NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

The clinical effectiveness and cost effectiveness of methylphenidate for hyperactivity in childhood

Version 2 – for consultation

Some information was submitted as 'commercial in confidence' to the Institute by Medeva. This information has been removed from this current version of the Assessment Report, though it was included in Version 1 that was sent to the Appraisal Committee prior to their meeting of 27th July.

Authors: J Lord and S Paisley

Correspondence to: Appraisals Group, NICE,
90 Long Acre, London WC2E 9RZ, UK

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CONTRIBUTIONS OF AUTHORS

SP provided advice on the design of the review, conducted the literature search and screened abstracts for inclusion, and commented on a draft of this report. JL selected papers for inclusion, assessed the quality of studies, extracted and analysed data and drafted the report.

CONFLICTS OF INTEREST

None.

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> Jadad AR, Boyle M, Cunningham C, Kim M and Schachar R. Treatment of Attention-Deficit/Hyperactivity Disorder. Evidence Report/Technology Assessment No. 11 (Prepared by McMaster University under Contract No. 290-97-0017). AHRQ Publication No. 00-E005. Rockville, MD: Agency for Healthcare Research and Quality. November 1999.

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We also base sections of the report on upon a review conducted for the Canadian Coordinating Centre for Health Technology Assessment by a group of researchers from the University of British Columbia:

> Miller A, Lee SK, Raina P, Klassen A, Zupancic J and Olsen L. A review of therapies for attention-deficit/hyperactivity disorder. 1998. Ottowa, CCOHTA.

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All responsibility for the content of the report remains with the authors.

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ABBRIEVIATIONS

ADD	Attention Deficit Disorder (DSM-I to DSM-III)
ADHD	Attention Deficit and Hyperactivity Disorder (DSM-IV)
AE	Adverse effects of treatments
AHCPR	Agency for Health Care Policy and Research
AHQR	Agency for Healthcare Research and Quality
CAMHS	Child and adolescent mental health services
CCOHTA	Canadian Coordinating Office of Health Technology Assessment
CD	Conduct disorder
C/G	Overall measure of core/global outcomes
Core	Measures of individual core “symptoms” - hyperactivity, inattention and impulsivity
CPRS	Conners Parent Rating Scales
CTRS	Conners Teacher Rating Scales
DEX	Dexamphetamine Sulphate
D/A	Depression/anxiety-related outcomes
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, version 3
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, version 4
HD	Hyperkinetic Disorder (ICD-10)
ICD-10	International Classification of Diseases, version 10
MAOI	Monoamine-oxidase inhibitor
MBD	Minimal Brain Disorder
MPH	Methylphenidate hydrochloride
ODD	Oppositional Defiant Disorder
QALY	Quality Adjusted Life Year
RCT	Randomised controlled trial
S/A	School/academic related measures of outcome
SPC	Summary of product characteristics
SSRI	Selective serotonin-reuptake inhibitor
SMD	Standardised mean difference
WMD	Weighted mean difference

SUMMARY

Background

Hyperkinetic Disorder (HD) is characterised by the presence of severe and pervasive signs of inattention, hyperactivity and impulsiveness. It is estimated that approximately 1% of children may meet the diagnostic criteria for HD. The broader definition of Attention Deficit/ Hyperactivity Disorder (ADHD) leads to higher estimates of prevalence. Methylphenidate is a central nervous system stimulant that is indicated for use as part of a comprehensive treatment programme for attention-deficit hyperactivity disorder (ADHD) when remedial measures alone prove insufficient.

Aims and Objectives

The aim of this review is to evaluate the clinical effectiveness and cost effectiveness of methylphenidate for hyperactivity in childhood.

Methods

This review was based largely upon a systematic review conducted for the US Agency for Health Care Policy and Research (AHRQ). Information from this source was supplemented from another systematic review conducted for the Canadian Coordinating Office for Health Technology Assessment (CCOHTA). These reviews were updated by a systematic review of recently published research and a search for other systematic reviews, guidelines and economic evaluations. Information from industry submission to the Institute was also considered.

Results

Quantity and quality of evidence

- The AHRQ review identified 77 RCTs, 48 with a crossover design and 29 with a parallel group design. One non-randomised study was included in the review of adverse effects. Overall, the quality of the methodological reporting of the trials was poor, and hence there is a relatively high probability of bias. Most of the studies also suffered from factors that limited their external validity or generalisability.
- Twenty-six studies met the inclusion criteria for the CCOHTA review. Of these, eight were relevant to the comparison of methylphenidate with placebo, which was not included in the AHRQ review.
- A further eight relevant trials were identified through our updated review.
- Four economic modelling studies were identified, including two cost-utility studies, one cost-effectiveness study and one cost-benefit analysis.

Clinical effectiveness evidence

- There is evidence from meta-analysis of placebo-controlled RCTs that methylphenidate is efficacious at improving core ADHD core behaviours, at least

in the short-term while children continue to take medication. There is some evidence of improvements across other outcome dimensions.

- There are few head-to-head randomised comparisons of methylphenidate and another stimulant medication (dexamphetamine) that is licensed for the treatment of childhood HD in the UK. The existing evidence is of relatively poor quality and gives inconsistent results.
- There is insufficient evidence to judge the relative effectiveness of methylphenidate and tricyclic antidepressants, which are sometimes used to treat HD.
- There is little evidence from randomised direct head-to-head comparisons of the relative effectiveness of methylphenidate compared to behavioural interventions. The studies that do exist are of relatively poor quality, but suggest that methylphenidate is more effective over the medium and short term than behavioural interventions.
- There is insufficient evidence to support the superiority of methylphenidate combined with a behavioural intervention over methylphenidate alone. The RCT evidence is of relatively poor quality and most comparisons fail to detect any significant difference, although some findings in favour of combined therapy have been reported.
- There is RCT evidence, some of relatively good quality, which suggests that the addition of methylphenidate to behavioural treatment programmes is beneficial. Improvements in short and medium term outcomes were observed across a number of dimensions.
- Evidence from placebo-controlled clinical trials shows that common side effects of methylphenidate are relatively mild and short-lived, and that more severe side-effects are very rare.

Economic evidence

- The additional cost per QALY gained for MPH compared to no treatment has been estimated at £9,200 (£4,700 to £28,200) per QALY gained and at £14,600 (£5,600 to £17,500) per QALY gained. A Canadian study has also estimated that MPH therapy costs an additional $386 ($444 to $714) for a gain of one standard deviation in the CTRS hyperactivity index.
- The Canadian review estimated that the addition of MPH to a relatively modest behavioural intervention would cost an additional $958 for a one standard deviation gain in the CTRS hyperactivity index. Estimates based on the MTA Collaborative Group trial suggest that the addition of medication to multimodal behavioural therapy costs an additional £1,600 (£700 to £4,500) for an additional one standard deviation gain in the SNAP hyperactivity/impulsiveness index.
- If all 6 to 16 year olds with HD in England and Wales, who are not currently receiving medication, were to start MPH therapy, the total cost to the NHS would be approximately £37.6 m in the first year.

Conclusions

Methylphenidate is licensed for use as a second-line adjunct to other non-drug interventions. The evidence included in this review indicates that the addition of

methylphenidate (or other stimulant medication) to behavioural treatment is clinically effective and has a relatively attractive incremental cost-effectiveness ratio. However, the evidence also suggests that this treatment strategy is sub-optimal compared to first-line treatment with stimulant medication, followed up if necessary by behavioural intervention.

Despite this, there may nevertheless be reasons for preferring a more conservative approach to the use of medication. In particular, parent preference and worries about long-term safety, the risks of addiction and abuse have been cited as reasons for continuing to treat medication as a second-line intervention. These concerns are difficult to prove or disprove from the current research base. Further, in the absence of long-term evaluations of the impact of methylphenidate on overall quality-of-life, it is difficult to weigh up the balance of risks and benefits.

1. AIM OF THE REVIEW

To evaluate the clinical effectiveness and cost effectiveness of methylphenidate for hyperactivity in childhood.

2. BACKGROUND

2.1 Description of underlying health problem

2.1.1 Diagnostic criteria

In Europe diagnosis is usually, though not exclusively, based upon the International Classification of Diseases (ICD-10) criteria (1). These define ***Hyperkinetic Disorder*** (HD) according to the presence of three cardinal features:

- *Inattention* – difficulty in concentrating on activities for very long.
- *Hyperactivity* – an inappropriate excess of movement.
- *Impulsivity* – acting without reflecting.

To meet the ICD-10 criteria for HD it is necessary that:

- all three core signs should be present 'to a degree that is maladaptive and inconsistent with the developmental level of the child',
- they should cause 'clinically significant distress or impairment in social, academic, or occupational functioning',
- they should be persistent over time (present for at least six months)
- and pervasive (present in more than one situation, usually at home and school).

Further, the disorder should not meet the criteria for pervasive developmental disorders, manic episode, depressive episode or anxiety disorders, and the onset of the disorder should be no later than the age of 7 years.

These ICD-10 criteria are conservative in comparison to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, which are most commonly used by US clinicians. Three main versions of the DSM criteria are available: the 3rd edition (DSM-III); the revised 3rd edition (DSM-IIIR); and the 4th edition (DSM-IV) criteria (9-11). The 1994 DSM-IV criteria define ***Attention-Deficit /Hyperactivity Disorder*** (ADHD) according to the presence of *either* signs of inattention *or* signs of hyperactivity/impulsivity. Three subtypes are defined: predominately inattentive type, predominately hyperactive/impulsive type, and combined type.

As with the ICD-10 criteria, DSM-IV requires that the signs should be persistent and of sufficient severity to be considered maladaptive and inconsistent with the child's developmental level, with clear evidence of clinically significant impairment in social, academic, or occupational functioning. However, DSM-IV requires only that *some* (not all) of the signs are pervasive and present before the age of seven. Also, they state only that ADHD symptoms do not occur 'exclusively' during the course of

pervasive developmental disorders or psychotic disorders and that they can not be 'better accounted for' by other diagnoses such as anxiety or depression. Thus HD may be seen as a subgroup of ADHD.

There is considerable controversy about the diagnostic validity of this disorder (47). Some people deny that it exists at all (116), others argue that it is a valid diagnosis requiring treatment (60;75). A number of features make the diagnosis of HD or ADHD problematic:

1. Hyperactivity appears to be normally distributed in the population and the cut-off between 'normal' and 'abnormal' children is essentially arbitrary. However, this applies to many accepted medical diagnoses, such as hyperlipidaemia. Further, there is evidence that the presence of signs of inattention and impulsivity, along with hyperactivity, does define a distinct group of children (109). A diagnosis of HD is also more predictive of a response to drug therapy than a diagnosis of ADHD (110). Thus, there is firmer evidence of discriminant validity for the ICD-10 diagnostic criteria than for the DSM-IV criteria (42).
2. The aetiology of ADHD/HD is still unclear. There is increasing evidence that it is a brain disorder, with a genetic component (38;50;60), although further research is needed to firmly establish this (75). Research suggests a range of risk factors including psychosocial along with genetic factors (109).
3. Comorbid disorders are common, including patterns of disruptive behaviour (oppositional defiant and conduct disorders), learning disorders, anxiety and depression, tic disorders and Tourettes syndrome.

There is further debate about whether patterns of hyperactive/impulsive/inattentive behaviour in children are best characterised as a homogenous disorder (as suggested by the HD diagnosis) or, rather, as two or more problem complexes (as in the subtypes of ADHD) (101;120).

2.1.2 Prevalence

Estimates of the prevalence of ADHD/HD vary widely within and between countries – one review finding a reported range from 1.7% to 17.8% (36). This is partly due to the use of different diagnostic criteria; one would expect the prevalence of HD to be lower than that of ADHD. Variations may also arise because of different methods of assessment and cultural differences in the interpretation of behaviour (43). It is also possible that there are some true variations in prevalence due to differences in underlying risk factors.

A systematic review of the prevalence of ADHD in the US unscreened school-age population (45) found big differences between studies – with prevalence estimates from 4% to 26%. Significant contributors to this variation were gender, diagnostic tool (DSM-III or DSM-IIIR) and setting (community or school), but not age. The review estimated the overall prevalence at 9% (95% CI: 6% to 14%) for boys and 3% (95% CI: 2% to 4%) for girls. It also noted the results of a study that demonstrated that the estimated prevalence of ADHD is much lower when impairment is required for diagnosis than when impairment is not required (7% compared to 16%) (123).

Estimates of prevalence based on the ICD-10 diagnosis of HD are less common.

One study of 7 to 8 year old boys in East London reported a 1.7% prevalence of HD (109). Allowing for the lower prevalence of this disorder in girls, this translates to an overall prevalence in this age group of around 1% (42). Community surveys of school-age children report a boy-to-girl ratio of about 2:1, though the ratio may be closer to 1:1 in older adolescents (36).

With a prevalence of 1% about 73,400 children between the ages of 6 and 16 in England and Wales would meet the diagnostic criteria for HD (**Table 1**).

