Health Technology Assessment 2006; Vol. 10: No. 23

A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents

S King, S Griffin, Z Hodges, H Weatherly,
C Asseburg, G Richardson, S Golder,
E Taylor, M Drummond and R Riemsma

July 2006

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents

S King,[1*] S Griffin,[2] Z Hodges,[1] H Weatherly,[2] C Asseburg,[2] G Richardson,[2] S Golder,[1] E Taylor,[3] M Drummond[2] and R Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK
[3] Institute of Psychiatry, King's College London, UK

* Corresponding author

Declared competing interests of authors: E Taylor acted as a representative of the RCP at the NICE Appraisal Committee meeting. R Riemsma is a member of the editorial board for *Health Technology Assessment*, but he was not involved in the editorial process for this report.

Published July 2006

This report should be referenced as follows:

King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al*. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. *Health Technol Assess* 2006;**10**(23).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/33/01. The protocol was agreed in July 2004. The assessment report began editorial review in May 2005 and was accepted for publication in July 2005. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents

S King,[1*] S Griffin,[2] Z Hodges,[1] H Weatherly,[2] C Asseburg,[2] G Richardson,[2] S Golder,[1] E Taylor,[3] M Drummond[2] and R Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK
[3] Institute of Psychiatry, King's College London, UK
* Corresponding author

Objectives: To assess the clinical and cost-effectiveness of oral methylphenidate hydrochloride (MPH), dexamfetamine sulphate (DEX) and atomoxetine (ATX) in children and adolescents (<18 years of age) diagnosed with attention deficit hyperactivity disorder (ADHD) (including hyperkinetic disorder).
Data sources: Electronic databases covering 1999–July 2004 for MPH, 1997–July 2004 for DEX and 1981–July 2004 for ATX.
Review methods: Selected studies were assessed using modified criteria based on CRD Report No. 4. Clinical effectiveness data were reported separately for each drug and by the type of comparison. Data for MPH were also analysed separately based on whether it was administered as an immediate release (IR) or extended release (ER) formulation. For all drugs, the data were examined by dose. Data for the core outcomes of hyperactivity (using any scale), Clinical Global Impression [as a proxy of quality of life (QoL)] and adverse events were reported. For crossover studies, the mean and standard deviation (SD) for each outcome were data extracted for end of trial data (i.e. baseline data were not considered). For parallel studies, change scores were reported where given, otherwise means and SDs were presented for end of trial data. In addition, mean differences with 95% confidence intervals were calculated for each study. For adverse events, self-ratings were reported when used, otherwise, parent reports were utilised. Percentages of participants reporting adverse events were used to calculate numbers of events in each treatment arm. All the clinical effectiveness data and economic evaluations (including accompanying models) included in the company submissions were assessed. A new model was developed to assess the cost-effectiveness of the alternative treatments in terms of cost per quality-adjusted life-year. To achieve this, a mixed treatment comparison model was used to estimate the differential mean response rates. Monte Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.
Results: In total, 65 papers met the inclusion criteria. The results suggest that MPH and DEX are effective at reducing hyperactivity and improving QoL (as determined by Clinical Global Impression) in children, although the reliability of the MPH study results is not known and there were only a small number of DEX studies. There was consistent evidence that ATX was superior to placebo for hyperactivity and Clinical Global Impression. Studies on ATX more often reported the study methodology well, and the results were likely to be reliable. Very few studies made direct head-to-head comparisons between the drugs or examined a non-drug intervention in combination with MPH, DEX or ATX. Adequate and informative data regarding the potential adverse effects of the drugs were also lacking. The results of the economic evaluation clearly identified an optimal treatment strategy of DEX first-line, followed by IR-MPH for treatment failures, followed by ATX for repeat treatment failures. Where DEX is unsuitable as a first-line therapy, the optimal strategy is IR-MPH first-line, followed by DEX and then ATX. For patients contraindicated to stimulants, ATX is preferred to no treatment. For patients in whom a midday dose of medication is unworkable, ER-MPH is preferred to ATX, and ER-MPH12 appears more cost-effective than ER-MPH8. As identified in the clinical effectiveness review, the reporting of studies

