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Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents

Review of Technology Appraisal 13

Technology Appraisal 98

Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents (review)

Ordering information

You can download the following documents from www.nice.org.uk/TA098

- The full guidance for this technology appraisal (this document).
- A quick reference guide, which has been distributed to healthcare professionals working in the NHS in England.
- Information for people with ADHD, their families and carers, and the public.
- The assessment report – details of all the studies that were looked at.

For printed copies of the quick reference guide or information for the public, phone the NHS Response Line on 0870 1555 455 and quote:

- N1010 (quick reference guide)
- N1011 (information for the public).

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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NOTE: This guidance replaces *Technology appraisal guidance* no. 13 issued in October 2000.

The Institute reviews each piece of guidance it issues. Following review and re-appraisal, the previous recommendations on the use of methylphenidate for attention deficit hyperactivity disorder in childhood have been updated and extended. This latest guidance provides recommendations on the use of methylphenidate, atomoxetine and dexamfetamine for the treatment of attention deficit hyperactivity disorder in children and adolescents.

1 Guidance

- 1.1 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.
- 1.2 The decision regarding which product to use should be based on the following:
 - the presence of comorbid conditions (for example, tic disorders, Tourette's syndrome, epilepsy)
 - the different adverse effects of the drugs
 - specific issues regarding compliance identified for the individual child or adolescent, for example problems created by the need to administer a mid-day treatment dose at school
 - the potential for drug diversion (where the medication is forwarded on to others for non-prescription uses) and/or misuse
 - the preferences of the child/adolescent and/or his or her parent or guardian.

- 1.3 If there is a choice of more than one appropriate drug, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed.
- 1.4 Drug treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD and should be based on a comprehensive assessment and diagnosis. Continued prescribing and monitoring of drug therapy may be performed by general practitioners, under shared care arrangements.

2 Clinical need and practice

- 2.1 ADHD is defined by the core signs of inattention, hyperactivity and impulsiveness. There are two main sets of diagnostic criteria in current use. The Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria define ADHD broadly to include three subtypes: a combined subtype in which all three core signs are present; a predominantly inattentive subtype in which inattention is present but not hyperactivity or impulsiveness; and a predominantly hyperactive-impulsive subtype in which hyperactivity and impulsiveness are present but not inattention. The DSM-IV definition of severe combined-type ADHD is similar to the International Classification of Mental and Behavioural Disorders 10th revision (ICD-10) definition of hyperkinetic disorder. The ICD-10 definition of hyperkinetic disorder requires abnormal levels of inattention, hyperactivity and impulsivity to be present for at least 6 months.
- 2.2 ADHD often coexists with other conditions such as oppositional defiant disorder, conduct disorder, learning disorders, anxiety, depression, epilepsy, tic disorders and Tourette's syndrome.
- 2.3 Estimates of the prevalence of ADHD vary widely within and between countries. It is estimated that around 5% of school-aged children and adolescents would meet the DSM-IV diagnostic criteria for ADHD, equivalent to 366,000 children and adolescents in England and Wales, but not all of

these children and adolescents would require treatment. Approximately 1% of school-aged children and adolescents would meet the diagnostic criteria for hyperkinetic disorder.

- 2.4 ADHD affects children and adolescents in different ways and degrees, but the consequences of severe ADHD can be serious for both the individual and their family and carers. Children with severe ADHD often have low self-esteem, develop emotional and social problems, and frequently underachieve at school. The signs of ADHD may persist into adolescence and adulthood, and are often associated with continuing emotional and social problems, substance misuse, unemployment, and involvement in crime.
- 2.5 Current treatments for ADHD include a range of social, psychological and behavioural interventions. These are mainly aimed at the child, but sometimes involve parents and/or guardians and teachers. Dietary interventions are often used when particular foods aggravate hyperactivity. The central nervous system (CNS) stimulants methylphenidate and dexamfetamine have been used in the treatment of ADHD for many years. Atomoxetine has been introduced more recently. Clinicians sometimes prescribe tricyclic and other antidepressant drugs, although these are not licensed for ADHD.

3 The technology

3.1 *Methylphenidate*

- 3.1.1 Methylphenidate is a CNS stimulant. It is licensed as part of a comprehensive treatment programme for ADHD, under specialist supervision, where remedial measures alone prove insufficient. It is a Schedule 2 controlled drug and is not currently licensed for use in children less than 6 years old. It is available in immediate-release tablets (Ritalin, Cephalon; Equasym, UCB Pharma) that are usually given in two or three daily doses. Methylphenidate is also available in modified-release formulations that enable once-daily dosing (Concerta XL, Janssen-Cilag; Equasym XL, UCB Pharma).

