for at least 1 month (78% on methylphenidate, 20% on atomoxetine and 11% on other treatments). About a quarter of the participants (24%) took 1 drug treatment for ADHD, 30% took 2 drugs, and 46% took 3 or more treatments. Exclusion criteria included active drug misuse, severe mental illness and IQ below 85.

Participants continued with drug treatment and were randomised to receive treatment as usual or a 15-session programme of CBT. This consisted of modules on learning strategies to improve ADHD symptoms (attention, memory and organisational skills, and reduce impulsivity), problem solving skills, emotional control (including the management of anger and anxiety), prosocial skills and critical reasoning skills. The primary outcome measure was change from baseline in K-SADS-PL, modified for adults and translated into Icelandic. Secondary outcome measures included CGI and self-reported assessment of symptoms, anxiety and depression.

After adjusting for baseline means, combined CBT and drug treatment significantly improved K-SADS-PL compared with drug treatment plus treatment as usual. This was seen at the end of treatment (effect size=1.03, \(p<0.01\)) and 3 months later (effect size=1.17, \(p<0.05\)). Although CGI showed no significant effect of CBT addition at the end of treatment, it was significantly improved at 3 months follow-up (effect size=1.31, \(p<0.05\)). At the end of treatment, 4 out of 10 self-reported assessments showed significant improvement (effect size=0.32–0.94, \(p\leq0.05\)) and all showed significant improvement at 3 months follow-up (effect size=0.58–1.46, \(p\leq0.05\)).

\(^2\) Evidence Updates do not provide commentary on drugs and indications covered by a NICE Evidence Summary: New Medicine issued in the 12 months before publication of the Evidence Update.

\(^3\) At the time of publication of this Evidence Update, methylphenidate and dexamfetamine did not have UK marketing authorisation for use in adults with ADHD. Informed consent should be obtained and documented.
Limitations of the study included the small sample size and lack of ability to control for stability in drug treatment and other non-drug treatments during the study. Nevertheless, the evidence showing a large treatment effect with the addition of CBT to drug treatment for ADHD is consistent with NICE CG72.

Key reference

Methylphenidate treatment in a prison population
Ginsberg and Lindefors (2012) carried out a placebo-controlled RCT of extended-release methylphenidate in adults with ADHD in a high security Swedish prison for adult males typically convicted of violent or drug-related crimes. Inclusion criteria included confirmed ADHD, agreement not to behave violently during the study and stable comorbidity. People with intellectual disability, cardiac illness (symptoms, history or family history), epilepsy or glaucoma were excluded. All 30 participants had lifetime substance misuse disorders (predominantly amphetamine) and conduct disorder. Most participants had antisocial personality disorder (n=29) and mood and anxiety disorder (n=22), and 13 were receiving concurrent treatment for psychiatric disorders. Most participants were housed in a dedicated ADHD wing, separate from other wings to prevent exchange of drugs and staffed by prison officers educated about ADHD.

Participants were randomised to receive extended-release methylphenidate 36 mg/day initially, titrated to 72 mg/day over 1 week (mean age of group=33.5 years, mean IQ=89) or placebo (mean age of group=35.3 years, mean IQ=85) for 5 weeks. All participants received methylphenidate during the 47-week open-label extension, with twice daily administration permitted if needed to maintain symptom relief throughout the day. The primary outcome measure was the change in Conners’ adult ADHD rating scale, assessed by observers. Secondary outcome measures included self-reported ADHD symptoms and CGI.

At week 5, the Conners’ score decreased from baseline by 19.6 points (95% CI 14.7 to 24.5) in the group receiving methylphenidate, compared with 1.9 points (95% CI −0.4 to 4.2) in the placebo group, giving a treatment effect size of 2.17 (p<0.001). Methylphenidate significantly outperformed placebo on all secondary measures of efficacy (effect size=1.62–2.36, p≤0.004). All outcome measures also improved from baseline in the open-label extension. Regular supervised urinary drug screening did not reveal any significant drug misuse during the study.

Limitations of the study included the small sample size and lack of control group in the open-label phase. It may also be difficult to generalise the findings to the UK prison population, where inmates are not usually housed in dedicated ADHD wings, despite the high proportion of prisoners with ADHD. The lack of placebo effect contrasts with findings in other populations and may reflect the lack of environmental variation in the prison setting.

The evidence is consistent with NICE CG72, supporting the provision of services for imprisoned adults with ADHD, including those with complex comorbidities. Further studies in the UK are needed to evaluate the long term effects of ADHD treatment in prison populations of male and female adults and young offenders.