was poor, therefore this should be borne in mind when interpreting the model results.
Conclusions: Drug therapy seems to be superior to no drug therapy, no significant differences between the various drugs in terms of efficacy or side effects were found, mainly owing to lack of evidence, and the additional benefits from behavioural therapy (in combination with drug therapy) are uncertain. Given the lack of evidence for any differences in effectiveness between the drugs, the economic model tended to be driven by drug costs, which differed considerably. Future trials examining MPH, DEX and ATX should include the assessment of tolerability and safety as a priority. Longer term follow-up of individuals participating in trials could further inform policy makers and health professionals. Such data could potentially distinguish between these drugs in a clinically useful way. In addition, research examining whether somatic complaints are actually related to drug treatment or to the disorder itself would be informative.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Adverse effect An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Attention deficit hyperactivity disorder A mental disorder characterised by a persistent pattern of inattention and/or hyperactivity–impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development.

Bias Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth.

Blinding (synonym: masking) Keeping secret group assignment (e.g. to treatment or control) from the study participants or investigators. Blinding is used to protect against the possibility that knowledge of assignment may affect patient response to treatment, provider behaviours (performance bias) or outcome assessment (detection bias). Blinding is not always practical (e.g. when comparing surgery with drug treatment). The importance of blinding depends on how objective the outcome measure is; blinding is more important for less objective outcome measures such as pain or quality of life.

Chi-squared (χ^2) test Any statistical test based on comparison of a test statistic with a chi-squared distribution.

Concealment of allocation The process used to prevent foreknowledge of group assignment in a randomised controlled trial, which should be seen as distinct from blinding. The allocation process should be impervious to any influence by the individual making the allocation by having the randomisation process administered by someone who is not responsible for recruiting participants, for example, a hospital pharmacy or a central office. Methods of assignment such as date of birth and case record numbers (see quasi-random allocation) are open to manipulation. Adequate methods of allocation concealment include: centralised randomisation schemes; randomisation schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes.

Conduct disorder A mental disorder characterised by a repetitive and persistent pattern of behaviour in which the basic rights of others or major age-appropriate societal norms or rules are violated, manifested by aggressive, defiant or antisocial behaviours.

Confidence interval A measure of precision of statistical estimate; quantifies the uncertainty in measurement. Usually reported as 95% CI, i.e. the range of values within which one can be 95% sure that the true values for the whole population lie.

continued

Glossary *continued*

Confounding (1) The masking of an actual association or (2) false demonstration of an apparent association between the study variables when no real association between them exists.

Construct validity An instrument exhibits this if it is demonstrated that it correlates with other trusted measures of the same effect being measured and that it can discriminate between groups with known differences.

Cost–benefit analysis An attempt to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared with the costs of the intervention. This involves measuring individuals' 'willingness to pay' for given outcomes, and can be difficult.

Cost–consequence analysis Costs are reported separately from health effects.

Cost-effectiveness analysis The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.

Cost-effectiveness acceptability curve A graphical representation of the probability of an intervention being cost-effective over a range of monetary values for society's willingness to pay for an additional unit of health gain.

Cost minimisation When two alternatives are found to have equal efficacy or outcomes (consequences). Therefore, the only difference between the two is cost. This is sometimes considered to be a subtype of cost-effectiveness analysis.

Cost–utility analysis The consequences of alternatives are measured in 'health state preferences', which are given a weighting score. In this type of analysis, different consequences are valued in comparison with each other, and the outcomes (e.g. life-years gained) are adjusted by the weighting assigned. In this way, an attempt is made to value the quality of life associated with the outcome so that life-years gained become quality-adjusted life-years gained.

Crossover trial A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this design is that the effects of the first treatment may carry over into the period when the second is given.

Discounting The process of converting future pounds sterling and future health effects to their present value.

Discriminant validity An instrument exhibits this for the extent to which it does not correlate with variables and measures thought to be unrelated to the construct being measured.

Dominance The state when an intervention under study is both less costly and more effective than the comparator(s).

Economic evaluation Comparative analysis of alternative course of action in terms of both their costs and effects.

Effectiveness The extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do.