Table 1. Estimated prevalence of ADHD/HD

	Age	*1997 Thousands of people*		
		Resident population[1]	*Prevalence of ADHD*	*Prevalence of HD*
			5%	1%
England	6-11	3,881	194.0	38.8
	12-16	3,035	151.8	30.4
	17-18	1,211	60.6	12.1
	6-16	6,916	345.8	69.2
	6-18	8,127	406.3	81.3
Wales	6-11	235	11.8	2.4
	12-16	189	9.5	1.9
	17-18	74	3.7	0.7
	6-16	424	21.2	4.2
	6-18	499	24.9	5.0
E&W	6-11	4,116.0	205.8	41.2
	12-16	3,224.0	161.2	32.2
	17-18	1,285.4	64.3	12.9
	6-16	7,340.0	367.0	73.4
	6-18	8,625.4	431.3	86.3

1 Mid-1997 estimates, Office for National Statistics (www.statistics.gov.uk/statbase/xsdataset.asp)
2 (13)
3 (109)

2.1.3 Natural history and comorbidity

ADHD is often accompanied by other psychiatric comorbidities, including oppositional defiant and conduct disorders (30%), conduct disorder (28%), anxiety (26%), depression (18%), and learning disabilities (12%) (45). In older children it may be associated with problems of substance abuse (94).

Prospective studies of school-age children with ADHD have shown persistence of symptoms, at least into early adolescence (36). Research in this area is problematic because of changing diagnostic criteria and differences in study design. However, most patients (70% to 80%) diagnosed with ADHD as children continue to show symptoms in adolescence, and continue to meet the diagnostic criteria (54). As adults, many patients (60%) still show symptoms, though fewer meet diagnostic criteria (54).

HD/ADHD has been linked to increased risk of poor academic achievement, emotional and social problems, unemployment, criminality and substance use in later life.

> "*… in some children there is a progression from hyperkinetic disorder, through comorbid conduct disorder to antisocial behaviour, delinquency and criminality…"* (42)

2.2 Guidelines and management

Six guidelines for the diagnosis and treatment of ADHD have been identified (6;17;24;31;44;111). Guidelines by the Scottish Intercollegiate Guidelines Network (SIGN) (6) and the British Psychological Society (BPS) (17) were made available for this report but are still at draft stage. Guidelines by the American Medical Association (AMA) for the AMA Council of Scientific Affairs (44) and the Council of Europe Pompidou Group (24) make recommendations for policy for the management of ADHD. These include the development of established standards of care and management in the form of guidelines, education and training for professionals involved in the management of ADHD and areas for further research. The Pompidou Group makes specific recommendations regarding the prevention of drug misuse. Guidelines published by the European Society for Child and Adolescent Psychiatry (the 'European Guidelines') (111) and the American Academy of Child and Adolescent Psychiatry (AACAP) (31) make recommendations for the diagnosis and treatment of individual patients. The management options for ADHD are also described in an issue of the Drug and Therapeutics Bulletin (2)

The published guidelines all acknowledge the problems associated with reaching consensus, particularly international consensus, on the management of ADHD. Barriers include:

- the differing diagnostic criteria (DSM-IV and ICD-10), (although the European Guidelines suggest the usefulness of being able to make a narrow or broad diagnosis depending on the individual);
- under-diagnosis or over-diagnosis irrespective of diagnostic criteria, leading to possible over-prescription of medication;
- and the differing licensing regulations for medication across different countries.

A subsequent paper by Overmeyer, one of the authors of the European Guidelines, places the guidelines in the context of the United Kingdom and makes recommendations for practice applicable to the UK (83).

The European and AACAP Guidelines (31;111) make broadly similar recommendations specifying the importance of thorough assessment and the development of treatment plans which make best use, for the individual, of the treatment options available. Both outline the complexity of problems or needs of children diagnosed as having HD/ADHD and state that multimodal treatment is usually indicated. The European Guidelines include a decision tree to aid treatment planning.

The following description of the available management options and recommendations for diagnosis and treatment are based largely on the 1995 Drug and Therapeutics Bulletin (2). Recommendations specific to the European or

AACAP guidelines are indicated.

2.2.1 Assessment and Investigations

Initial assessment in primary care should include asking the parent(s) about the child's behaviour and direct observation of the child in the consulting room. Rating scales (see section 3.3 on page 13) may be useful in deciding whether a child should be referred to a specialist for full assessment. However, it is not recommended that such scales should be the sole basis of diagnosis (2).

A full specialist assessment will usually include questioning parents and teachers about the child's behaviour, direct observation of the child, and a family assessment. Again, rating scales may be used to inform diagnosis. Physical examination and tests may be appropriate to rule out other possible causes of hyperactivity or inattention such as hearing loss, epilepsy, thyroid disorders, fragile X syndrome or side effects of drug treatments.

Once diagnosis is established, the nature of the disorder and prognosis and the treatment alternatives should be discussed with the carer(s).

> "*It is important that parents know that there is a large genetic component in hyperactivity and that they are helped to understand the child's predicament and feel that their own difficulties are acknowledged. They need to know how they can help the child by a positive and encouraging approach.*" (2)

Contact with parent support groups may be helpful.

The European Guidelines state the importance of assessing the child more than once as part of the full specialist assessment (111). The AACAP Guidelines describe how assessment parameters might differ for different age groups (pre-school, 6-12 years, adolescents and adults) (31)

2.2.2 Non-drug therapy

Many non-drug intervention strategies exist. Behavioural approaches aim to modify problem behaviours by providing internal or external rewards and reinforcement. The approach may focus on the child, the parent(s) and/or the whole family. Educational interventions aim to improve classroom behaviour and performance by minimising distractions and focussing on the child's interests and abilities. The choice of approach should be tailored to the child, the family and the school (2). It is often difficult to determine the exact nature of behavioural interventions from study reports because of limited descriptive information (55).

Dietary interventions are seen as possibly useful in cases where a parent has observed that a particular food aggravates hyperactivity. However the European and AACAP guidelines state that dietary interventions are often difficult to implement and maintain and that there is no evidence linking diet with hyperactivity. Both recommend that dietary interventions should not be prescribed routinely.

2.2.3 Drug therapy

Pharmacological interventions are generally recommended only as an adjunct to non-drug interventions. Medication remains controversial, largely because of concerns over long-term safety and the risk of abuse (93). Opponents also argue that medications may be inappropriately prescribed, in the interests of parents or

teachers rather than in the interests of the child (90).

Methylphenidate hydrochloride (Ritalin® produced by Novartis Pharmaceuticals and Equasym® by Medeva Pharma) is the most commonly used medication for this disorder in the UK. It is a central nervous system stimulant, licensed for use:

> "… *as part of a comprehensive treatment programme for attention-deficit hyperactivity disorder (ADHD) when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders*."

Diagnosis may be made according to DSM-IV or ICD-10 criteria. A comprehensive treatment programme is defined to include psychological, educational and social measures. MPH is licensed as a Schedule 2 controlled drug, and so is subject to requirements relating to prescriptions, safe custody and the need to keep registers.

The Summary of Product Characteristics (SPC) documents for Ritalin and Equasym note that MPH is not indicated in all cases of ADHD, but that it should only be used after detailed history taking and evaluation. The decision to prescribe MPH should depend on an assessment of the severity of symptoms and their appropriateness for the child's age. MPH is not indicated for use in children less than six years of age. The SPCs note that drug treatment is usually discontinued during or after puberty, although no firm guidelines for withdrawal of treatment are given.

Treatment should be initiated at 5mg once or twice daily, and increased up to a maximum of 60mg per day. If improvement of symptoms is not observed after appropriate dosage adjustment over one month, the drug should be discontinued. It is also recommended that MPH should be discontinued periodically (under careful supervision) to assess the child's condition.

Contraindications include: marked anxiety, agitation or tension; symptoms or family history of tics or Tourette's syndrome; hyperthyroidism; severe angina or cardiac arrhythmia; glaucoma; and thyrotoxicosis. The SPC also notes that MPH should not be used to treat severe depression. Caution is advised in the use of MPH for patients with epilepsy and psychotic disorders. Because of the danger of misuse, care is needed for emotionally unstable patients, such as those with a history of drug or alcohol dependence.

Nervousness and sleeplessness are very common (>=10%) at the beginning of treatment, but can usually be controlled by dose adjustment. Common side effects (>=1% of patients) include: headache, drowsiness, dizziness and dyskinesia; abdominal pain, nausea and vomiting; dry mouth; tachycardia, palpitations, arrhythmias, changes in blood pressure and heart rate; rash, pruritus, urticaria, fever, arthralgia and hair loss.

Moderately reduced weight gain and slight growth retardation have been reported, so careful monitoring of growth is recommended. It is also recommended that blood pressure should be monitored, particularly in patients with hypertension. Because of the absence of long-term safety and efficacy data, patients on long-term therapy should be carefully monitored and complete and differential blood counts and platelet counts performed periodically

Dexamphetamine sulphate (Dexedrine®, Medeva Pharma) (DEX) is also licensed for adjunctive use (under specialist supervision) in the management of refractory hyperkinetic states in children (age 6 and over). The contraindications and side

effects are similar to those of MPH. The British National Formulary warns that both stimulant medications should be used with caution because they retard growth and the effect of long-term therapy has not been evaluated.

Another stimulant medication, ***magnesium pemoline***, is now only available in this country on a named patient basis because of concerns over its liver toxicity (111).

The ***tricyclic antidepressants*** amitriptyline, imipramine and nortriptyline are licensed for use for nocturnal enuresis in children. They are sometimes prescribed, "off-label", to children with ADHD/HD, particularly where anxiety is also present.

A number of ***other drugs*** are occasionally used, including clonidine, monoamine-oxidase inhibitors (MAOIs), selective serotonin-reuptake inhibitors (SSRIs) and beta-blockers. Concerns have been expressed over the lack of safety and efficacy data to support the use of these drugs in children.

2.2.4 Current service provision

It is difficult to obtain reliable Information on the use of methylphenidate for children with HD/ADHD. Prescription Pricing Authority and Welsh Office data shows that the cost of dispensing the drug in the community was approximately £3.3m for England and Wales in 1998/99 (**Table 2**). Most of this expenditure would have been for children with HD/ADHD, although MPH is also prescribed for adults. Expenditure on dexamphetamine is very much lower (about £0.4m). These data do not include items dispensed in hospitals.

Table 2. Expenditure on central nervous system stimulants

	England	Wales	Total
Net ingredient cost 1999 (£)			
Methylphenidate	£3,100,300	£160,200	£3,260,500
Dexamphetamine	£349,400	£15,800	£365,200
Total	£3,449,700	£176,000	£3,625,700
Number of annual doses			
Methylphenidate (30mg/day)	15,250	788	16,037
Dexamphetamine (15mg/day)	9,307	421	9,728
Total	24,556	1,209	25,765

Information is not available on the number of people for whom MPH was prescribed. A lower limit may be crudely estimated by dividing the net ingredient cost by the average annual cost of the medication, say £203 at an average daily dose of 30mg. This calculation suggests that upwards of 25,000 people were prescribed MPH in England and Wales in 1998/99. Novartis report that an estimated 20,000 children are currently receiving methylphenidate (80).

There has been a large increase in MPH prescribing over recent years. This probably reflects increasing awareness of the disorder amongst clinicians, parents and teachers, rather than any true increase in prevalence. The proportion of children receiving psychostimulants remains low in the UK compared to the US and some other countries (63). Whether this relatively conservative approach is appropriate or not is a matter for debate.

MPH is licensed in the UK for use only under specialist supervision and so is usually

prescribed by paediatricians or child psychiatrists. General practitioners, though, may often be responsible for repeat prescribing. Data from the national Morbidity Survey (3) are shown in **Table 3**. These figures indicate that most children consulting because of HD see the GP only once because of this problem. Overall, only about one in a hundred prevalent cases see their GP because of HD in a year (using a 1% prevalence rate). Consultation rates are higher for boys than for girls, and higher for pre-school than for school-age children.

Table 3. Primary care consultation rates

	Rates per 10,000 person years at risk		
	Age 0-4	Age 5-15	All ages
Patients consulting			
Male	17	5	2
Female	5	1	0
Male and female	11	3	1
Consultations with doctor			
Male	22	5	2
Female	6	2	1
Male and female	15	4	1
New and first ever episodes			
Male	15	5	2
Female	5	0	0
Male and female	10	2	1

Source: (3)

These low primary care consulting rates may not be surprising, since many children with HD access services through alternative routes, including voluntary and self-help schemes, community or hospital based child and adolescent mental health services (CAMHS) and educational support services.

The Audit Commission has criticised the level of service provision for children and young people with mental health problems, including HD/ADHD (13). They found high levels of variation around the country and argued that there was a need for more co-ordination between agencies.

2.3 Outcome measures

Measuring the outcomes of interventions for HD/ADHD is complex – the disorder impacts on many aspects of health and well being, and there are many alternative measurement instruments available. In their review of treatments for ADHD, Jadad *et al* (55) selected six main dimensions of interest (see **Box 1**). There is a wide range of instruments that may be used to measure outcomes across these various dimensions. These include direct observation methods, psychometric testing and behavioural rating scales. Rating scale questionnaires are usually intended for completion by parents or teachers.