- 3.1.2 Treatment with immediate-release formulations of methylphenidate should be initiated at a dose of 5 mg once or twice daily, and increased if necessary to a maximum of 60 mg per day.
- 3.1.3 There are two modified-release formulations of methylphenidate. Concerta XL (Janssen-Cilag) is formulated to replace three times daily dosing with the immediate-release formulation and is used where treatment effects are required to persist into the evening. Treatment should be initiated at a dose of 18 mg once daily (in the morning), and increased if necessary up to a maximum of 54 mg once daily. Equasym XL (UCB Pharma) is formulated to be similar to twice-daily dosing with the immediate-release formulation. The recommended dose is 10 mg once daily initially, increased if necessary to a maximum of 60 mg once daily. Alternatively, the initial dose titration may be carried out with the immediate-release formulation.
- 3.1.4 Methylphenidate should be discontinued if there is no response after 1 month, and treatment should be suspended periodically to assess the child's condition.
- 3.1.5 Common adverse effects of treatment include insomnia, nervousness, headache, decreased appetite, abdominal pain and other gastrointestinal symptoms, and cardiovascular effects such as tachycardia, palpitations and minor increases in blood pressure. For full details of adverse effects and contraindications, see the relevant Summary of Product Characteristics.
- 3.1.6 At licensed doses, the annual cost of methylphenidate treatment is as follows:
- Ritalin 5–60 mg in one to two divided doses, £34–£407
 - Equasym 5–60 mg in one to two divided doses, £34–£364
 - Concerta XL 18–54 mg once daily, £329–£776
 - Equasym XL 10–60 mg once daily, £304–£730.

Costs are taken from the *British National Formulary*, 49th edition and exclude VAT. The cost of Equasym XL is based on information supplied by the manufacturer. However, costs may vary in different settings because of negotiated procurement discounts.

3.2 Dexamfetamine

- 3.2.1 Dexamfetamine (Dexedrine, UCB Pharma) is a CNS stimulant. It is licensed as an adjunct in the management of refractory hyperkinetic states in children, under specialist supervision. It is a Schedule 2 controlled drug and is not currently licensed for use in children less than 3 years old. Treatment should be initiated at a dose of 2.5 mg daily for children aged 3–5 years and 5–10 mg daily for children over 6 years, and increased if necessary up to a usual maximum of 20 mg per day (some older children have required 40 mg or more daily for an optimal response).
- 3.2.2 Common adverse effects are similar to those of methylphenidate. For full details of adverse effects and contraindications, see the Summary of Product Characteristics.
- 3.2.3 At its usual licensed dose (2.5–40 mg daily), the annual cost of dexamfetamine excluding VAT is £20–£313 (*BNF* 49). However, costs may vary in different settings because of negotiated procurement discounts.

3.3 Atomoxetine

- 3.3.1 Atomoxetine (Strattera, Eli Lilly) is licensed for the treatment of ADHD in children 6 years and older and in adolescents, under specialist supervision. It is a selective noradrenaline reuptake inhibitor, although the precise mechanism by which it works on ADHD is unknown. For children/adolescents of up to 70 kg body weight, treatment should be initiated at a dose of 500 micrograms/kg daily, and increased if necessary up to a maximum of 1.8 mg/kg daily, either as a single dose or in two divided doses. For adolescents of over 70 kg body weight treatment should be initiated at a daily

dose of 40 mg and increased according to response to a usual maintenance dose of 80 mg.

3.3.2 Common adverse effects of treatment include abdominal pain, decreased appetite, nausea and vomiting, early morning awakening, irritability and mood swings. Increased heart rate and small increases in blood pressure were observed in clinical trials. For full details of adverse effects and contraindications, see the Summary of Product Characteristics.

3.3.3 The annual cost of atomoxetine treatment excluding VAT is £712 when one tablet is given daily, and this doubles to £1424 if two tablets are given daily (*BNF* 49). However, costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (see Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group found a total of 64 randomised controlled trials that met the inclusion criteria for the systematic review. An additional trial (the Multimodal Treatment Study of Children with ADHD [MTA] study) that did not meet the inclusion criteria was also included. This study did not meet the inclusion criteria because it assessed 'medical management' rather than a specific drug, but its objectives were still relevant to this appraisal.

4.1.2 The clinical studies used a large number of different instruments to measure key outcomes, core symptoms, and/or quality of life. This makes comparisons across the different trials difficult.

Methylphenidate compared with placebo

4.1.2.1 A large proportion of the studies found by the Assessment Group included a comparison between methylphenidate and placebo. Most of these

studies were considered in the previous appraisal of methylphenidate in ADHD. The results of the additional studies used for this review were consistent with those in the previous appraisal. The evidence from short-term randomised placebo-controlled trials suggests that methylphenidate is an effective treatment to reduce core symptoms of ADHD in children who continue to take the medication.