Extended dominance The state when a strategy is both more costly and less effective than a linear combination of two other strategies with which it is mutually exclusive.

External validity The ability to generalise the results from a particular experiment to a larger population.

First-line treatment The first regimen given to patients

Incidence The number of new cases of a disease or event in a population during a specific period of time.

Incremental cost-effectiveness ratio An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean

continued

Glossary *continued*

effects. Sometimes expressed with confidence intervals.

Intention-to-treat An ITT analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not. ITT analyses are favoured in assessments of effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.

Internal validity The degree to which a study is logically sound and free of confounding variables.

Markov Chain Monte Carlo
A mathematical model containing a finite number of mutually exclusive and exhaustive health states, with uniform time periods and in which the probability of movement from one state to another depends on the current state and remains constant over time.

Methodological quality (synonyms: validity, internal validity) The extent to which the design and conduct of a study are likely to have prevented systematic errors (bias). Variation in quality can explain variation in the results of studies included in a systematic review. More rigorously designed (better 'quality') trials are more likely to yield results that are closer to the 'truth'.

Meta-analysis The statistical pooling of the results of a collection of related individual studies, to increase statistical power and synthesise their findings.

Mixed treatment comparison Mixed treatment comparison is a form of meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A versus B and B versus C trials) and indirect comparisons (A versus C trials); also, it facilitates simultaneous inference regarding all treatments in order to select the best treatments.

***p*-Value** In the context of significant tests, the *p*-value represents the probability that a given difference is observed in a study sample, when such a difference does not exist in the relevant population. Small *p*-values indicate stronger evidence to reject the null hypothesis of no difference.

Parallel group trial (synonym: independent group design) A trial that compares two groups of people, one of which receives the intervention of interest and one of which is a control group. Some parallel trials have more than two comparison groups and some compare different interventions without including a non-intervention control group.

Prevalence The measure of the proportion of people in a population who have some attribute or disease at a given point in time or during some time period.

Oppositional defiant disorder
A mental disorder characterised by a pattern of negativistic, defiant, disobedient and hostile behaviour towards authority figures as evident in such behaviour as temper tantrums, argumentativeness, refusing to comply with requests and deliberately annoying others.

Placebo An inactive substance or procedure administered to a patient, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit to the patient through a belief that they are receiving treatment. Placebos are used in clinical trials to blind people to their treatment allocation. Placebos should be indistinguishable from the active intervention to ensure adequate blinding.

Quality of life A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity and also other factors which might affect their physical, mental and social well-being.

Quality-adjusted life-year An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

continued

Glossary *continued*

Randomised controlled trial (synonym: randomised clinical trial) An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.

Relative risk (synonym: risk ratio) The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. RR = 1 indicates no difference between comparison groups. For undesirable outcomes an RR that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Second-line treatment The second regimen administered either as a result of relapse after first-line therapy or immediately following on from first-line therapy.

Sensitivity analysis A mathematical method that examines uncertainty associated with parameters estimated into the analysis to test the robustness of the analysis findings. In one-way sensitivity analysis each parameter is varied individually, for multi-way analysis two or more parameters are varied at the same time, threshold analysis identifies the critical values above or below which the results of a study vary and analysis of extremes is used to examine the most pessimistic and the most optimistic scenarios. Finally, probabilistic sensitivity analysis attributes distributions of probabilities to uncertain variables that are incorporated within a model.

Standard gamble Measuring a health state utility by comparing life in a particular given health state with a gamble with a probability that perfect health is the outcome and that immediate death is the outcome. The probability is varied until a point of indifference between the two choices (i.e. until the preference for the given health state is equal to the preference for the gamble).

Statistical significance An estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance, usually expressed as a p-value. For example, a p-value of 0.049 for a risk difference of 10% means that there is less than a one in 20 (0.05) chance of an association that is as large or larger having occurred by chance and it could be said that the results are 'statistically significant' at $p = 0.05$. The cut-off for statistical significance is usually taken at 0.05, but sometimes at 0.01 or 0.10. These cut-offs are arbitrary and have no specific importance. Although it is often done, it is inappropriate to interpret the results of a study differently according to whether the p-value is, say, 0.055 or 0.045 (which are similar values, not diametrically opposed ones).