A review commissioned by the US AHCPR assessed the validity and reliability of behavioural rating scales (45)[1]. These included both specific scales designed to screen for ADHD, and "broad-band" scales designed to screen for various symptoms including ADHD symptoms. Some of the scales are available in more than one version, often with different parent and teacher versions. Most of the scales have subscales to measure outcomes across more than one dimension. The scales are suitable for different age groups, though most are not suitable for very young children. Some scales include adolescents, others do not.

Box 1. Outcome dimensions included in the AHRQ review (55)

1. ***Core/global "symptoms" (C/G)***[2] – including overall assessment of symptoms, overall assessment of the core features of ADHD and functional performance.
2. ***Individual core "symptoms"* (Core)** – separate assessments of hyperactivity, inattention and impulsivity.
3. ***School/academic performance (S/A)*** – including achievement tests, grades, verbal skills, reading, mathematics, spelling and measures of social competence.
4. ***Depression/anxiety-related outcomes (D/A)*** – including measures of emotional well being, crying, sadness, global mood and self-esteem as well as measures of depression and anxiety.
5. ***Conduct/oppositional-disorder-related outcomes (CD/ODD)*** – including specific measures for oppositional defiant disorder, conduct disorder, aggressiveness and other behaviour disturbances.
6. ***Adverse effects (AE)*** – including changes in appetite, effects of growth, somatic effects, mood changes, motor tics and drug addiction.

Green *et al* found that the Conners Rating Scales (1997 revised version) (26) contained scales that were highly effective at discriminating between referred ADHD children and normal controls. None of the broad-band scales effectively discriminated between referred and non-referred children.

Of the disease-specific scales, there was good evidence of validity and reliability for the Attention Deficit Disorders Evaluation Scale (ADDES) and some of the Conner's rating scales, particularly the Connors Teacher Rating Scales (CTRS) and the hyperactivity index of the 39-item scale (CTRS-39-HI). For the broad-band scales, good evidence of validity and reliability was available for the Behaviour Assessment System for Children (BASC) and some versions of the Child Behaviour Checklists (CBCL).

[1] Summary report and information about obtaining the full report are available from http://www.ahrq.gov/clinic/adhdsutr.htm

[2] Jadad *et al* note that the core features of hyperactivity, inattention and impulsivity are really "signs" not "symptoms", since they are observed phenomena rather than subjective experiences of the patients.

3. CLINICAL EFFECTIVENESS

3.1 Review questions

The study question for this current review was to appraise "*the clinical and cost effectiveness of methylphenidate for children with hyperactivity*".

This broad question was interpreted in terms of seven specific questions that are particularly relevant to clinical practice for this group of patients in this country:

A) *Is MPH more effective than no treatment (placebo)?*

B) *Is MPH more or less effective than other licensed stimulants (DEX)?*

C) *Is MPH more or less effective than the tricyclic antidepressants licensed for use in children (amitriptyline, imipramine or nortriptyline)?*

D) *Is MPH more or less effective than non-drug interventions?*

E) *Do non-drug interventions add to the effectiveness of MPH?*

F) *Does MPH add to the effectiveness of non-drug interventions?*

G) *How common are adverse effects with MPH (compared to placebo, DEX or the tricyclic antidepressants)?*

Given that stimulants are licensed as a secondary adjunct to programmes of psychosocial therapy, question F is particularly pertinent. The question "a*re non-drug interventions more effective than no treatment?"* is clearly important as well. However, this does not strictly fall within the remit of this technology appraisal (since it does not relate to the use of methylphenidate).

3.2 Systematic Reviews

3.2.1 The AHRQ review

The US government's Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic review of the literature on treatments for ADHD from researchers at McMaster University in 1997 (55)[3]. The questions addressed in the AHRQ review are listed in **Table 2**. It did not include a separate analysis of the short-term effects (<3 months) of stimulants compared to placebo (though the long-term placebo-controlled effects of stimulants were included, 5ai). The decision to exclude short-term placebo-controlled evaluations of stimulants was based upon the fact that a team of researchers commissioned by the Canadian Coordinating Office for Health Technology Appraisal (CCOHTA) were looking at this question (see below). Jadad and colleagues had access to a pre-publication version of the CCOHTA report (73). They also obtained information from three earlier meta-analyses (61;82;113).

[3] Selected sections of the AHRQ report are provided as an annex to this document. A summary of the findings and information about how to obtain the full report is available at www.ahrq.gov/clinic/adhdsum.htm.

Table 2. Questions addressed in the AHRQ review

COMPARISONS	*Question*
1. Drug-to-drug comparisons	
a. Same drug comparisons[4]	-
b. Stimulant vs. stimulant comparisons:	-
i. MPH vs. DEX	B
ii. MPH vs. pemoline	-
iii. DEX vs. pemoline	-
c. Stimulant Vs tricyclic antidepressants:	
i. MPH vs. desipramine	-
ii. MPH vs. imipramine	C
2. Drug vs. non-drug comparisons	
a. DEX vs. Efamol (a dietary supplement)	-
b. DEX vs. behavioural	-
c. MPH vs. behavioural	D
d. Medication vs. behavioural (MTA trial)	(D)
3. Evaluation of therapies given in combination	
a. Stimulant vs. combination of drugs	
i. MPH vs. MPH + other (caffeine, thioridazine, haloperidol, desipramine)	-
ii. DEX vs. DEX + other drug (caffeine)	
b. Stimulant vs. stimulant plus non-drug intervention	-
i. MPH vs. MPH + behavioural	
ii. DEX vs. DEX + behavioural	E
iii. Medication vs. behavioural (MTA trial)	-
c. Non-drug vs. stimulant plus non-drug intervention	(E)
i. MPH + behavioural vs. behavioural	
ii. DEX + behavioural vs. behavioural	F
iii. Medication + behavioural Vs. behavioural (MTA trial)	-
	(F)
4. Tricyclic antidepressants vs. placebo	
a. Desipramine vs. placebo	-
b. Imipramine vs. placebo	-
5. **Evaluation of long-term therapies** (>=12 weeks)	
a. MPH evaluations	
i. MPH vs. placebo	A
ii. MPH vs. thioridazine	-
iii. MPH vs. imipramine	C
iv. MPH vs. behavioural	D
b. DEX vs. other (placebo, lithium carbonate, behavioural)	-
c. Medication vs. behavioural, combined and community controls (MTA trial	(D)
6. **Evaluation of therapies for ADHD in adults** (>18 years)	-
7. Evaluation of adverse effects of medications	
a. MPH Vs. placebo	G
b. MPH Vs. DEX	G
c. MPH Vs. other (bupropion, pindolol, pemoline, thioridazine, desipramine)	-
d. DEX Vs. other (placebo, L-Amph, hydroxyzine, chlorpromazine)	

[4] Comparison of different entantiomers and regular/sustained release preparations.

The AHRQ review team used rigorous methods for searching the literature, for appraising the methodological quality of identified studies, and for extracting relevant data. They only included randomised controlled trials (RCTs), of either parallel or crossover design (48 out of the 77 RCTs used a crossover design). One non-randomised study was included in the evaluation of adverse events. Quantitative meta-analysis was not used to summarise results, because of concern over clinical heterogeneity, inconsistency in outcome measurements, low methodological quality, and incomplete data reporting.

3.2.2 The CCOHTA Review

Another systematic review was conducted at the same time as the AHRQ review by a team of researchers at the University of British Columbia (73)[5]. The Canadian Co-ordinating Office of Health Technology Assessment (CCOHTA) commissioned this work. The objectives were to "*estimate the relative efficacy of various treatment strategies for ADHD in children (age < 18 years)*", including:

1. Drug vs. placebo contrasts
2. Efficacy of psychological/behavioural treatments
3. Combination therapy vs. placebo/no-treatment contrasts
4. Combination therapy vs. drug-only therapy contrasts
5. Combination therapy vs. psychological/behavioural treatments

Systematic search methods were used to identify studies published after 1980, with parallel or crossover RCT design. Unlike the AHRQ review, the CCOHTA review included quantitative meta-analyses and an economic evaluation. To make this possible, they adopted strategies to narrow the scope of the review and to reduce the degree of heterogeneity in the data extracted. Firstly, they adopted inclusion criteria designed to select studies that were methodologically similar and "ecologically relevant".

Secondly, they focussed on outcomes measured by behavioural rating scales, and specifically the Hyperactivity Index (HI) of the Conners Teacher Rating Scale (CTRS), also known as Abbreviated Symptom Questionnaire (ASQ) or the Abbreviated Conners Teacher Rating Scales (ACTRS). This is a commonly used measure, with good evidence of validity and reliability (45). If the CTRS was not available, data was extracted from the parent version of the Conners rating scales (CPRS) or from a similar behavioural rating scale selected according to a specified algorithm. Data was extracted for only one teacher and one parent scale from each study. Where necessary, data was manipulated to ensure comparability and pooled for different sub-scales or for mutually exclusive patient subgroups. Data was extracted for only one dose level from each study - in multiple dose studies the study arm that was closest to the most commonly used dose was selected. When outcomes were reported for more than one time point, the result from the first post-treatment assessment was taken.

Meta-analysis was conducted using the method of DerSimonian and Laird. Results were presented as weighted mean differences (WMD), where studies reported a common outcome measures, or standardised mean differences (SMD), where studies reported different outcome measures. The SMD, also called the *effect size*, gives the difference between the mean in the treatment group and the mean in the

[5] The full report is available at http://www.ccohta.ca/main-e.html

control group in units of control group standard deviations. A random effects model was used, as this is more appropriate in situations of heterogeneity. Despite attempts to select similar studies with similar outcomes, the CCOHTA team felt that it was likely that considerable differences would remain.

3.2.3 Other reviews

A number of other reviews (46;50;59;61;82;113;119) and 'reviews of reviews' (56;119) have been conducted.

3.3 Methods

This current review is based primarily upon the evidence from the AHRQ report. Because of the high methodological quality of the AHRQ review, we did not think it necessary to repeat a full literature search. However, we did re-run the search strategy (see Appendix D, page 269 in the AHRQ report) to identify any additional articles published since 1997. Abstracts were screened for inclusion by one of the authors (SP) using a *pro forma* (see Appendix 1). Full copies of papers that passed this screen were then obtained and assessed for relevance to the study questions A-G (JL). Placebo-controlled trials were assessed for inclusion using the CCOHTA review study eligibility criteria, which are more restrictive than those adopted by the AHRQ team (see Appendix 2). All included papers were assessed for methodological quality using the Jadad checklist (Appendix F, page 283 in the AHRQ report).

Evidence from the AHRQ review, supplemented where necessary with evidence from more recent publications, is summarised in the results section below. Formal meta-analysis techniques have not been used because of the concerns over heterogeneity and poor study quality expressed by the AHRQ review group. Instead, we present summary results in tabular form for the seven key questions. Study results are presented for the categories of outcomes used in the AHRQ report (see page 8 above). Results for the most frequently used outcome measure (the CTRS hyperactivity index) are presented in the form of 'forest plots'. These graphs, produced using the Cochrane RevMan software (4), are illustrative of the overall direction and strength of evidence.

We also summarise the results of the CCOHTA review for placebo-controlled trials of MPH. Data from recently published trials that met the CCOHTA inclusion criteria are also presented. Quantitative pooled estimates are not presented because of the aforementioned concerns over heterogeneity.

3.4 Quantity and quality of research available

3.4.1 Evidence from the AHRQ Report

Jadad and colleagues identified 78 studies that met their inclusion criteria. The general characteristics of these studies are summarised in Evidence Table A (page 69 to 78) of the AHRQ report. Characteristics of specific studies are described in Evidence Tables B1 to I3 (page 79 to 170) and in the Supplemental Evidence Tables B4 to G8 (page 173 to 227).

3.4.1.1 Study design and quality

All but one of the included studies were RCTs (one non-randomised study was included for the review of adverse events). Of the 77 RCTs, 48 used a crossover design, with individual children receiving two or more interventions over successive days or weeks. The other 29 RCTs had a parallel group design, with children being randomly assigned to a single treatment group.

Overall, the methodological quality of the trials was considered to be poor, and hence there is a relatively high probability of bias in the findings. Only one study (the MTA Cooperative Group Study (58)) was given a maximum score of 5 on the Jadad methodological quality scale. Only 18 of the 77 RCTs were given 3 or more points. Jadad *et al* note that studies with scores of less than 3 have been shown to be more likely to exaggerate treatment effects. The stated reasons for the poor scores were failure to describe the method of randomisation, failure to describe the methods for double blinding, and poor description of withdrawals and dropouts.

Most of the studies also suffered from factors that limited their external validity or generalisability. The AHRQ team identified *a priori* twenty clinically relevant factors that they thought should be reported to enable adequate assessment of generalisability. Only one study (again, the MTA Cooperative Group Study (58)) included information on all 20 clinically relevant factors.

3.4.1.2 Patient populations

Most studies included children between the ages of 5 and 18, a few included pre-school children or adults. The subjects were recruited from a range of settings, mostly from psychiatric and other hospital outpatient clinics, but also from school and community settings. Most of the studies used a diagnosis of ADD (DSM-III) or ADHD (DSM-IIIR or DSM-IV). Only two were based on an ICD-10 diagnosis of HD. This is not surprising since the vast majority of research has been conducted in the USA (66 of the 78 studies were published in the US). No UK published studies were identified.