Methylphenidate immediate-release compared with modified-release

- 4.1.2.2 There were seven studies comparing modified-release formulations of methylphenidate given once daily with immediate-release formulations administered two or three times daily. Of these, four were crossover studies and three were parallel studies. Of the four crossover studies, three used a modified-release formulation that is not marketed in the UK. All but one of the comparisons between modified- and immediate-release formulations included a placebo control.
- 4.1.2.3 With the exception of two very small crossover studies, most placebo-controlled studies found both immediate-release and modified-release methylphenidate to be superior to placebo in improving one or more core outcomes (thereby demonstrating that the effectiveness of both had been measured). Most studies did not indicate statistically significant differences in terms of measures of effectiveness when comparing the immediate-release and modified-release formulations with each other.
- 4.1.2.4 One 8-week comparison between Concerta XL and immediate-release methylphenidate in 145 children aged 6–12 years found that the mean change from baseline in a parent-administered symptom rating scale (SNAP IV) was significantly greater in the group who received Concerta XL. However, this study was open-label and so should be interpreted with caution.
- 4.1.2.5 In general, no statistically significant differences in the incidence of adverse effects were detected between immediate-release and

modified-release formulations apart from in one study in which there was higher incidence of headache in participants assigned to the modified-release formulation.

- 4.1.2.6 Overall, the Assessment Report concluded that there was little evidence of a difference in the effectiveness of immediate-release and modified-release formulations of methylphenidate.

Dexamfetamine compared with placebo

- 4.1.2.7 Eight of the studies included in the Assessment Report compared dexamfetamine with placebo, and one study compared amfetamine with placebo. Of these, one study did not report effectiveness endpoints (this was a study of adverse events only and compared dexamfetamine with chlorpromazine and hydroxyzine as well as placebo). The remaining studies found improvements in behavioural symptoms with dexamfetamine (or amfetamine) relative to placebo, one of which related to a modified-release formulation of dexamfetamine (which is not available in the UK). The quality of these studies was considered to be variable by the Assessment Group and most studies did not score well in the quality assessment.

Comparisons of dexamfetamine and methylphenidate

- 4.1.2.8 The Assessment Report included four crossover studies that directly compared dexamfetamine and methylphenidate. Two of the four studies included a placebo control.
- 4.1.2.9 One of the placebo-controlled studies was a three-way crossover comparison in which participants received methylphenidate, dexamfetamine and placebo for 3 weeks each. Results from two instruments used for rating behavioural problems (Conners' Teachers' Rating Scale and Conners' Parent Questionnaire) were presented graphically. For both instruments, differences between dexamfetamine and

placebo, and methylphenidate and placebo were reported to be statistically significant. The authors concluded that both drugs were highly and equally efficacious, but noted that frequently one drug or the other was preferable for any individual child.

- 4.1.2.10 The other study with a placebo group was a five-way crossover comparison of immediate- and modified-release methylphenidate, modified-release dexamfetamine (Dexedrine spansule), pemoline, and placebo. However, this study has limited relevance to this appraisal because neither modified-release dexamfetamine nor pemoline are licensed for use in the UK, nor the formulation of modified-release methylphenidate used in this study.
- 4.1.2.11 The studies without a placebo group comprised one two-way crossover comparison of methylphenidate and dexamfetamine, and a three-way crossover comparison—the third arm being treatment with caffeine capsules. The two-way comparison reported that methylphenidate was statistically significantly more effective than dexamfetamine when assessed using teacher-rated scales, but not when assessed using parent-rated scales. This study compared methylphenidate at a dose defined as ‘medium’ dose by the Assessment Group (0.6 mg/kg/day) while the dose of dexamfetamine was defined as ‘low’ (0.3 mg/kg/day). For the three-way comparison, methylphenidate and dexamfetamine were not statistically significantly different from each other for any of the effectiveness outcomes (it appears that both were significantly more effective than caffeine).
- 4.1.2.12 It appears that no statistically significant differences with respect to adverse effects were found between dexamfetamine and methylphenidate.

Atomoxetine compared with placebo

- 4.1.2.13 Eight of the studies included in the Assessment Report compared atomoxetine with placebo. Six of these studies were efficacy studies over

6–9 weeks in which participants were randomised to atomoxetine or placebo. Three of the studies used a once-daily dosing regimen for atomoxetine; the other three used a twice-daily regimen. All six of these studies found statistically significant differences in favour of atomoxetine on measures of hyperactivity and clinical global impression. However, one study that compared three doses of atomoxetine found that differences in hyperactivity and clinical global impression did not reach statistical significance in the lowest dose group (0.5 mg/kg/day).

4.1.2.14 Adverse effects included an increased risk of loss of appetite and weight loss in the atomoxetine-treated groups in some of the studies. Atomoxetine did not appear to be associated with an increased risk of headache, stomach ache or insomnia.

4.1.2.15 The other two studies investigated atomoxetine withdrawal. In one study, a total of 416 children and adolescents who had responded to open-label treatment with atomoxetine were randomised to continued atomoxetine or placebo for 9 months under double-blind conditions. At 9 months, fewer participants in the atomoxetine group had relapsed (relapse is defined as a return to 90% of baseline symptom severity) than in the placebo group (22.3% vs 37.9%; $p = 0.002$). Fewer details of the other discontinuation study are available in the Assessment Report. The authors concluded that discontinuation of atomoxetine was well tolerated.