Systematic review (synonym: systematic overview) A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Time trade-off Measuring a health state by trading off life-years in a state of less than perfect health for a shorter life span in a state of perfect health.

Utility A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises health-related quality of life. Hence utility has been described as a global measure of health-related quality of life. Sometimes 'utility' is only used to refer to preferences (on the 0–1 scale) that are elicited using methods which introduce risky scenarios to the respondent (standard gamble), with the term 'values' used to refer to other types of preferences.

Values An alternative measure of the strength of an individual's preference for a given health state or outcome. In contrast to utilities, values reflect preferences elicited in a riskless context.

Visual analogue scale Direct rating where rates are asked to place a mark at a

continued

Glossary *continued*

point between two anchor states appearing at either end of the line. It is used as a method of valuing health states.

Washout period The stage in a crossover trial when treatment is withdrawn before the second treatment is given. Washout periods are usually necessary because of the possibility that the intervention administered first can affect the outcome variable for some time after treatment ceases. A run-in period before a trial starts is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

List of abbreviations

ACTeRS	ADD-H Comprehensive Teachers' Rating Scale
ADD	attention deficit disorder
ADD-H	attention deficit disorder with hyperactivity
AE	adverse event
ADHD	attention deficit hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
ARS	ADHD Rating Scale
ASQ	Abbreviated Symptoms Questionnaire
ATX	atomoxetine hydrochloride
BM	behaviour modification
BNF	British National Formulary
BSEQ	Barkley Side Effects Questionnaire
BT	behavioural therapy
CBCL	Child Behaviour Checklist
CBT	cognitive behavioural therapy
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CCT	Children's Checking Test
CCT	clinically controlled trial
CD	conduct disorder
CEAC	cost-effectiveness acceptability curve
C-GAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression improvement subscale
CGI-S	Clinical Global Impression severity subscale
CHQ	Child Health Questionnaire
CI	confidence interval
CIC	commercial-in-confidence
CNS	central nervous system
CON	concerta
CPRS-R	Conners' Parent Rating Scale – Revised
CPRS	Conners' Parent Rating Scale
CPRS-H	Conners' Parent Hyperactivity Subscale
CTRS-R	Conners' Teacher Rating Scale – Revised
CTRS	Conners' Teacher Rating Scale
CTRS-H	Conners' Teacher Hyperactivity Subscale
DEC	Development and Evaluation Committee
DEX	dexamfetamine sulphate
DEX-SR	sustained-release dexamfetamine sulphate
DEX-TR	time-release dexamfetamine sulphate
DSM-III	*Diagnostic and Statistical Manual of Mental Disorders* (3rd edition)

continued

List of abbreviations *continued*

DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders* (4th edition)
ECG	electrocardiogram
EEG	electroencephalogram
EQ-5D	EuroQol instrument
ER-MPH	extended-release methylphenidate hydrochloride
FFD	Freedom from Distractability Factor
GDS	Gordon Diagnostic System
HKD	hyperkinetic disorder
HRQoL	health-related quality of life
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th revision)
ICER	incremental cost-effectiveness ratio
IHRQoL	Index of Health-related Quality of Life
IOWA	Inattention/Overactivity with Aggression
IOWA-C	Inattention/Overactivity with Aggression Conners' Rating Scale
IQ	intelligence quotient
IR-MPH	immediate-release methylphenidate hydrochloride
ITT	intention-to-treat
MCD	Metadate CD
MCMC	Markov Chain Monte Carlo
MD	mean difference
MFFT	Matching Familiar Features Test
MPH	methylphenidate hydrochloride
MPH-SR	sustained-release methylphenidate hydrochloride
MTA	Multimodal Treatment Study of ADHD
MTC	mixed treatment comparison
NICE	National Institute for Health and Clinical Excellence
NS	not significant
ODD	oppositional defiant disorder
PACS	Parental Account of Childhood Symptoms
PEM	pemoline
PIAT	Peabody Individual Achievement Test
PPA	Prescription Pricing Authority
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SEM	standard error of the mean
SERS	Side Effects Rating Scale
SG	standard gamble
SHS	Schenectady Hyperkinetic Scale
SKAMP	Swanson, Kotkin, Agler, M-Flynn and Pelham (scale)
SNAP	Swanson, Nolan and Pelham (scale)
SR	systematic review
STESS	Subject's Treatment Emergent Symptom Scale
STP	Summer Treatment Programme
TIP	Telephone Interview Probe
TOTS	Loney's Time on Task Scale
TTO	time-trade-off
VAS	visual analogue scale
WISC-R	Weschlar Intelligence Scale for Children – Revised
WRAT	Wide Range Achievement Test