It is likely that many of the studies focussed on children with more severe types of ADHD, due to the use of various inclusion criteria. However, the quality of reporting does not allow us to separate out in a meaningful way those studies, or patient sub-groups, with "HD-like" forms of ADHD (e.g. pervasive combined type ADHD).

3.4.1.3 The nature of the interventions

The most frequently studied interventions were placebo (64 studies), methylphenidate (56 studies), and dexamphetamine (18 studies). Studies of behavioural/psychological interventions were scarce compared to studies of drug therapies (only 22 studies included non-drug interventions). Most interventions were brief (57 of 12 weeks or less).

3.4.1.4 Outcome measurement

A large variety of outcome measures were used. A minority of studies reported a global assessment of symptoms (22 studies), a combined score for core symptoms (20 studies) or separate scores for hyperactivity (30 studies), inattention (29 studies) and impulsiveness (12 studies). The instruments included behavioural rating scales, observational and psychometric methods. The most frequently used measurement

instruments were the Connor's Teacher and Parent Rating Scales (CPRS and CTRS).

3.4.2 Supplemental Evidence from the CCOHTA Report

Twenty-six studies met the inclusion criteria for the CCOHTA review (73). Of these, eight were relevant to the comparison of methylphenidate with placebo. The CCOHTA reviewers judged that the methodological standard of the included studies was "reasonably high", though variable. There was a strong correlation between the validity score and the year of publication, with quality improving over time. However, the studies included in the CCOHTA review are highly selected, and are unlikely to be representative of the literature as a whole.

3.4.3 Supplemental Evidence from Recent Publications

We identified 67 recent publications that appeared to be relevant by screening citations and abstracts. Full copies of 65 of these papers were obtained (two were not obtainable (106;118)). Nine papers were judged to be relevant to our update review. Six papers (53;69;71;88;124;125), relating to five trials, met the CCOHTA inclusion criteria for the MPH vs. placebo comparison. Three studies (84;86;96) included comparison of MPH to placebo concomitant with a behaviour modification programme. Though these three papers all related to the same summer treatment programme, the patient samples appeared to be different. A number of reports of the MTA Cooperative Group study (see below) were also found (5;22;28;57;108;112).

Thirty-nine reports of placebo-controlled evaluations of MPH were excluded from the update review, for the following reasons:

- Study design - not RCT (23;25;32;40;48;78;79;92;95;107;121;122)
- Sample – not general ADHD/HD sample:
    - Subjects selected by prior MPH response (104;105)
    - Subjects selected by presence of comorbid disorder (8;14;20;29;41;65;66;70;77;81)
- Duration of interventions less than one week (15)
- Outcome measures not standard behavioural rating scales (87;103;114)
- Data not presented in manner consistent with extraction (62;98)

Eight references were found to relate to trials already included in the AHRQ or CCOHTA review (30;34;35;64;67;74;100;102). The remaining references were not considered to be relevant to the review questions (27;89;115).

3.4.4 The MTA trial

The Multimodal Treatment Study of Children with ADHD (MTA) was cosponsored by the US National Institute of Mental Health and the US Department of Education (5;112). The MTA study is by far the largest and the best conducted and reported study to date of treatments for children with ADHD. It is the only study to be given a maximum score for methodological quality and for the reporting of clinically relevant factors by the AHRQ review group.

Children between the ages of 7 and 9 with a diagnosis of ADHD Combined Type (DSM-IV) were recruited through six centres. Subjects had a range of comorbid conditions, although children with conditions thought likely to prevent full participation in the treatments or assessments were excluded. Participants were randomised (n=579) to one of four groups:

1. **Medication management.** Children had an initial 28 day double blind, placebo-controlled dose titration of MPH ("n of 1" trial). This was followed by open titration of other medications for children with inadequate response to MPH. Children were maintained on optimal medication (including 'no medication' where appropriate) for 13 months, with half-hour monthly medication maintenance visits to a pharmacotherapist, who offered "support encouragement, and practical advice (but not behavioural treatment)". Further algorithm-guided dose adjustments were allowed.
2. **Behavioural treatment.** This included three main components. First, a parent training programme with 27 group and 8 individual sessions per family. Second, a child-focused treatment programme, which comprised an 8 week, 5 days per week, 9 hours per day summer camp. Third, a school-based programme included 10 to 16 sessions of biweekly teacher consultation and 12 weeks of a part-time, behaviourally trained classroom aide. Daily report cards were completed by teachers, to link school and home. These behavioural interventions were tapered, with intensive initial inputs fading to once-monthly contacts by the end of the 14-month treatment period.
3. **Combined treatment.** This included both of the above treatment programmes, but was not the simple addition of the other two strategies. To co-ordinate treatment, information was shared between the teacher, consultant and pharmacotherapist. Average medication doses received also varied between the medication management and combined treatment groups.
4. **Community care.** Here subjects were provided with a report of their initial study assessments and a list of community mental health resources, then discharged to their own provider. In accordance with US practice, most of the children in this group received pharmaceutical therapy. The level of psychotherapeutic interventions in this group has not yet been reported.

Outcomes were measured across six major domains: ADHD symptoms, oppositional/aggressive symptoms, social skills, internalising symptoms (anxiety and depression), parent-child relationships and academic achievement. Open parent and teacher ratings for these dimensions were augmented with blinded observational ratings of classroom behaviour. Assessments were conducted at baseline, 3, 9 and 14 months. Further follow-up assessments are planned.

Analyses were conducted on an intention-to-treat basis using random-effects regression methods.

The study was designed to assess the relative effectiveness of alternative treatment strategies. These strategies met "good practice" ideals, although the subjects were intended to be representative of "real-world" patients (57). It is important to note that this trial did not include a placebo or 'no treatment' control group. Thus, the MTA trial can not be used to assess the efficacy of the single treatment modalities (medication or behavioural therapy alone). Also, the community care group is of little direct relevance in the UK, because of the large differences between current practice in the US and UK (108). Most of the children in the community care group (97/146) received stimulant medication

This trial does not strictly fall within the remit of this review – since 'medical management' included the option to use various drugs, not just methylphenidate. However, given the importance of this study and its relevance to practice, its key results are summarised below (section 3.5.8, p33).

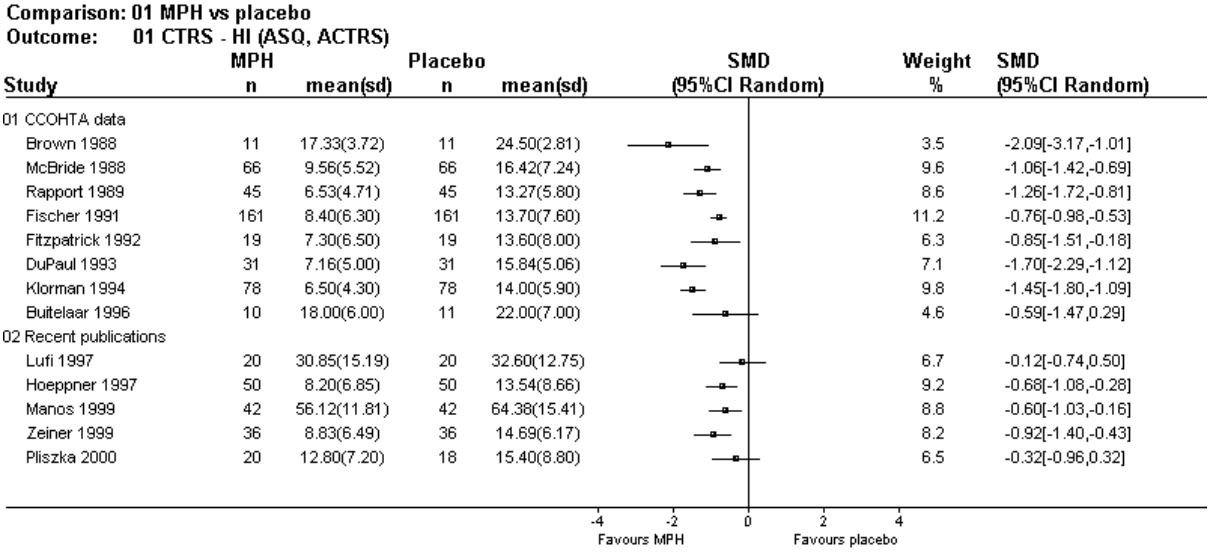
3.5 Summary of results

3.5.1 Is MPH more effective than no treatment?

See page 51-2, Evidence Table F1 (pp109-110), Evidence Table I1 (p154-161) and Supplemental Table F4-F8 (pp211-224) in the AHRQ report.

Details about the eight trials with MPH Vs. placebo comparisons that were included in the CCOHTA review are shown in Table 4. All except one of these trials showed a significant benefit in favour of MPH on the CTRS hyperactivity index. We identified a further five studies that met the inclusion criteria for the CCOHTA review (also shown in Table 4) (53;69;71;88;124;125). All of these trials reported a statistically significant improvement in global/core outcome measures. Data from the 13 studies with CTRS data are illustrated in Figure 1.

Figure 1. Comparison of MPH and placebo (CTRS)



Three previous meta-analyses (61;82;113) reached similar conclusions, although the methodological quality of these reviews has been criticised (55;73).

Information on a broader range of studies is available from the AHRQ review. This included 39 RCTs with MPH and placebo arms (34 short-term and 5 long-term studies). Data on relevant outcomes was available from 17 of these studies (15 short-term and 2 long-term), see Table 4. Overall these studies support the findings of the CCOHTA and previous meta-analyses, although non-significant differences were found for many of the comparisons. This probably reflects the fact that inclusion criteria for the AHRQ review were much less stringent than those for the CCOHTA review, so the studies are more heterogeneous in terms of subject characteristics, outcome measures and methodological quality.

There is evidence from meta-analysis of placebo-controlled RCTs that methylphenidate is efficacious at improving core ADHD core behaviours, at least in the short-term while children continue to take medication. There is some evidence of improvements across other outcome dimensions.

Table 4. Effectiveness of methylphenidate compared to placebo

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Studies included in the CCOHTA report										
DuPaul 1993	c	6-11	ST	85%	31	MPH>placebo	Not reported in CCOHTA report			
Klorman 1994	c	5-12	ST	91%	78	MPH>placebo				
Brown 1988	c	12-14	ST	76%	11	MPH>placebo				
McBride 1988	c	6-17	ST	71%	66	MPH>placebo				
Rapport 1989	c	5-12	ST	85%	45	MPH>placebo				
Fitzpatrick 1992	c	6-12	ST	79%	19	MPH>placebo				
Fischer 1991	c	2-17	ST	94%	161	MPH>placebo				
Buitelaar 1996	p	6-13	ST	91%	21	NS				
Studies identified through updated literature search										
Hoeppner 1997	c	5-18	ST	3	50	MPH>placebo	-	-	-	-
Lufi 1997	c	7-12	ST	3	20	MPH>placebo	-	MPH>placebo	-	-
Manos 1999	c	5-17	ST	4	42	MPH>placebo	MPH>placebo		-	-
Pliszka 2000	p	5-12	ST	4	58	MPH>placebo	MPH>placebo	-	MPH>placebo	-
Zeiner 1999	c	7-11	ST	4	36	MPH>placebo	-	-	MPH>placebo	-

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Studies identified from AHRQ report										
Schachar 1997	p	5-12	MT	4	91	MPH>placebo	MPH>placebo	-	MPH>placebo ODD and aggressiveness for teachers	-
Conners 1980	p	5-12	ST	3	60	?	?	?	?	?
Kupietz 1988	p	5-12 13-18	MT	3	58	MPH>placebo	MPH>placebo for high dose	NS	MPH>placebo	-
Pelham 1993	c	5-12	ST?	3	31	-	?	-	-	-
Spencer 1995	c		ST	3	25	MPH>placebo	MPH>placebo	-	-	NR
Stein 1996	c	5-12	ST	3	25	MPH > placebo for high dose	MPH > placebo for high dose	-	-	-
Arnold 1978	c	5-12	ST	2	29*	?	-	?	-	-
Elia 1991	c	5-12	ST	2	48*	?	?	-	?	?
Fitzpatrick 1992	c	5-12	ST	2	19*	MPH>placebo	-	-	?	?
Gadow 1995	c	5-12	ST	2	34*	MPH>placebo	-	-	-	-
Garfinkel 1981	c	5-12	ST	2	6	MPH>placebo	MPH>placebo	-	MPH>placebo	-
Klorman 1987	c		ST	2	19	MPH>placebo	MPH>placebo	-	-	-

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Klorman 1990	c	5-12 13-18	ST	2	48	MPH>placebo	MPH>placebo	-	-	-
Pelham 1987	c	5-12	ST	2	13*	?	-	-	?	-
Pelham 1990	c	5-12 13-18	ST	2	22*	?	-	-	?	?
Wender 1985	c		ST	2	37*	MPH>placebo	MPH>placebo	-	NS	MPH>placebo for POMS depression & anxiety
Werry 1980	c	5-12	ST	2	30	?	?	?	?	?

c – crossover RCT design. p – parallel group RCT design.
ST – short term (<=3 months). MT – medium term (12 weeks to 12 months). LT – long term (>=12 months).
MPH – methylphenidate. P – placebo.
NR – Not reported. NS – not significant. > better than. - not measured.