Atomoxetine compared with dexamfetamine and methylphenidate

4.1.2.16 There were no studies directly comparing atomoxetine and dexamfetamine. There were three studies comparing atomoxetine and methylphenidate, two of which were unpublished. Two of these studies were open-label and did not include a placebo control. Because of this lack of blinding, the results of both studies should be interpreted with caution.

- 4.1.2.17 The published study was a 10-week open-label comparison between immediate-release methylphenidate and atomoxetine in children aged 7–15 years who had previously responded favourably to methylphenidate. There was no placebo control. The group sizes were uneven; 184 patients were randomised to atomoxetine, and 44 to immediate-release methylphenidate. This study reported no difference between the two drugs for hyperactivity or clinical global impression. However, a finding of no difference on subjective outcomes is difficult to interpret in the absence of a placebo group because it cannot be certain that drug effects were successfully measured in either group.
- 4.1.2.18 One unpublished study was a randomised, double-blind, placebo-controlled study comparing atomoxetine with modified-release methylphenidate (OROS formulation, Concerta XL) during acute treatment for 6 weeks. The study population comprised 516 children aged 6–16 years with ADHD (atomoxetine, n = 222; modified-release methylphenidate, n = 220; and placebo, n = 74). Patients may or may not have received previous treatment with stimulants, but those who had previously had an inadequate response to stimulant treatment were excluded from the study. The primary endpoint was response rate (defined as a reduction of 40% or more in ADHD rating scale [ADHD-RS] total symptom score from baseline). The response rate was 45% in the atomoxetine group, 56% in the modified-release methylphenidate group, and 24% in the placebo group. The response rates for both drugs were statistically significantly different from placebo, and the response rate for atomoxetine compared with modified-release methylphenidate was statistically significantly different ($p = 0.016$). Results of subgroup analyses for previously treated and treatment-naïve participants were presented, but these were not interpreted using appropriate statistical tests for identifying subgroup effects.
- 4.1.2.19 The other unpublished study was a 3-week, open-label comparison of the OROS formulation of modified-release methylphenidate (that is,

Concerta XL) and atomoxetine in 1323 children aged between 6 and 12 years. Participants were randomised in a 2:1 ratio to methylphenidate or atomoxetine; those who were known to be non-responders to treatments indicated for ADHD were excluded. This study reported significantly greater symptom improvement with modified-release methylphenidate than with atomoxetine in the ADHD rating scale for hyperactivity. This study did not score well in the Assessment Group's quality assessment.

4.2 Cost effectiveness

4.2.1 Seven published studies were found; five of these were economic evaluations and two were quality of life studies. The Assessment Group developed a model to compare the cost effectiveness of different drug strategies. Three consultees included economic evaluations in their submissions.

4.2.2 The results of the published economic evaluations are difficult to compare due to the use of different outcome measures. All studies suffered from a lack of data, and none considered the long-term outcomes or adverse events associated with ADHD. Only one study incorporated utility values and this reported an incremental cost-effectiveness ratio (ICER) of £9200 per quality-adjusted life year (QALY) gained for immediate-release methylphenidate compared with placebo.

4.2.3 The Assessment Group developed a probabilistic cost–utility model to compare the use of the drugs under consideration, both alone and in combination with behavioural therapy for a cohort of children with ADHD aged 6 years. In the base-case analysis, a 1-year time horizon was used. A secondary analysis extended the time horizon to the point when the cohort reached 18 years of age using an estimate of the age-dependent decline of symptoms. The base-case analysis considered alternative strategies featuring three active treatments (atomoxetine, dexamfetamine and one of the methylphenidate formulations), followed by no treatment as the last in the sequence.

- 4.2.4 The decision by the Assessment Group to consider three drug strategies rather than one or two, was based on their finding that each active treatment was cost effective relative to no treatment. The Assessment Group therefore considered it reasonable to assume that it would always be cost effective to change to the next untried drug, rather than stopping treatment after the first or second drug is found to be ineffective or not tolerated. This analysis relies on modelling assumptions, two of which are that response to one drug is independent of the response to another, and that response and withdrawal rates for second- and third-line treatments are the same as those for first-line treatment.
- 4.2.5 Clinical response was measured as a score of 1 or 2 (much improved or improved) on the clinician-rated clinical global impression improvement (CGI-I) subscale. Withdrawal rates were based on all reported withdrawals within trials. As non-response was included as a reason for withdrawal in some trials, this resulted in some double counting of non-responders. Non-drug costs were based on a published study that obtained estimates of resource use from a panel of experts. Drug costs were based on the average dose of active medication taken from the trials used in the calculation of response rates. Utility values were based on a published poster which derived utilities from EQ-5D questionnaires completed by the parents of 142 children with ADHD in the UK. Utility values were 0.837 for responders and 0.773 for non-responders, regardless of treatment type.
- 4.2.6 In the base-case analysis, 19 relevant strategies were compared, including a no treatment option. All strategies were cost effective compared with no treatment, with ICERs falling below £7000 per QALY gained. Given the limited data used to inform response and withdrawal rates and the small differences in QALY gains generated, it is not possible to distinguish between the different strategies on the grounds of cost effectiveness.
- 4.2.7 The results of the model comparing different treatment strategies with no treatment were relatively robust to the sensitivity analyses undertaken,