Key reference
1.8 How to use drugs for the treatment of ADHD

Risk of cardiovascular problems

NICE CG72 recommends that heart rate and blood pressure are monitored and recorded on a centile chart before and after each change in dose of ADHD medication, and routinely every 3 months. People taking methylphenidate, dexamfetamine or atomoxetine who have sustained tachycardia, arrhythmia or systolic blood pressure greater than the 95th percentile (or a clinically relevant increase) measured on 2 occasions should have their dose reduced and be referred to a paediatrician or adult physician.

A systematic review by Martinez-Raga et al. (2013) evaluated the risk of serious cardiovascular problems with drug treatments for ADHD. A total of 81 publications were included (number of participants not reported). Clinical studies and reports of licensed drugs for ADHD in children, young people and adults were included, as well as retrospective and prospective population-based studies of drug treatments for ADHD that reported cardiovascular adverse events. The review did not list the studies included. It was also unclear how the data selection and extraction processes were conducted, and there was no quality assessment of included studies.

Meta-analysis was not carried out. Results were reported as a narrative review for individual drugs, considering findings from controlled and open-label extension studies separately from population-based studies. The authors concluded that, despite a small but significant increase in blood pressure and heart rate, the risk of serious cardiovascular adverse events and sudden cardiac death associated with therapeutic doses of drugs for ADHD appears to be extremely low. The authors also suggested that further research should focus on the risk of cardiovascular symptoms or disease in adults who received drug treatment for ADHD as children.

Given the limitations of the review with regard to studies included and the analysis conducted, the conclusions should be interpreted with caution. However, the review findings are consistent with the recommendations of NICE CG72 to monitor carefully the cardiovascular parameters of children, young people and adults treated with these drugs.

Key reference
Martinez-Raga J, Knecht C, Szerman N et al. (2013) Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. CNS Drugs 27: 15-30
2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

**Prerequisites of treatment and care for all people with ADHD**
- Long term effects of pharmacological and non-pharmacological treatment for ADHD
- Interventions to improve attitudes towards treatment and treatment compliance among young people with ADHD

**Diagnosis of ADHD**
- Effect of stimulant medication on grey matter volumes in patients with ADHD

**Post-diagnostic advice**
- Restricted elimination diets for ADHD

**Treatment for children and young people**
- Behavioural interventions for ADHD
- Telephone-based mental health interventions for children with ADHD
- Homework, organisation, and planning skills for school children with ADHD
- Cognitive training for ADHD
- Neurofeedback for ADHD
- Comparative educational outcomes of different drug treatments for childhood ADHD
- Educational outcomes of atomoxetine in childhood ADHD
- Cost effectiveness of lisdexamfetamine in children and young people with ADHD

**Treatment of adults with ADHD**
- Short and long term benefits of methylphenidate for adult male prison inmates with ADHD

**How to use drugs for the treatment of ADHD**
- Do minor increases in heart rate and blood pressure caused by central nervous system stimulants in attention deficit-hyperactivity disorder (ADHD) patients result in adverse cardiovascular effects?

Further evidence uncertainties for ADHD can be found in the [UK DUETs database](https://www.ukduets.org) and in the [NICE research recommendations database](https://www.nice.org.uk/). UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.
Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Attention deficit hyperactivity disorder. NICE clinical guideline 72 (2008).

 Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 19 May 2011 (the end of the search period for the latest review of the need to update NICE clinical guideline 72) to 22 February 2013:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- ERIC (Educational Resources Information Centre)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- MEDLINE In-process
- PsycINFO

A supplementary search of PubMed was conducted up to 21 March 2013.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The initial broad search term ((attent* or disrupt* or impulsive* or inattenti*).sh) used in the search for the reference guideline was omitted and replaced with the more focused first term shown in Table 1. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews.

Additionally, 4 studies were identified outside of the literature search or in follow-up searches, of which 3 were included in the Evidence Update (Prasad et al. 2013, Simonoff et al. 2012 and Sonuga-Barke et al. 2013). Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NICE Evidence Services website.
Table 1 MEDLINE search strategy (adapted for individual databases)

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Figure 1 Flow chart of the evidence selection process

8187 records identified through search

2419 duplicates from searching

5768 records after duplicates removed

4506 records excluded at first sift

1262 records included after first sift

1082 records excluded at second sift

180 records included after second sift

146 records excluded at critical appraisal and evidence prioritisation

38 records discussed by EUAG

4 additional records identified by EUAG and supplementary search outside original search

19 records included by EUAG in published Evidence Update

19 records excluded by EUAG

EUAG – Evidence Update Advisory Group
Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group
The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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