3.5.2 Is MPH more or less effective than dexamphetamine?

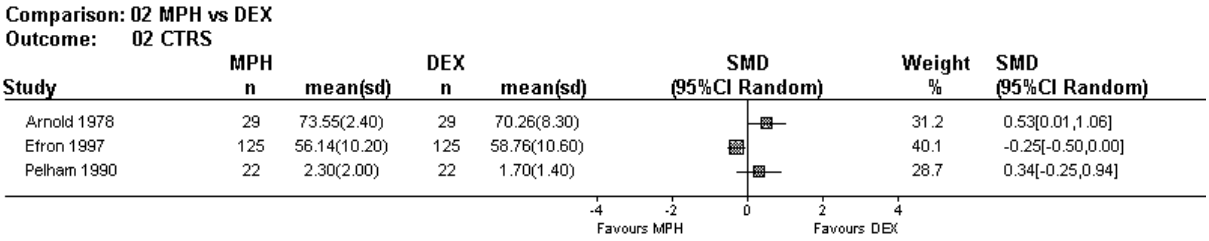
See page 32, Evidence Table B1 (pp79-82) and Supplemental Tables B4-B8 (pp173-184) in the AHRQ report.

Four trials providing data of interest to this comparison were identified in the AHRQ report (12;33;37){Pelham 1990}. These all used a crossover design, and measured short-term outcomes. They were judged to be of poor methodological reporting quality (2 out of 5 on the Jadad scale).

Three of the studies did not report any statistically significant differences in the outcomes of interest (12;37){Pelham 1990}. The other study (33) showed better outcomes with methylphenidate than with dexamphetamine for some measures, but no significant differences for other measures (see Table 5).

The results for the CTRS outcome measure are illustrated in Figure 2.

Figure 2. Comparison of MPH with DEX (CTRS)



There are few head-to-head randomised comparisons of the stimulant medications (MPH and DEX) that are licensed for the treatment of childhood ADHD in the UK. The existing evidence is of relatively poor quality and gives inconsistent results.

Table 5. Effectiveness of methylphenidate compared to dexamphetamine

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Studies identified from AHRQ report										
Efron 1997	c	5-12	ST	2	125	NR	MPH>DEX, except for parent report of impulsivity (NS)	NS	MPH>DEX for teacher NS for parent	MPH>DEX and NS
Elia 1991	c	5-12	ST	2	48	NS	NS	-	NS	NS
Arnold 1978	c	5-12	ST	2	29	NS	NR	NS	NR	NR
Pelham 1990	c	5-18	ST	2	22	NR	NR	-	-	-

ST – short term (<=3 months). MT – medium term (12 weeks to 12 months). LT – long term (>=12 months).
MPH – methylphenidate. DEX – dexamphetamine.
NR – Not reported. NS – not significant. > better than. - not measured.

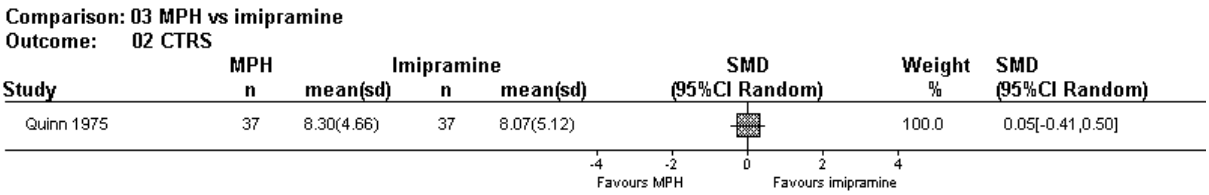
3.5.3 Is MPH more or less effective than tricyclic antidepressants?

See page 33-34, Evidence Table C1 (pp87-88) and Supplemental Tables C4-C8 (185-191) in the AHRQ report.

Two trials provided data of interest for the comparison of MPH with tricyclic antidepressants license for use in children in the UK (91;117). These were both crossover trials comparing MPH with imipramine, and were of poor methodological reporting quality (Jadad score of 2).

The Quinn trial did not report any significant differences in the outcome measures of interest over one year of treatment and follow-up. The Werry trial showed some short-term advantages for imipramine over methylphenidate, although no significant difference was found for some of the outcome measures used (see Table 6). The results of the Quinn trial for the CTRS hyperactivity index are shown in Figure 3. The results of the Werry trial can not be shown on the figure because standard deviations were not reported.

Figure 3. Comparison of MPH with imipramine (CTRS)



There is insufficient evidence to judge the relative effectiveness of methylphenidate and tricyclic antidepressants licensed for use in children in the UK.

Table 6. Effectiveness of methylphenidate compared to imipramine

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Studies identified from AHRQ report										
Quinn 1975	p	?	LT	2	75	-	NS	NR	NS	NS
Werry 1980	c	5-12	ST	2	30	IM>MPH	NS (except for one parent report of IM>MPH)	NS	IM>MPH for parent; NS for teacher	NS

ST – short term (<=3 months). MT – medium term (12 weeks to 12 months). LT – long term (>=12 months).
MPH – methylphenidate. IM – imipramine.
NR – Not reported. NS – not significant. > better than. - not measured

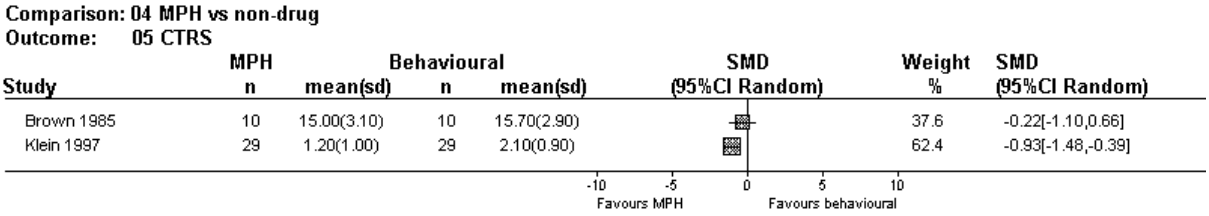
3.5.4 Is MPH more or less effective than non-drug interventions?

See page 34, Evidence Table C1 (pp87-88) and Supplemental Tables C4-C8 (pp185-191) in the AHRQ report.

Three studies provided data on the effectiveness of methylphenidate compared to non-drug interventions (the MTA study comparing 'medical management' with psychosocial interventions is described separately below, p33). Brown 1985 and Klein 1997 (19;64) compared MPH to cognitive behavioural therapy (CBT). Firestone 1986 (39) compared MPH to a 'child training' (CT) behavioural intervention. The studies suffered from quite serious limitations due to poor reporting of methods and clinical characteristics (Jadad scores of 1 or 2).

Two studies (39;64) report significantly benefits for MPH over behavioural interventions (Table 7). Two studies report results for the CTRS outcome measure (Figure 4). The differences between the intervention groups were significant for one of these trials.

Figure 4. Comparison of MPH with behavioural interventions (CTRS)



There is little evidence from randomised direct head-to-head comparisons of the relative effectiveness of methylphenidate compared to behavioural interventions. The studies that do exist are of relatively poor quality, but suggest that methylphenidate is more effective over the medium and short term than behavioural interventions.

Table 7. Effectiveness of methylphenidate compared to non-drug interventions

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Studies identified from AHRQ report										
Brown 1985	p	5-12	MT	1	30	NR	NR	NR	-	-
Firestone 1986	p	5-12	MT	2	73	MPH>PT	MPH>PT	NS	MPH>PT	-
Klein 1997	p	5-12	ST	1	89	NS	MPH>CBT	MPH>CBT	MPH>CBT	NS

ST – short term (<=3 months). MT – medium term (12 weeks to 12 months). LT – long term (>=12 months).
MPH – methylphenidate. PT – parent training. CBT – cognitive behavioural therapy.
NR – Not reported. NS – not significant. > better than. - not measured

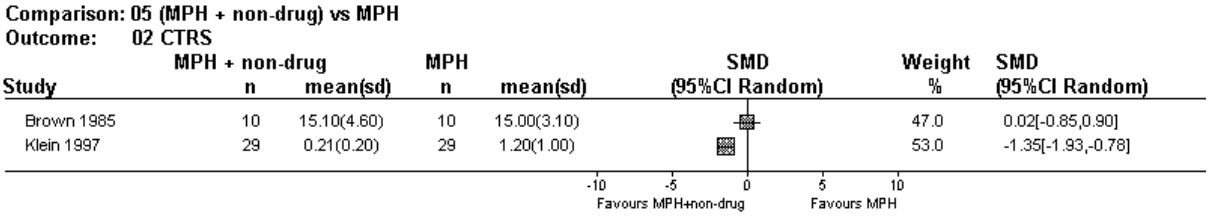
3.5.5 Do non-drug interventions add to the effectiveness of MPH?

See page 36-7, Evidence Table D1 (pp92-93) and Supplemental Tables D4-D8 (pp192-204) in the AHRQ report.

Four studies provided data on this question (see Table 8). Again, these studies suffered from serious methodological reporting limitations (Jadad scores of 1 or 2 out of five). The behavioural interventions tested were cognitive behavioural therapy (19;64), 'parent training' (PT) (39), and bibliotherapy (68).

Two of the studies (19;39) failed to show any significant medium-term benefit of adjunctive behavioural therapy over MPH. Two other studies (64;68) did show some short-term benefits for adjunctive behavioural therapy, though for some outcome measures differences were not statistically significant. Two of the trials reported data on the CTRS outcome scale (Figure 5).

Figure 5. Comparison of (MPH+non-drug) with MPH (CTRS)



There is insufficient evidence to support the superiority of methylphenidate combined with a behavioural intervention over methylphenidate alone. The RCT evidence is of relatively poor quality and most comparisons fail to detect any significant difference, although some findings in favour of combined therapy have been reported.

Table 8. Effectiveness of adding non-drug interventions to methylphenidate

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Studies identified from AHRQ report										
Brown 1985	p	6-11	MT	1	30	NS	NS	NS	-	-
Firestone 1986	p	5-9	MT	2	73	NS	NS	NS	NS	-
Klein 1997	p	6-12	ST	1	89	MPH+CBT> MPH	MPH+CBT> MPH	NS	NS	NS
Long 1993	p	6-11	ST	1	32	MPH+PT>MPH	NS	MPH+PT>MPH	-	-

ST – short term (<=3 months). MT – medium term (12 weeks to 12 months). LT – long term (>=12 months).
MPH – methylphenidate. PT – parent training. CBT – cognitive behavioural therapy.
NR – Not reported. NS – not significant. > better than. - not measured

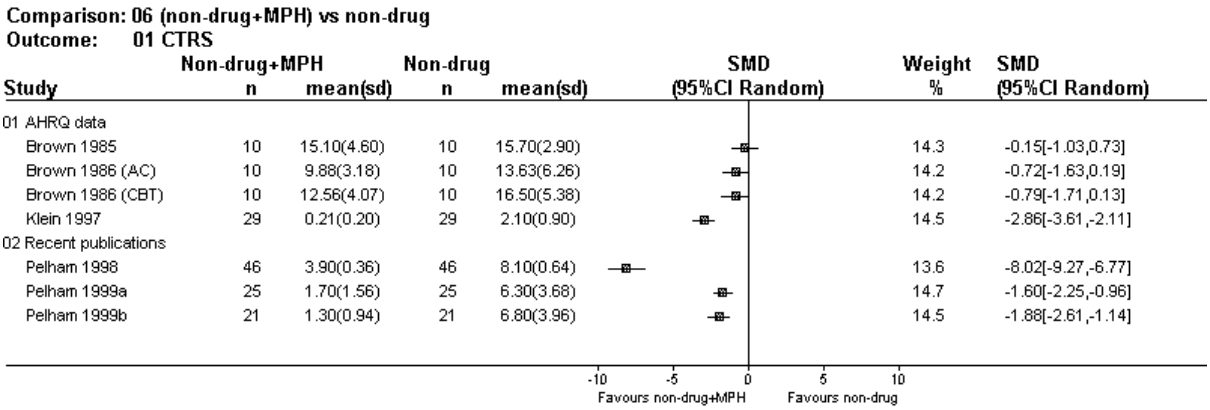
3.5.6 Does MPH add to the effectiveness of non-drug interventions?

See page 38-9, Evidence Table D1 (pp94-97) and Supplemental Tables D4-D8 (pp192-204) in the AHRQ report.