including the addition of behavioural therapy, the use of different definitions of response, and the use of alternative utility values. The results were also robust when the time horizon was extended beyond 1 year using an estimated rate of remission. However, due to the limited data available, the long-term model did not incorporate the possible long-term adverse effects and benefits of treatment.

- 4.2.8 The manufacturer of Concerta XL (Janssen-Cilag) submitted a cost–utility analysis in which Concerta XL is compared over a 1-year period with immediate-release methylphenidate, atomoxetine, Equasym XL, and behavioural therapy in children with severe ADHD. The model assumes that children whose condition fails to respond to first-line therapy, or who experience intolerable side effects within 1 month, are switched to second-line treatment with behavioural therapy, combination therapy (behavioural therapy plus first-line pharmacotherapy) or other drug treatment (methylphenidate for patients receiving first-line behavioural therapy, otherwise dexamfetamine). Children not responding to second-line therapy within 1 month are assumed to discontinue all treatment. Based on these assumptions, Concerta XL is associated with an ICER of £5000 per QALY gained compared with immediate-release methylphenidate and dominates Equasym XL, atomoxetine, and behavioural therapy (that is, it is associated with more QALYs and a net cost saving relative to these alternative treatments).
- 4.2.9 The manufacturer of Equasym XL (UCB Pharma) submitted a cost–utility analysis in which Equasym XL is compared with no treatment in children with severe ADHD unable to comply with twice-daily immediate-release methylphenidate, over a 1-year period. A secondary analysis also compared Equasym XL with twice-daily immediate-release methylphenidate. The model assumes that children whose condition fails to respond to Equasym XL or who experience intolerable side effects within the 42-day titration period progress to second-line treatment with dexamfetamine. Non-compliers are assumed to continue on treatment, but experience no health benefits. Of those who discontinue second-line therapy, 50% progress to behavioural

therapy and experience health benefits, while 50% progress to no treatment and experience no benefits. In the base-case analysis, Equasym XL is associated with an ICER of £14,700 per QALY gained compared with no treatment. In the secondary analysis, the ICER for Equasym XL compared with immediate-release methylphenidate is £11,000 per QALY gained.

4.2.10 The manufacturer of atomoxetine (Eli Lilly) submitted a cost–utility analysis examining the addition of atomoxetine to an existing medical management strategy for ADHD, over a 1-year period. The existing strategy consists of either immediate- or modified-release methylphenidate first line, followed by dexamfetamine second line and finally no treatment, with atomoxetine being added as an option prior to methylphenidate. A number of subgroups are considered depending on prior treatment history (naïve or previously exposed to methylphenidate) and on whether the use of stimulants is appropriate (that is, whether they are contraindicated or not). The model assumes that children responding to treatment can relapse in subsequent cycles, and that adverse events either resolve in these cycles or result in discontinuation of treatment. For the different subgroups considered, the ICERs for atomoxetine compared with the relevant medical management strategy ranged from £11,500 per QALY gained for stimulant-naïve patients with contraindications to stimulants to £15,400 per QALY gained for stimulant-exposed patients who responded to stimulants.

4.2.11 To summarise, the results of the published economic evaluations are difficult to compare. All studies suffer from a lack of data, and none consider the long-term outcomes or adverse events associated with ADHD. The results of the Assessment Group model suggest that methylphenidate, dexamfetamine and atomoxetine are all cost-effective treatments for ADHD. However, given the limited data used to inform response and withdrawal rates and the small differences in benefits between different treatments, it is not possible to compare different drug strategies. All three manufacturers adopted different approaches to the estimation of treatment effectiveness and associated utility

values. However, the models all generated ICERs falling below £20,000 per QALY gained.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of methylphenidate, atomoxetine and dexamfetamine, having considered evidence on the nature of ADHD and the value placed by users on the benefits of these drugs, from children and adolescents with ADHD, their parents and guardians, those who represent them, and clinical experts. The Committee was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.
- 4.3.2 The Committee considered the evidence on clinical effectiveness and concluded that methylphenidate, atomoxetine and dexamfetamine are effective in controlling the symptoms of ADHD relative to no treatment. While some studies had included direct comparisons of different drugs and formulations, in general they reported few differences in measures of effectiveness between the products. In some studies, there were statistically significant differences in measures of effectiveness between drugs (see paragraphs 4.1.2.4, 4.1.2.18 and 4.1.2.19), but these studies had methodological flaws. In particular, the Committee considered the double-blind, placebo-controlled comparison of atomoxetine and modified-release methylphenidate (see 4.1.2.18). They considered that the exclusion of patients who have previously failed to respond to stimulants could have biased the result of this and other clinical studies comparing atomoxetine with methylphenidate. The Committee was not persuaded that superiority of one drug over another had been established in these trials. Given the large variations across the trials in measures of efficacy, the variable reporting of adverse events, and the lack of long-term studies, the Committee was not able to differentiate between the drugs on the grounds of clinical effectiveness.