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Attention deficit hyperactivity disorder (ADHD) (including hyperkinetic disorder) is defined by the 'core' signs of inattention, hyperactivity and impulsivity, and is characterised by an early onset. The estimated prevalence for ADHD in school-aged children varies widely (e.g. 3–7%), being dependent on a number of variables, including the methods of ascertainment, the informants, the population sampled, the diagnostic criteria applied and the sex of the affected individual. Data on prevalence in adolescence and adulthood are limited. The disorder is frequently observed in greater numbers of males than females, with ratios ranging from 2:1 to 9:1 depending on subtype and setting.

There are two generally used diagnostic criteria: the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria. The ICD-10 presents details on the diagnosis of hyperkinetic disorders (HKD) and the DSM-IV criteria define ADHD more broadly to include three subtypes: a combined subtype in which all three core signs are present, a predominantly inattentive subtype in which inattention is present but not hyperactivity/impulsivity and a predominantly hyperactive–impulsive subtype in which hyperactivity/impulsivity are present but not inattention. As the ICD-10 criteria are similar to the severe combined type ADHD defined by the DSM-IV criteria, prevalence rates may be higher using the DSM-IV criteria than when diagnosed using the ICD-10 criteria.

Current treatments for ADHD include social, psychological and behavioural interventions in addition to medical management. Medications currently licensed for the treatment of ADHD in the UK include methylphenidate hydrochloride (MPH), dexamfetamine sulphate (DEX) and atomoxetine (ATX), although clinicians sometimes prescribe tricyclic and other antidepressants. MPH is available in immediate-release (Ritalin® and Equasym®) and extended-release forms [Concerta® XL and Equasym XL® (a licence application for Equasym XL had been submitted; it has been specifically developed to provide efficacy across the school day and replace the need for twice daily dosing for children who do not consistently require evening medication)]. They are all indicated in children over 6 years of age, and in adolescents. DEX can be given to children as young as 3 years, whereas ATX (licensed in the UK in May 2004) is indicated in children aged 6 years and above.

Objective

The objective was to assess the clinical and cost-effectiveness of oral MPH, DEX and ATX in children and adolescents (under 18 years of age) diagnosed with ADHD (including hyperkinetic disorder).

Methods

This systematic review incorporated studies from, and built upon, three previous systematic reviews:

- A review conducted by the American Agency for Healthcare Research and Quality (AHRQ) published in 1999 (Jadad and colleagues, 1999).
- A report for the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) (Miller and colleagues, 1999).
- A previous National Institute for Health and Clinical Excellence (NICE) review, which was also based primarily on evidence from the AHRQ report (Lord and Paisley, 2000).

Search strategy

The searches, conducted in July 2004, aimed to retrieve both published and unpublished papers with no language restrictions. A date restriction of 1999 onwards was placed on the methylphenidate searches to update the report produced by Lord and Paisley published in 2000. A date restriction of 1997 onwards was placed on the searches for dexamfetamine to update the AHRQ report (which included a review of this drug). Research on atomoxetine was searched for from 1981 onwards. The search strategy was based on that used in the AHRQ report.

Inclusion/exclusion criteria

To be eligible for inclusion, studies had to be randomised controlled trials (RCTs) of at least 3 weeks' duration (3 weeks per treatment arm in parallel studies and 3 weeks in overall trial length for crossover studies). In addition, systematic reviews were included to examine adverse events data. For the assessment of cost-effectiveness, a broader range of studies was considered.