The AHRQ report included eight studies with data relevant to this question (see Table 9). These studies included a range of behavioural interventions, including CBT (18;19;52;64), attention control (AC) (18;51;99), CT (51), PT (39) and behavioural contingencies/modification (BC/Mod) (85). Two of the studies (Brown 1986 and Solanto 1997) were judged to be of relatively good methodological quality (3 out of 5 on the Jadad scale). The other studies scored less well (less than 3 on the Jadad scale). A further three trials were identified through the updated search strategy (Table 9) (84;86;97). These all related to the treatment of children at the same summer behavioural programme, during which placebo-controlled crossover trials of MPH therapy were conducted (the samples did appear to be different). The studies were of quite good methodological reporting standards (3 or 4 on the Jadad scale).

These trials reported significant improvements from the addition of MPH to behavioural treatments across core symptoms, academic measures, and oppositional behaviours, but not anxiety/depression. Six trials reported results on the CTRS outcome measure (Figure 6). Overall, these show an improvement in ADHD behaviours with methylphenidate/behavioural combination therapy compared to behavioural therapy alone.

Figure 6. Comparison of (non-drug + MPH) with MPH (CTRS)



There is RCT evidence, some of relatively good quality, which suggests that the addition of methylphenidate to behavioural treatment programmes is beneficial. Improvements in short and medium term outcomes were observed across a number of dimensions.

Table 9. Effectiveness of adding methylphenidate to non-drug interventions

Study	*Design*	*Age Groups*	*Duration*	*Quality score (0-5)*	*n*	*Global/core*	*Hyperactivity/ Inattention/ Impulsivity*	*School/ Academic*	*CD/ ODD*	*Depression/ anxiety*
Studies identified from AHRQ report										
Brown 1985	p	6-11	MT	1	30	NR	NR	NR	-	-
Brown 1986	p	5-13	MT	3	40	NS	NS	NS	NS	-
Firestone 1986	p	5-9	MT	2	73	MPH+PT>PT	MPH+PT>PT	NS	MPH+PT>PT	-
Klein 1997	p	6-12	ST	1	89	MPH+CBT>CBT	MPH+CBT>CBT	MPH+CBT>CBT	MPH+CBT>CBT	NS
Hinshaw 1984	c	8-13	ST	2	24	-	-	MPH+AC>AC		
Hinshaw 1989	c	6-12	?	2	24	-	MPH+CBT>CBT	-	-	-
Pelham 1993	c	5-10	ST	1	31	-	MPH+AC>AC	-	-	-
Solanto 1997	c	6-10	ST	3	22	?	MPH+BC>BC	MPH+BC>BC	MPH+BC>BC	-
Studies identified through updated literature search										
Pelham 1998	c	12-18	ST	3	49	MPH+BC>BC	MPH+BC>BC	-	MPH+BC>BC	-
Pelham 1999a	c	5-12	ST	4	25	-	MPH+BC>BC	MPH+BC>BC	MPH+BC>BC	-
Pelham 1999b	c	6-12	ST	3	21	-	MPH+BC>BC	MPH+BC>BC	MPH+BC>BC	-

ST – short term (<=3 months). MT – medium term (12 weeks to 12 months). LT – long term (>=12 months).
MPH – methylphenidate. PT – parent training. CBT – cognitive behavioural therapy. CT – child training. AC – attention control. BC - behaviour control programme.
NR – Not reported. NS – not significant. > better than. - not measured

3.5.7 What are the adverse effects of MPH?

See pages 48-51 and Evidence Tables H1a-H3 (pp 122-153) in the AHRQ report.

Information on the frequency of adverse effects with MPH from the AHRQ report is summarised in **Table 10**.

Table 10. Evidence of adverse effects from clinical trials

	Number of studies reporting significant increase in frequency or severity of adverse effect/ number of studies reporting test of significance		
Adverse effect	*MPH vs. placebo*	*DEX vs. placebo*	*MPH vs. DEX*
Sleep disorders	4/20	1/8	-
Headaches	2/10	0/2	-
Motor tics	1/2	1/1	0/1
Appetite/ anorexia	7/12	3/3	0/2
Abdominal pain	2/10	0/2	0/1
Irritability	2/9	0/2	0/1

SPC - Summary of product characteristics.
MPH - methylphenidate. DEX - dexamphetamine.

3.5.8 Results of the MTA trial

The MTA trial was designed to answer three questions (58).

1. *"Do medication and behavioural treatments result in comparable levels of improvement in pertinent outcomes at the end of treatment?"*

   Medication management was superior to behavioural treatment for three (of five) measures of ADHD core symptoms. No significant differences were observed across the other key dimensions.

2. *"Do participants assigned to combined treatment show higher levels of improvement in overall functioning in pertinent outcome domains than those assigned to either medication management or behavioural treatment at the end of treatment (1-tailed hypotheses)?"*

   a Combined treatment and medication management not differ significantly across any domain.

   b Combined treatment was superior to behavioural management on three (of five) measures of ADHD core symptoms, for one (of three) measures of aggression/oppositional behaviour, for one (of three) measure of anxiety depression, and for one (of three) measure of academic achievement. No significant differences were observed in social skills or parent-child relations.

3. *"Do participants assigned to each of the 3 MTA treatments (medication management, behavioural treatment, and combined treatment) show greater improvement over 14 months than those assigned to community care (1 tailed)?"*

   a Medication management was superior to community care for three (of five) measures of ADHD symptoms, for two (of three) measures of aggression/oppositional behaviour and for one (of two) measures of social skills. No significant differences were observed in anxiety/depression or parent-child relations.

   b No significant differences between behavioural management and community care were observed for any outcome domains.

   c Combined treatment was superior to community care for four (of five) measures of ADHD symptoms, for two (of three) measures of aggression/oppositional behaviour, for one (of three) measures of anxiety/depression, for both measures of social skills, for one (of two) measures of parent-child relations, and for one (of three) measures of academic achievement.

The MTA Cooperative Group conducted further analysis to identify patient sub-groups with better or worse response to the various treatment strategies (5). This analysis should be seen as "exploratory", because of the danger of repeated statistical testing with a sample not designed for this purpose. There was no difference in treatment response by sex, prior treatment or presence of comorbid disruptive disorders. Behavioural treatment appeared to be more effective in children with anxiety disorders and children from deprived backgrounds.

4. ECONOMIC EVIDENCE

4.1 Existing Studies

Four economic evaluations were identified, two published by Health Technology Assessment organisations (42;73) and two from industry submissions to NICE (72;80). These evaluations have been appraised against a standard checklist of methodological principles for economic evaluations, the 'Drummond checklist' (see Appendix 3). The results of the appraisal are shown in **Table 11**. Some key estimates from the four evaluations are summarised in **Table 12**.

4.1.1 Wessex DEC report

A Development and Evaluation Committee (DEC) report (42) published in March 1998 by the Wessex Institute for Health Research and Development estimated the cost per QALY for methylphenidate treatment compared to no treatment. The costs and effects of behavioural therapy were not estimated. The perspective adopted was that of the commissioner (third-party payer) and all costs and effects were estimated over a one-year time horizon.

The most likely scenario was based on the assumption of a quality of life improvement of 0.086 per person over a year. This was estimated by experts using the Index of Health Related Quality of Life measure (HRQoL) [6]. It was also assumed that 6% of children would discontinue treatment due to side effects. The response rate for those remaining on treatment was assumed to be 70%.

The model included only direct costs, including drug costs (£203pa) and follow-up in a hospital setting (£95 per visit). It was assumed that all patients who started treatment would have two hospital visits, and that those who continued would have another three visits in the first year. Those who discontinued treatment were assumed to have 6 weeks of treatment. The average cost per patient over one year of treatment was £520.

The best estimate of the cost of MPH compared to no treatment £9,200. An extensive sensitivity analysis suggested a range of £4,700-£28,200 per QALY gained.

4.1.2 CCOHTA report

A group of researchers at the University of British Columbia conducted a cost-effectiveness study as part of the CCOHTA commissioned review (73). They used a decision analytic model to compare six treatments: methylphenidate, dexamphetamine, pemoline (high-dose and low-dose), non-drug therapy, combined therapy and no treatment. Results were calculated both including and excluding pemoline. The latter are reported below, as these are of most relevance in the UK. The perspective was that of third-party payers (public and private) for health care and pharmaceuticals. A one-year time horizon was adopted.

[6] Assuming a change from P1D2E3 (no pain, slight social disability and moderate emotional distress) to P1D1E2 (no pain, no physical or social disability, slight emotional distress) on response to treatment.

The magnitude of clinical effects was estimated from the CCOHTA meta-analysis using the CTRS hyperactivity index (Figure 1). Costs were also presented per 6-point change on the CTRS scale. This is approximately a one standard deviation, and was thought to be a 'clinically relevant' effect size. Cost-utility analysis was not performed because of the absence of health-related quality-of-life data for children with ADHD. Based on a survey of treatment practice in British Columbia, they estimated only 35% of children started on MPH would continue to be treated at 6 months, and 15% at one year.

Direct costs were calculated, including medication, physician visits and hospitalisation. Information about typical resource utilisation was obtained from three expert panels. Patients on MPH were assumed to have two specialist visits and four GP visits over one year, along with two CBC tests (at baseline and 12 months). Those on DEX were assumed to have two specialist visits and three GP visits. Behavioural therapy included 16 hours of child counselling, 8 hours of parent training and 2 hours of teacher training. Combined therapy comprised MPH and behavioural therapy. Children on no treatment were assumed to have an extra four visits to their GP over the year.

The analysis excluding pemoline found MPH to be the most cost-effective treatment strategy: it was estimated to be both cheaper and more effective than DEX, behavioural therapy and combined treatment. The incremental cost effectiveness ratio for MPH compared to no treatment was $64 for each point gained on the CTRS scale, or $386 for a 6 point (1 SD) gain.

Under sensitivity analysis the cost-effectiveness ratio[7] for MPH compared to no treatment varied from $74 to $119 per CTRS point gained. MPH remained the dominant strategy under most of the assumptions tested. Under the 'worst case' scenario, which was most favourable to behavioural therapy and least favourable to MPH, the combined strategy was no longer dominated, although it was still relatively less cost-effective (compared to no treatment) than MPH treatment.

Using figures from the CCOHTA study, the cost of adding MPH to behavioural treatment may be estimated at $160 per additional point gained on the CTRS scale, or £958 for 6 point (1SD) gain.

4.1.3 Novartis submission

The economic evaluation carried out by Novartis (80) followed similar methods to that conducted by the Wessex DEC group, with a health care payer perspective and a one year time horizon. However, unlike the Wessex DEC group, Novartis estimated the cost-effectiveness of behavioural therapy.

Novartis used the EuroQOL-5D to estimate the effect of MPH therapy on quality of life. They assumed that without treatment children would be in health state 11211 (indicating some difficulties with performing usual activities), and that with treatment 60% would be returned to full health (11111), yielding a gain of 0.6*(1-0.883)=0.07 QALYs per patient treated for a year. It was assumed that the health gain from behavioural therapy would be the same as for MPH therapy over one year.

[7] The incremental cost-effectiveness ratios (that is (MPH cost - cost with no treatment)/(MPH effect - no treatment effect)) is not reported for the sensitivity analysis. Instead ratios given are: MPH cost/(MPH effect – no treatment effect)

The company estimated the cost of an average dose of MPH at £203 per person per annum, and the cost of a high dose at £407 per person per annum. In addition, they estimated the cost of assessment and follow-up at £824 for each patient over a year. This includes an initial two-your assessment (with a consultant psychiatrist), four follow-up consultations (with a member of the child psychiatry team) and a one hour case conference (with the psychiatry team). They estimated the cost of a behavioural intervention at £34,443 per child. This estimate is based on the levels of resource utilisation reported for the MTA study, with NHS unit costs (112). It comprises £16,680 for the summer intensive therapy programme, £15,038 for school therapy and £2,725 for family therapy.

The incremental cost per QALY of MPH treatment compared to placebo was estimated at £14,639. This fell to £5,561 with the assumption of additional health benefits for anxiety[8], and rose to £17,540 with a high dose of methylphenidate.

4.1.4 Medeva submission

Confidential information removed.

[8] Baseline EuroQol-5D score assumed to be 11212 (ie. some difficulty with usual activities and moderate anxiety/depression). If 60% of children are returned to perfect health (1111), the QALY gain is 0.6*(1-0.692)=0.1848.