- 4.3.3 The Committee understood that the individual drugs are associated with different contraindications and precautions for use. These may greatly influence the selection of appropriate therapy in children and adolescents with comorbid conditions. For example, atomoxetine may be preferred to methylphenidate and dexamfetamine for children with coexistent tic disorders or Tourette's syndrome. The Committee accepted the importance of having a range of drug treatment options.
- 4.3.4 The Committee noted the potential difficulties created by multiple daily dosing. In particular, concerns were raised regarding compliance and the social stigma associated with taking medicine, the availability and willingness of schools and school staff to store and administer medicine, and the potential for drug diversion (where the medication is forwarded on to others for non-prescription uses). The Committee therefore acknowledged that there would be situations in which a single-dose regimen, which can be achieved with modified-release formulations, would be the preferred treatment approach. However, the Committee concluded that there could be circumstances in which the limited range of dosage strengths available in the modified-release formulations would make titration difficult and an immediate-release formulation would be preferable.
- 4.3.5 With regard specifically to the use of dexamfetamine, the Committee noted that the licensed indication is limited to refractory hyperkinetic states. The evidence from clinical trials is generally of poor quality and relatively few studies have been conducted in recent years. The Committee also noted the concerns of the clinical and patient experts that dexamfetamine has a greater potential for diversion and misuse than the other drugs under consideration. Because of these limitations, the Committee acknowledged that dexamfetamine was unlikely to be used as a first-line drug for the majority of children or adolescents with ADHD. However, it concluded that dexamfetamine should remain a treatment option for use in specific situations. The Committee expected that clinicians experienced in the management of

ADHD would take into account these considerations when initiating drug treatment for a child or adolescent with ADHD.

- 4.3.6 The Committee carefully considered all of the evidence on cost effectiveness and concluded that all three drugs are cost effective relative to no drug treatment. It reviewed the Assessment Group's modelling approach and noted the differential cost effectiveness of adopting different drug treatment sequences according to this analysis. The Committee noted that some of the strategies considered in the cost effectiveness analysis might be unsuitable for some individuals because of considerations of adverse events, comorbidities and concordance with therapy. On this basis and given the limitations inherent in the models, the Committee was unable to draw conclusions on the relative cost effectiveness of different drug treatment strategies. Although each of the drugs being appraised is acceptably cost effective versus no treatment, the Committee understood that some treatment strategies might be more cost effective than others in individual patient circumstances.
- 4.3.7 The Committee noted the variation in the costs of the drugs and treatment regimens. It also noted that since the unit cost of a dose of atomoxetine is the same regardless of the strength, twice-daily dosing could double the cost of treatment with this drug. The Committee considered that for the majority of potential users, where there is a choice of more than one appropriate product on clinical grounds, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed.
- 4.3.8 Overall, the Committee concluded that there were a number of important factors to be taken into account when selecting a treatment for an individual child or adolescent with ADHD. These included consideration of concordance and compliance issues, particularly with respect to the timing of doses, and whether the individual has difficulties relating to the administration of doses during the day, for example at school. Other important considerations include

previous adverse effects, comorbidities, and the preferences of patients and carers. All of these factors may influence the choice of product.

- 4.3.9 On the basis of evidence from experts, the Committee concluded that treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD and should be based on a comprehensive assessment and diagnosis. However, the Committee agreed that continued prescribing and monitoring of drug therapy may be performed by general practitioners, under shared care arrangements.

5 Recommendations for further research

- 5.1 Given that ADHD is a chronic condition which may require long-term treatment, there is a need for further data on long-term outcomes of drug treatments.
- 5.2 Further research is required to determine the utility values associated with ADHD and different treatment strategies, including drug therapy and the associated adverse event profiles of different drugs. Ideally, utilities should be obtained with the use of a generic health valuation measure, valued with public preferences.
- 5.3 Research is required to develop and validate the QALY measure when applied to child and adolescent populations for any condition.

6 Implications for the NHS

- 6.1 Prescribing of stimulant drugs for ADHD has steadily increased in recent years. In 1998 there were approximately 220,000 prescriptions in England for stimulant drugs (methylphenidate and dexamfetamine) at a net ingredient cost of about £5 million; in 2004 the number of prescriptions for these drugs had almost doubled to 418,300 at a cost of almost £13 million. In 1998 there were no licensed modified-release formulations of methylphenidate, and the use of unlicensed formulations accounted for only a tiny proportion of stimulant

prescriptions. In 2004, modified-release formulations accounted for 54% of all methylphenidate prescriptions and 79% of the total net ingredient costs for this drug. Atomoxetine was licensed in the UK in May 2004. In 2004 there were approximately 15,500 prescriptions for atomoxetine in England at a cost of £1.2 million. It is not anticipated that this guidance will result in a major increase over current trends in the rate of prescribing for ADHD.