The studies had to examine MPH, DEX or ATX used alone or in combination with non-drug interventions and be compared with placebo, with one another in head-to-head comparisons or with non-drug interventions. Non-drug interventions included any type of psychological and behavioural strategies (e.g. cognitive behavioural therapy, child or parent training, bibliotherapy) and/or nutritional interventions. Studies that compared MPH, DEX or ATX with other drugs (e.g. Adderall) not licensed in the UK for ADHD were included as long as there was a placebo group. This was applied to both efficacy and adverse events data.

Participants included children and adolescents under 18 years of age diagnosed with ADHD (including hyperkinetic disorder). There was no lower age limitation (although there was no lower age limitation for the report, it is noted that MPH is indicated for children older than 6 years, and ATX is indicated for children aged 6 years and over). The diagnosis must have been made in an explicit way, preferably using either the ICD-10 criteria or the DSM-IV criteria. Studies including participants with conditions other than ADHD (e.g. Tourette's syndrome) were excluded unless they reported separate analyses for patients with ADHD alone.

To be included in the review, trials had to report results on one or more of the following:

- core symptoms (including measures of inattention, hyperactivity, impulsivity)
- quality of life (QoL) (Clinical Global Impression or overall severity indices were used as a proxy of QoL)
- adverse effects (including loss of appetite, insomnia, headache, stomach ache and weight loss).

Studies that only examined tests of psychological function (e.g. the continuous performance test), measures of depression and/or anxiety, or measures of coexistent problems (including poor peer relationships, and conduct/oppositional-disorder-related outcomes) were not included in the review. Studies that presented results in figures without presenting actual numbers, or only significance values for comparisons, were excluded from the review.

Studies that met the inclusion criteria above, but were only published as abstracts or as conference presentations were not included in the review unless a full paper could be obtained that related to the abstract.

Two reviewers independently screened all titles and abstracts, including economic evaluations, identified in the updated literature search. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. In addition, full paper copies of relevant studies presented in the NICE, AHRQ and CCOHTA reports were obtained. The full papers were then assessed against the inclusion criteria by one reviewer and checked by another. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted.

Data extraction and quality assessment

The quality of the clinical effectiveness studies was assessed using modified criteria based on CRD Report No. 4. Each study was assessed and data were extracted by one reviewer and independently checked for agreement with a second reviewer. Disagreements were resolved by consensus and, if necessary, a third reviewer was consulted.

Methods of analysis/synthesis

Clinical effectiveness data were reported separately for each drug and by the type of comparison. Data for MPH were also analysed separately based on whether it was administered as an immediate release or extended release formulation. For all drugs, the data were examined by dose. Data for the core outcomes of hyperactivity (using any scale), Clinical Global Impression (as a proxy of QoL) and adverse events were reported. For crossover studies, the mean and standard deviation (SD) for each outcome were data extracted for end of trial data (i.e. baseline data were not considered). Where possible, we aimed to calculate mean difference and standard errors for crossover studies in order to facilitate meta-analysis. However, owing to the lack of information needed to calculate mean differences in many of the studies, this was not possible. For parallel studies, change scores were reported where given, otherwise means and SDs were presented for end of trial data. In addition,

mean differences with 95% confidence intervals were calculated for each study. For adverse events, self-ratings were reported when used, otherwise, parent reports were utilised. Percentages of participants reporting adverse events were used to calculate numbers of events in each treatment arm.

For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables.

Handling company submissions

All the clinical effectiveness data included in the company submissions were assessed. Where these met the inclusion criteria they were included in the clinical effectiveness review. All economic evaluations (including accompanying models) included in the company submissions were assessed and detailed assessments of the assumptions underlying the submitted analyses were undertaken.

A new model was developed to assess the cost-effectiveness of the alternative treatments in terms of cost per quality-adjusted life-year. To achieve this, a mixed treatment comparison model was used to estimate the differential mean response rates. Monte Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

Results

Clinical effectiveness

In the previous systematic reviews (NICE, AHRQ and CCOHTA), 65 studies were identified as potentially relevant to the current systematic review, and full paper copies were ordered. Of these, 40 met the inclusion criteria. In the updated search, a total of 2908 titles and abstracts relating to clinical effectiveness or systematic reviews of adverse events were identified and screened for relevance. Of these, 409 full paper copies were examined in detail and assessed for inclusion. Of these, 20 RCTs and one systematic review met the inclusion criteria. In addition, four commercial-in-confidence papers were included. Overall, this gives a total of 65 papers.