Table 11. Appraisal of economic evaluations

	Wessex DEC	*CCOHTA*	*Novartis*	*Confidential*
Well defined question posed?	Yes	Yes	Yes	
Description of competing alternatives?	No – did not consider behavioural therapy.	Yes	Yes	
Effectiveness established?	Yes	Yes	Yes	
Important costs/ consequences identified?	Yes? – cost/ consequences of side effects and impact on other services excluded.	Yes? – cost of severe side effects included, but not mild/moderate.	Yes? – cost/ consequences of side effects and impact on other services excluded.	
Costs/consequences measured accurately?	Yes – resource use based on local practice.	Yes – information from expert panels.	Yes? – costing methodology for behavioural treatment not fully explained.	
Costs/consequences valued credibly?	No – QoL gains based on reasonable assumptions, but no empirical evidence.	Yes	No – QoL gains based on reasonable assumptions, but no empirical evidence.	
Adjustment for differential timing?	NA – one year time horizon.	NA – one year time horizon.	NA – one year time horizon. Not stated whether discounting is used for extrapolation of costs/effects of behavioural therapy.	
Incremental analysis?	No – comparison with no treatment only.	Yes	No – comparison with no treatment only.	
Uncertainty?	Yes – extensive one-way sensitivity analysis.	Yes – extensive one-way sensitivity analysis.	Yes – limited one-way sensitivity analysis for dose and QoL gains.	
Discussion	Yes	Yes	Yes	

Table 12. Comparison of economic evaluation results

	Wessex DEC	*CCOHTA*	*Novartis*	*Confidential*
EFFECTIVENESS (per patient treated per annum)				
No treatment	0.884 QALYs	0 CTRS points	0.883 QALYs	
MPH	0.9406 QALYs	6.7 CTRS points	0.9532 QALYs	
DEX	-	4.7 CTRS points	-	
Behavioural	-	0.3 CTRS points	0.9532 QALYs	
Combined	-	3.8 CTRS points	-	
MPH Vs. no treatment	0.0566 QALYs	6.7 CTRS points	0.0702 QALYs	
Beh Vs. no treatment	-	3.8 CTRS points	0.0702 QALYs	
Combined Vs. beh	-	3.5 CTRS points	-	
COST (per patient treated per annum)				
No treatment	£0	$128	£0	
MPH	£519	$559	£1,028	
DEX	-	$566	-	
Behavioural	-	$1,946	£34,443	
Combined	-	$2,505	-	
MPH Vs. no treatment	£519	$431	£1,028	
Beh Vs. no treatment	-	$1,818	£34,443	
Combined Vs. beh	-	$559	-	
COST-EFFECTIVENESS				
MPH Vs. no treatment *(sensitivity analysis)*	£9,177 /QALY (£4,691-28,190)	$386/ one SD gain in CTRS ($444 - 714)*	£14,639 /QALY (£5,561-17,540)	
Beh Vs. no treatment	-	$2,871/ one SD gain in CTRS	£490,641 /QALY	
Combined Vs. beh	-	$958/ one SD gain in CTRS	-	

* Range for incremental cost-effectiveness ratio not reported. Figures quoted are for ratio of cost of MPH treatment over incremental effect of MPH compared to no treatment.

4.2 Variation in effectiveness estimates

The two studies that estimated the effectiveness of methylphenidate therapy in terms of QALYs (Wessex and Novartis) provided quite similar estimates – a gain of 0.06 and 0.07 QALYs per child treated per annum, respectively. These estimates are based on reasonable assumptions using well-accepted measures of health-related quality-of-life. However, they are not based on empirical evidence of the actual impact of MPH on health status or quality-of-life, since no such evidence is available. The magnitudes of the estimated QALY gains are possibly more reflective of the capacity of the IHRQoL and EQ-5D instruments to differentiate between relatively small increments in health status, rather than of the true impact of MPH treatment.

There are also some drawbacks with the approach taken in the CCOHTA study. Here estimates of clinical effectiveness were taken from empirical evidence, reflecting the pooled results of RCTs identified through a systematic review (73). For some comparisons, however, only a small number of studies (sometimes only one) provided data in a form suitable for extraction. These data were highly selected and may be prone to bias. It is also difficult for decision-makers to assess the value of a one point (or one SD) change in the CTRS in relation to health gains from other health technologies. Particularly as this index only measures one aspect of health and well being.

Despite these criticisms, no better methods of assessing the overall effectiveness of MPH are currently available.

4.3 Variation in cost estimates

The current NHS net prices of the medications are shown in Table 13. Methylphenidate costs around £200 pa for an average dose and £400 pa for a high dose. Other than uncertainty over the average dose that is actually prescribed, there is no dispute over the cost of the drug. However, estimates of the total cost of MPH therapy do vary, from about £500 to £1,000 (Table 12). This is due to differences in assumptions about the resources required for initial assessment, dose titration and follow-up. Assumptions about drop-out and response rates also influence average costs.

Table 13. Medication costs

		Price (p/mg)[1]	Daily dose (mg)			Annual cost (£)		
			Min	Mean[2]	Max	Min	Mean	Max
Stimulants								
Methylphenidate	Ritalin	1.86	5	30	60	£34	£203	£407
	Equasym	1.66	5	30	60	£30	£182	£364
Dexamphetamine	Dexedrine	0.69	5	15	20	£13	£38	£50
Antidepressants								
Amitriptyline	NP tablets	0.07	10	30	50	£3	£8	£13
	NP oral solution	0.90	10	30	50	£33	£99	£164
	Lentizol	0.17	10	30	50	£6	£19	£31
Imipramine	NP	0.06	25	50	75	£6	£11	£17
	Tofranil tablets	0.15	25	50	75	£13	£27	£40
	Tofranil syrup	0.41	25	50	75	£38	£76	£114
Nortriptyline	Allegron	0.93	10	23	35	£34	£76	£118

NP Non-proprietary
1 British National Formulary, 39, March 2000. NHS Net Price for maximum strength, maximum pack size available.
2 World Health Organisation Defined Daily Dose where available. Otherwise midpoint of dose range.

Making meaningful estimates of the cost of behavioural therapy is particularly difficult. Estimates in the above economic studies vary from just under $2,000 Canadian dollars (CCOHTA) to over £30,000 UK pounds (Novartis). This variation arises largely from the use of different assumptions about the level of resource inputs. The Canadian cost estimate was based on information about local resource use. The Novartis study was based upon a much higher intensity of intervention, as reported in the MTA trial.

No estimates of the cost of NHS behavioural interventions for children with HD/ADHD were identified through our literature search. However, some estimates of the cost of services for children with behavioural problems were available (7;13;21;49) . These varied from £1,300 pa (21) to £8,300 pa (13), including NHS, local authority social and education service and voluntary sector costs. It is important to note that these figures relate to services for children with 'behavioural problems', not HD or ADHD as such. However, they do illustrate that the 'gold standard' multimodal behavioural intervention of the MTA trial was very much more intensive than current real-life provision in this country.

4.4 Cost-effectiveness estimates from the MTA trial

We have used data from the MTA trial to provide additional information on cost-effectiveness. We only consider the comparison between the combined treatment group and the behavioural treatment group. This is most relevant from a UK point of view – since the stimulants are only licensed for use as a secondary adjunct to a comprehensive treatment programme, including behavioural, social and educational components. Also, this approach avoids the difficulties of costing behavioural interventions, since we need only consider the additional (incremental) costs of medication.

Costs are estimated in 1999 UK pounds, from an NHS perspective, over the time

period of the MTA trial (14 months). Levels of resource use are based on those in the trial (112). Unit costs are derived from UK published sources (16;76). No discounting was applied, because of the short time horizon.

Medication use for the combination therapy group was costed using the following assumptions:

- 94% of children started the 28-day dose titration, during which they took an average 10mg MPH per day,
- 70% of children received an average dose of 30mg/day of MPH over the 13 month maintenance period,
- 12% of children received an average dose of 15mg/day of DEX over the 13 month maintenance period,
- and 2% of children received an average dose of 50mg/day of imipramine.

The trial protocol required regular visits to pharmacotherapists for assessment and follow-up. It is stated that monthly visits of half an hour were made during the maintenance period. We assume that two visits were made during the titration month. We further assume that the 6% of patients who did not start titration, and the 7% who remained persistently unmedicated during the maintenance period, did not make these visits. Titration visits are costed at £122 (£244 per hour of client contact for a consultant psychiatrist) (76). Follow-up visits are costed at £29 (£58 per hour of client contact with a member of an NHS child clinical psychiatry team, including psychiatrists, nurses and other care staff) (76).

Table 14. Estimated cost of medication for the MTA combined treatment group

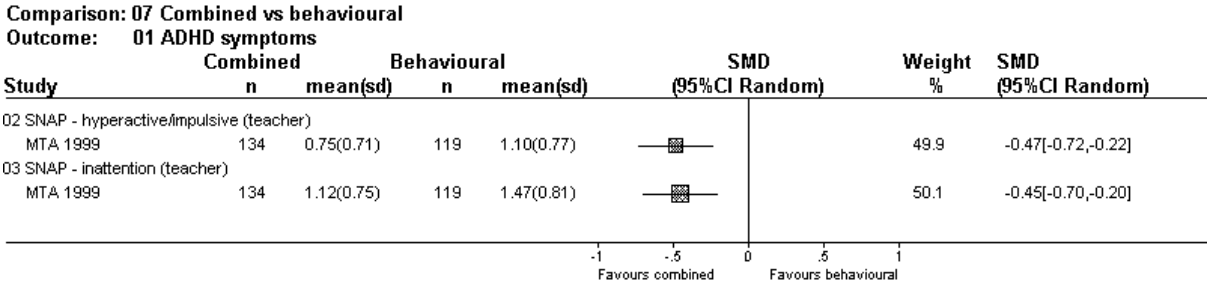
DRUG COSTS					
Item	***% patients***	***duration (days)***	***dose (mg/day)***	***unit cost (p/mg)***	***Cost***
MPH during titration period	94%	28	10	1.86	£4.89
MPH during maintenance	70%	390	30	1.86	£152.06
Other stimulants	12%	390	15	0.69	£4.81
Tricyclic antidepressants	2%	390	50	0.15	£0.57
Total drug cost					£162.33
FOLLOW-UP COSTS					
Item	***% patients***	***Number of visits***	***Duration of visit (hours)***	***unit cost (p/mg)***	***Cost***
Visits during titration period	94%	2	50.0%	£244	£229.36
Visits during maintenance	93%	13	50.0%	£58	£350.61
Total follow-up cost					£579.97
TOTAL COSTS					
					£742.30

We assume that the resource inputs for the behavioural component of combination therapy are the same as for the behavioural therapy group. Thus, the incremental

cost for combined therapy compared to behavioural therapy is estimated at approximately £750 per patient over the 14-month study period (Table 14). For sensitivity analysis we varied this estimate between £500 and £1,000, to reflect the Wessex DEC and Novartis estimates, respectively.

The selection of one outcome measure from the battery of 19 measures used by the MTA group to present the results of their trial is not straightforward. There is no single summary measure representing global outcomes or 'quality-of-life'. The CCOHTA economic evaluation made use of the CTRS index of hyperactivity (teacher version) to summarise effects. The closest measure to this in the MTA trial is the SNAP index of hyperactivity/impulsivity (teacher version). The effect size at 14 months for combined treatment compared to behavioural treatment was 0.47 (95% confidence interval 0.22 to 0.72) (see Figure 7). This means that hyperactive and impulsive behaviours were approximately half a standard deviation better with combined treatment than with behavioural treatment alone.

Figure 7. Comparison of combined vs. behavioural treatment from MTA trial



The best estimate of the incremental cost-effectiveness ratio for combined therapy compared to behavioural therapy is thus about £1,600 per 1SD gain in the SNAP hyperactivity/impulsiveness index (see Table 15). Sensitivity analysis suggests that this ratio could be as low as £700, or as high as £4,500.

Table 15. Cost-effectiveness estimates based on MTA trial results

	Incremental effect (standardised mean difference in SNAP teacher hyperactive/impulsive dimension at 14 months)		
	Lower CL	*Mean*	*Upper CL*
Incremental cost	0.22	0.47	0.72
£500	£2,273	£1,064	£694
£750	£3,409	**£1,596**	£1,042
£1,000	£4,545	£2,128	£1,389

4.5 Estimate of Budgetary Impact

Estimates of the NHS budgetary impact of the extended use of methylphenidate are shown in Table 16. These are based upon the estimated population of 6-16 year olds with HD (1% prevalence) in England and Wales (see Table 1). The numbers of children currently taking MPH have been estimated from current levels of expenditure (Table 2). Thus, there are approximately 48,000 children in England and Wales who are potential candidates for methylphenidate therapy.

Drug costs are based on an average dose of 30 mg/day. This is the usual recommended dose, and is close to the average dose prescribed, after careful dose titration, in the MTA trial. It is assumed that 30% of children will not continue with the drug after a one-month trial, due to lack of response or adverse effects. The 70% of 'responders' are assumed to continue to take methylphenidate for a whole year. The maximum additional cost of the drug over one year is thus estimated at £7 m for England and Wales.