- 6.2 Atomoxetine and the modified-release formulations of methylphenidate are more expensive than immediate-release formulations of dexamfetamine and methylphenidate. The costs associated with treatment monitoring are likely to be highest during the initial titration stages as doses are adjusted. The immediate-release formulations are often used at this stage because of the greater flexibility in dosage increments.
- 6.3 This guidance is not likely to have a significant impact on other resources. However, any increase in the uptake of modified-release methylphenidate and once-daily atomoxetine regimens may reduce the need to administer in-school doses of immediate-release methylphenidate and dexamfetamine.

7 Implementation and audit

- 7.1 NHS organisations that offer treatment for children and adolescents with ADHD and general practitioners should review their current practice and policies to take account of the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to the care of children and adolescents with ADHD should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
 - 7.3.1 Drug treatment for a child or adolescent with ADHD is initiated only by an appropriately qualified healthcare professional with expertise in ADHD, and is based on a comprehensive assessment and diagnosis.

7.3.2 Where drug treatment is considered appropriate, methylphenidate, atomoxetine or dexamfetamine is offered, within licensed indications, as an option in the management of ADHD in a child or adolescent.

7.3.3 The decision regarding which product to use considers the following:

7.3.3.1 the presence of comorbid conditions

7.3.3.2 the different adverse effects of the drugs

7.3.3.3 specific issues regarding compliance identified for the individual child or adolescent

7.3.3.4 the potential for drug diversion and/or misuse

7.3.3.5 the preferences of the child or adolescent and/or his or her parent or guardian.

7.3.4 If there is a choice of more than one appropriate drug, the drug with the lowest cost is prescribed.

7.4 Local clinical audits on the management of ADHD in children or adolescents could also include the following: ensuring that children or adolescents and their parents are informed about ADHD, treatment options, and the importance of medication compliance; clinician follow-up on any effects of drug treatment; compliance with national or local guidelines on the management of ADHD or shared care arrangements with local GPs; and planning for the continuation of care for adolescents who are approaching the age for moving from child and adolescent care services to adult services.

8 Related guidance

- 8.1 The Institute plans to publish guidance on parent training/education programmes for the treatment of conduct disorders in children in 2006.
- 8.2 The Institute plans to publish a clinical guideline on pharmacological and psychological interventions for ADHD in children, young people and adults in 2008.

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 9.2 The guidance on this technology will be reviewed in March 2009.

Andrew Dillon
Chief Executive
March 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE. The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair and vice-chair between them attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam

Radiologist, St George's Hospital, London

Professor Ron Akehurst

Dean of School of Health and Related Research, University of Sheffield

Dr Sunil Angris

General Practitioner, Waterhouses Medical Practice, Staffordshire

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Stirling Bryan

Professor of Health Economics, Health Economics Facility, Health Services Management Centre, University of Birmingham

Professor John Cairns

Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine.

Professor David Chadwick

Professor of Neurology, Department of Neurological Science, Walton Centre for Neurology & Neurosurgery, Liverpool

Dr Lorna Duggan

Consultant Forensic Psychiatrist in Developmental Disabilities, St Andrew's Hospital, Northampton

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Dr Trevor Gibbs

Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford

Professor Philip Home (Vice-Chair)

Professor of Diabetes Medicine, Department of Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, Molecular & Clinical Pharmacology, University of Sheffield

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary, Newcastle-Upon-Tyne

Dr George Levvy

Chief Executive, Motor Neurone Disease Association, Northampton

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England, Solihull, West Midlands

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Professor John Lumley

Honorary Consultant, The Ernest Cooke Clinic Microvascular Unit, Great Ormond Street, Bart's and the Royal London NHS Trust, Barbican, London

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Christa Roberts

UK Manager Vascular Intervention, Guidant Ltd.

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, Westlake Surgery, Somerset

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Professor Mary Watkins

Professor of Nursing, University of Plymouth

B. NICE Project Team

Each appraisal of a technology is assigned to one or more Health Technology Analysts and Technology Appraisal Project Managers within the Institute.

Tina Eberstein and Janet Robertson

Technical Leads, NICE project team

Dr Sarah Cumbers and Alana Miller

Project Managers, NICE project team

Appendix B. Sources of evidence considered by the Committee

- A The Assessment Report for this appraisal was prepared by Centre for Reviews and Dissemination, University of York.

King S, Riemsma R, Drummond M et al. *A systematic review of the clinical and cost-effectiveness of methylphenidate hydrochloride, dexamfetamine sulphate and atomoxetine for attention deficit hyperactivity disorder (ADHD) in children and adolescents*, December 2004.