Table 16. NHS budgetary impact of extended use of methylphenidate

	England	*Wales*	*Total*
NUMBERS OF CHILDREN (AGE 6-16)			
Prevalence (1% HD)	69,200	4,200	73,400
Estimated current users	24,600	1,200	25,800
Potential additional users	44,600	3,000	47,600
Potential non-responders (30%)	13,380	900	14,280
Potential responders (70%)	31,220	2,100	33,320
POTENTIAL ADDITIONAL COST OF DRUG IN FIRST YEAR			
For non-responders (30mg/day for 1 month)	£226,685	£15,248	£241,933
For responders (30mg/day for 12 months)	£6,347,182	£426,941	£6,774,123
Total	£6,573,867	£442,188	£7,016,056
POTENTIAL ADDITIONAL COST OF FOLLOW-UP IN FIRST YEAR			
Initial assessment for non-responders (2 hrs @ £244)	£6,529,440	£439,200	£6,968,640
Initial assessment for responders (2 hrs @ £244)	£15,235,360	£1,024,800	£16,260,160
*Follow-up for responders (4 *1/2 hr @ £58)*	£3,621,520	£243,600	£3,865,120
Case conference (all children @ £220)	£9,812,000	£660,000	£10,472,000
Total	£35,198,320	£2,367,600	£37,565,920
TOTAL POTENTIAL COST IN FIRST YEAR			
TOTAL (100% uptake)	£41,772,187	£2,809,788	£44,581,976
TOTAL (25% uptake)	£10,443,047	£702,447	£11,145,494

The associated costs of assessment and follow-up have been estimated using assumptions about current practice made in the Novartis submission (80) - including a two-hour initial assessment by a consultant psychiatrist, four half-hour follow-up consultations with a member of the psychiatry team, and a one-hour case conference. We further assume that all children initiating methylphenidate therapy have the initial assessment and case conference, but only those who respond to therapy have the follow-up visits. These assumptions are similar to those made by the Wessex DEC team (42), who assume that there would be two initial visits, and three follow-up visits for 'responders'. The unit costs of these services are

taken from published national estimates (76). The maximum additional cost of assessment and follow-up in the first year of drug therapy is estimated at about £38 m for England and Wales.

Thus, if all 6 to 16 year olds with HD in England and Wales, who are not currently receiving medication, were to start MPH therapy, the total cost would be approximately £45 m in the first year (including drug, assessment and follow-up costs). Of course, the potential cost would be proportionately lower if less than 100% of families were offered methylphenidate therapy, or if less than 100% of them chose to accept such treatment. There are many other uncertainties surrounding this estimate of NHS impact.

5. DISCUSSION AND CONCLUSION

5.1 Summary of effectiveness evidence

The conclusions that can be drawn from the AHRQ (55), CCOHTA (73) and other published reviews of drug therapy for children with ADHD are reasonably consistent (46;50;56;59;61;82;113;119;119). They suggest that methylphenidate is effective at reducing hyperactivity, inattention and impulsiveness in the short-term, and possibly in the longer-term. There appears to be little difference in effectiveness between methylphenidate and dexamphetamine (the other central nervous system stimulant that is currently licensed for this purpose in the UK). Although, this could be due to a lack of adequately powered direct head-to-head comparisons of these drugs. There is insufficient evidence to judge the relevant effectiveness of methylphenidate and tricyclic antidepressants, or other drugs that are sometimes used "off-license" for the treatment of ADHD. Thus, we may conclude that 'medication management' is efficacious, though not which pharmacological treatment strategy is optimal.

Direct comparison of stimulant medication and behavioural interventions in the MTA trial suggests that the former is relatively more effective. This finding is supported by two of three RCTs comparing methylphenidate with behavioural therapy (Figure 4). However, the MTA group and others have urged caution in interpreting this result (22;28;57;108;112). Firstly, it is clear that the MTA trial does not demonstrate a lack of effectiveness of behavioural therapy. There was no placebo or 'no treatment' control group to test such a hypothesis. Also, there were marked reductions in ADHD symptoms across all four groups (including the behavioural treatment group). More than 75% of subjects in the behavioural treatment group were successfully managed without medication over the 14-month study period. Secondly, there were some features of the study design that may have favoured pharmacological over behavioural intervention. In accordance with commonly accepted procedures, the behavioural intervention was 'faded out' over the 14 months, whereas medication was maintained constantly throughout. It has also been argued that the outcome measures used favour pharmacological interventions (28). Parent satisfaction ratings were higher for the combined and behavioural groups than for the medication management group. It is also possible that evaluation at 14 months is too early to show the developmental benefits of behavioural interventions.

The MTA group have also advised caution in interpreting their failure to find any statistically significant differences between medication management and combined therapy (57). The overall pattern of results suggested that combined treatment yielded greater gains than medication management alone. Combined treatment was placed first on 12 (of 19) outcome measures, whereas medication management was placed first on 4 measures, and behavioural treatment on only 2. Though large, the study did not have sufficient power to detect small effects, "such as those that might exist between combined treatment and medication management". Thus, they suggest that there is an "absence of evidence" rather than "evidence of absence". It is also interesting to note that medication doses were lower in the combined treatment group than in the medication management group. Thus, it may be said that some of the additional benefits of behavioural therapy for the combined therapy group were consumed in the form of reduced exposure to the risks of medication,

rather than in the form of behavioural improvements (108).

One finding of the MTA trial that was quite clear was that combined treatment was superior to behavioural intervention alone. Other published RCT evidence supports this conclusion.

5.2 Summary of economic evidence

The additional cost per QALY gained for MPH compared to no treatment has been estimated at £9,200 (£4,700 to £28,200) per QALY gained (42) and at £14,600 (£5,600 to £17,500) per QALY gained (80). A Canadian study has also estimated that MPH therapy costs an additional $386 ($444 to $714) for a gain of one standard deviation in the CTRS hyperactivity index (73).

The Canadian review estimated that the addition of MPH to a relatively modest behavioural intervention would cost an additional $958 for a one standard deviation gain in the CTRS hyperactivity index (73). Estimates based on the MTA trial suggest that the addition of medication to multimodal behavioural therapy costs an additional £1,600 (£700 to £4,500) for an additional one standard deviation gain in the SNAP hyperactivity/impulsiveness index.

Attempts to estimate the cost-effectiveness of various modes of treatment for children with HD/ADHD are hampered by a lack of evidence of the overall impact on the health and well being for children and their families. A wide variety of instruments have been used to measure outcomes in clinical trials, but no single measure adequately captures the complexity of real-life impacts of HD/ADHD and its treatment. The only estimates of QALY gains that are available are based upon assumptions made by researchers about changes in health state brought about by treatment.

Economic evaluation is also made difficult by uncertainties over the level of services that are required for psychosocial interventions and for assessment and follow-up with medication management.

5.3 Relevance of the evidence to UK practice

The clinical and cost-effectiveness evidence must be placed within the context of UK opinion and practice. Methylphenidate is licensed for use "… *as part of a comprehensive treatment programme for attention-deficit hyperactivity disorder (ADHD) when remedial measures alone prove insufficient.* " (SPC). Thus, methylphenidate is seen as a **second-line adjunct** to other non-drug interventions. The evidence reported above indicates that the addition of methylphenidate (or other stimulant medication) to behavioural treatment for children with an inadequate response to behavioural approaches is clinically effective and has a relatively attractive incremental cost-effectiveness ratio.

However, the evidence also suggests that this treatment strategy is sub-optimal compared to first-line treatment with stimulant medication, followed up if necessary by behavioural intervention.

There may nevertheless be reasons for preferring a more conservative approach to the use of medication (108). In particular, parent preference and worries about long-

term safety, the risks of addiction and abuse have been cited as reasons for continuing to treat medication as a second-line intervention (108). The concerns are difficult to prove or disprove from the current research base. Further, in the absence of long-term evaluations of the impact of methylphenidate on overall quality-of-life, it is difficult to weigh up the balance of risks and benefits. Evidence from placebo-controlled clinical trials shows that common side effects of methylphenidate are relatively mild and short-lived, and that more severe side-effects are very rare. "*In contrast to frequently expressed concerns, children given combined treatment and medication management tolerated medication well...*" (112). However, these data are based on relatively short-term treatment and follow-up (no more than a year or two). None of the studies reported in the AHRQ review studied the risk of addiction or abuse with methylphenidate (55).

It is important to note that the medication and behavioural strategies used in the MTA trial represented a 'gold-standard' with very high inputs of resources that certainly do not reflect current UK practice (108). The behavioural programme included parent-focussed, child-focussed and school-based interventions. The number of sessions per family was very high. Medication was preceded by a placebo-controlled titration of methylphenidate (an "n of 1" trial). If necessary, other medications were also tried. During routine maintenance therapy, families were seen for half an hour monthly to check progress, to provide support, and to adjust medication if necessary. It is not clear which elements of the treatment strategies were responsible for the observed improvements. Thus, it is not clear which elements should be adopted in routine practice. However, it does seem that at least part of the benefit of medication management was due to the method of assessment and follow-up rather than to the medication *per se*.

Another important difference between practice in the clinical trials and routine practice in the UK lies in the definition of the patient population. In the UK, as in most of Europe, treatment (both pharmacological and behavioural) is targeted at children diagnosed with HD. However, clinical trials have almost exclusively included a broader group of children diagnosed with ADHD. The implications of this difference are unclear. The relative effectiveness of treatments for children with other concurrent conditions, such as anxiety or conduct disorders, is also unclear.

5.4 Limitations of the research base

There is a very large body of research on the effectiveness of methylphenidate for ADHD in children. However, the usefulness of this research is limited by a number of factors:

- There is an almost total absence of research investigating the effectiveness of methylphenidate and other interventions for children with a diagnosis of HD, rather than the broader diagnosis of ADHD. This limits the generalisability of research in the UK.
- Few studies make direct head-to-head comparisons between methylphenidate and alternative medications or behavioural management strategies.
- The use of different outcome measures, and different versions of the same measurement instruments, makes comparison of study results

problematic. In particular, the absence of a measure of overall quality-of-life or well being makes quantification of risks and benefits impossible.

- The length of treatment and follow-up has generally been brief, with most studies of less than three months duration. A few studies evaluate effectiveness over more than a year.
- Most studies are restricted to children between the ages of 5 to 12. Less information is available for adolescents.
- The general standard of reporting has been poor, with inadequate details about research methods and relevant clinical details. This makes it difficult to assess the validity and relevance of findings.
- Most clinical studies have small sample sizes and are probably under-powered to detect clinically significant differences between interventions, if such differences do exist.

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Appendix 1. Abstract review form

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Ritalin

Abstract selection form:

Author, year:
Journal: Reviewer: JL/SP

	Y	N	C / T	Comments
Design: 1. prospective RCT or x-over (specify)				
Population: Aged 5 – 18 (specify if stated)				
Diagnosis ADHD .or hyperkinetic disorder	ICD –10 DSM IV Not specified			
Comparison: a. MPH Vs. placebo b. MPH Vs. DEX c. MPH Vs. amitriptyline / imipramine / nortripty. d. MPH Vs. non-drug interventions e. Non-drug + MPH Vs. MPH f. Non-drug + MPH Vs. non-drug g. MPH + other drug Vs. MPH h. MPH + other drug Vs. other drug • More than one of the above (tick relevant) • Other (specify) • Can't tell				
Outcomes: (specify tests if stated) 1. core global 2. hyperactivity / inattention / impulsivity 3. academic 4. psychological 5. conduct 6. adverse effects (specify if stated) • can't tell				

Appendix 2. CCOHTA Inclusion Criteria

Table 1. Study Eligibility Criteria (73)

AREA	CRITERIA
1. Date of Publication	1981 or later
2. Study design	Prospective studies of an intervention or interventions which had to be either parallel- group designs with random assignment of subjects to treatment conditions or within- subject crossover designs with random assignment of subjects to treatment order. Observational (cohort) and single subject studies were ineligible.
3. Target population	Children 0-18 years with a diagnosis of ADD, ADDH or ADHD made in an explicit and reproducible way.
4. Co-morbidity	Studies involved subjects unselected as to the presence of specific associated or co- existing diagnoses such as Tourette or other tic disorder, mental retardation, autism, learning disability or conduct disorder. However the presence of these and other comorbidities such as anxiety, depression and aggression was acceptable provided that the focus of the study was not the effect of an intervention on a specific ADHD sub- population as defined by the presence of such comorbid diagnoses.
5. Intervention	Effects of at least 1 week of stimulant medication (MPH, DAS, pemoline) administered on consecutive days. Effects of a course of psychosocial intervention which may include: -contingency management methods (behaviour modification, parent-or teacher - mediated) -cognitive-behavioural therapy -individual psychotherapy -parent training and education -teacher training and education -parent or family counseling/therapy -social skills training -EEG biofeedback or relaxation therapy
6. Outcome measures	The focus was on effects of intervention on aspects of behaviour that are discernible to teachers, and/or parent, and/or clinicians in everyday life. Outcomes were measured with standardized behaviour rating scale-type of instruments which measure in a broad-based way core ADHD behaviours (inattention, distractibility, impulsiveness and hyperactivity) as well as the disruptive behaviours that are the most salient associated feature of ADHD. Excluded were outcome measures specific to academic performance, cognitive function, neurological/physiological measures and other laboratory-based measures.
7. Data presentation	Outcome data to be presented in a form that is complete and suitable to be extracted for meta-analysis.

Appendix 3. Economic evaluation checklist

	Yes	No	Not clear	NA
1. Was a well-defined question posed in answerable form				
2. Was a comprehensive description of the competing alternatives given?				
3. Was the effectiveness of the programmes or services esablished?				
4. Were all the important and relevant costs and consequences for each alternative identified?				
5. Were costs and consequences measured accurately in appropriate physical units?				

	Yes	No	Not clear	NA
6. Were the costs and consequences valued credibly?				
7. Were the costs and consequences adjusted for differential timing?				
8. Was an incremental analysis of costs and consequences of alternatives performed?				
9. Was allowance made for uncertainty in the estimates of costs and consequences?				
10. Did the presentation and discussion of study results include all issues of concern to users?				