- B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturers/sponsors:

- Celltech Group Plc
- Cephalon (UK)
- Eli Lilly and Company
- Janssen-Cilag Ltd
- Rubio Laboratorios S.A.

II Professional/specialist and patient/carer groups:

- ADDERS
- Barnardo's
- National Attention Deficit Disorder Information and Support Service
- Neonatal & Paediatric Pharmacists Group
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Paediatrics and Child Health

- Royal College of Psychiatrists
- Royal Pharmaceutical Society
- The Paediatric Psychopharmacology Group
- Young Minds
- Department of Health
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- National Collaborating Centre for Mental Health
- NHS Quality Improvement for Scotland
- National Public Health Service for Wales

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Ms Andrea Bilbow, Founder and Director, National Attention Deficit Disorder Information and Support Service
- Mr Mike Heimann, Clinical Nurse Specialist, Child and Adolescent Mental Forum
- Mrs Jenny Missen, Chairperson, ADDISS and Hounslow and Spelthorne Parents' Support Group
- Ms Jackie O'Connell, Consultant Nurse for ADHD, East Sussex County Healthcare NHS Trust
- Ms Noreen Ryan, Nurse Consultant, Royal Bolton Hospital
- Professor Eric Taylor, Head of Department, Child & Adolescent Psychiatry, Institute of Psychiatry, Kings College London

Appendix C. Detail on criteria for audit of the use of methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents

Possible objectives for an audit

An audit could be carried out to ensure that methylphenidate, atomoxetine and dexamfetamine are prescribed appropriately for children and adolescents who have ADHD.

Possible patients to be included in the audit

An audit could be carried out on all children and adolescents who are referred with symptoms of ADHD in a reasonable time period for audit, for example, 6 months to 1 year, and for whom it is considered that drug treatment is appropriate.

Alternatively, the audit could include all children and adolescents who are referred with symptoms of ADHD and drug treatment not considered to be appropriate could be specified as an exception in those audit measures that refer to drug treatment.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of methylphenidate, atomoxetine and dexamfetamine for ADHD are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. Drug treatment for a child or adolescent with ADHD is:</p> <p>a. initiated only by an appropriately qualified healthcare professional with expertise in ADHD and</p> <p>b. based on a comprehensive assessment and diagnosis.</p>	100% of children and adolescents in the audit for whom drug treatment is prescribed for 1a and b.	None	<p>Clinicians will need to agree locally on the data source for determination of who initiated the drug treatment. Clinicians will need to agree locally on defining an appropriately qualified healthcare professional with expertise in ADHD, for audit purposes, for example, a child and adolescent psychiatrist or a paediatrician or learning disability expert with specialised training and experience in ADHD. Clinicians will need to agree locally on what constitutes a comprehensive assessment and diagnosis, for audit purposes.</p>
<p>2. For those children for whom drug treatment is determined to be appropriate, methylphenidate, atomoxetine or dexamfetamine is offered, within licensed indications, as an option.</p>	100% of children and adolescents in the audit for whom drug treatment is determined to be appropriate.	None	<p>Methylphenidate is available as Ritalin, Equasym, Concerta XL or Equasym XL. Atomoxetine is available as Strattera. Dexamfetamine is available as Dexedrine. Methylphenidate and atomoxetine are not currently licensed for use in children less than 6 years of age. Dexamfetamine is not currently licensed for use in children less than 3 years of age. Clinicians will need to agree locally on how it is determined that drug treatment is appropriate and how the offering of the option of drug therapy is documented, for audit purposes.</p>
<p>3. The decision regarding which product to use considers the following:</p> <p>a. the presence of</p>	100% of children and adolescents in the audit who are prescribed methylphenidate	None	<p>'Comorbid conditions' include tic disorders, Tourette's syndrome or epilepsy. See the Summary of Product</p>

<p>comorbid conditions and</p> <p>b. the different adverse effects of the drugs and</p> <p>c. specific issues regarding compliance identified for the individual child or adolescent and</p> <p>d. the potential for drug diversion and/or misuse and</p> <p>e. the preferences of the child or adolescent and/or his or her parent or guardian.</p>	<p>or atomoxetine or dexamfetamine.</p>		<p>Characteristics for adverse effects of the drugs. 'Specific issues regarding compliance' could include problems created by the need to administer a mid-day dose at school. 'Drug diversion' could include where the medication is forwarded to others for non-prescription uses. Clinicians will need to agree locally on how consideration of 3 (a)–(e) is documented, for audit purposes.</p>
<p>5. If there is a choice of more than one appropriate drug, the drug with the lowest cost is prescribed.</p>	<p>100% of children and adolescents who are prescribed drug treatment.</p>	<p>None</p>	<p>'Cost' takes into account daily required dose and product price per dose. Clinicians will need to agree locally on the source of cost information, for audit purposes.</p>

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **excep**tion listed}{\text{Number of patients to whom the **meas**ure applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.