As reported in the previous NICE report, and in the AHRQ and CCOHTA reviews, the plethora of MPH studies suggest that MPH is effective at reducing hyperactivity and improving QoL (as determined by Clinical Global Impression) in children. It was noted, however, that the majority of studies that evaluated the effectiveness of MPH did not adequately report their study methodology. Hence, the reliability of the study results is not known. There appears to be little evidence supporting a difference in the effectiveness of immediate-release (IR) and extended-release (ER) MPH.

Similarly, DEX also appears to be effective at reducing hyperactivity and improving QoL, although this is based on a small number of studies. Only one study adequately reported the study methodology.

There was consistent evidence that ATX was superior to placebo for hyperactivity and Clinical Global Impression. Studies on ATX more often reported the study methodology well, and the results are likely to be reliable.

Very few studies made direct head-to-head comparisons between the drugs. The previous NICE report stated that there appeared to be little evidence of difference in the effectiveness of MPH and DEX. No recent studies were found in the updated search. Although the studies reported variable results, the one study that reported no statistically significant differences between the two drugs was deemed to be of good quality, whereas the quality of the others was uncertain given the poor reporting of study methodologies.

One study that compared MPH and ATX reported no differences between the drugs for hyperactivity or Clinical Global Impression. This study did not adequately report study methodology, and the results should be interpreted with caution. **[Confidential information removed]**.

Few studies were included in the review that examined a non-drug intervention in combination with MPH, DEX or ATX. Generally, the results were variable. The studies were, however, heterogeneous regarding the type of non-drug interventions examined and the scales used to measure outcomes.

Adequate and informative data regarding the potential adverse effects of MPH, DEX and ATX are lacking. Overall, higher dosages of IR-MPH appear to be associated with the occurrence of headache, lost appetite, stomach ache and insomnia compared with placebo. ER-MPH appears to be associated with decreased appetite and increased insomnia. However, a previous

systematic review highlighted the need for further research into somatic complaints, which may be associated with the disorder itself rather than methylphenidate treatment. Similarly, high doses of DEX appear to be associated with decreased appetite and increased sleeping problems. ATX of any dose may impair appetite.

Cost-effectiveness

The review highlighted a number of potential limitations in the existing literature. In particular, the review highlighted limitations in estimating treatment effectiveness and associated utility values. These limitations may stem from a lack of available data. A new economic model was developed for this report. Pooling was limited in the clinical effectiveness review, owing to heterogeneity between trials. However, some degree of pooling is necessary to proceed with an economic model. The issue of heterogeneity was overcome by basing the base case on trials that are more similar in terms of how they measure the outcome of interest. In a series of sensitivity analyses more trials were included by relaxing the criterion of similarity in outcome measurement. Data on resource use associated with ADHD in the UK were lacking, and so the model relies on estimates from experts.

Given the lack of available evidence for statistically significant differences in efficacy between the alternative drugs, the results of the economic model were largely driven by drug cost, in which there are marked differences. The economic evaluation clearly suggests an optimal treatment strategy, that is, DEX first-line, followed by IR-MPH for treatment failures, followed by ATX for repeat treatment failures. If DEX is considered not suitable as a first-line therapy, the optimal strategy is IR-MPH first-line, followed by DEX as second-line and ATX again as third-line. For patients contraindicated to stimulants, ATX is preferred to no treatment. For patients in whom a midday dose of medication is unworkable, ER-MPH is preferred to ATX, and ER-MPH12 appears more cost-effective than ER-MPH8.

The model is not without limitations. As identified in the clinical effectiveness review, the reporting of studies was poor, there are few data to discriminate between the drugs in efficacy or adverse events and there are few data on long-term efficacy and adverse events associated with medical management of ADHD. The data do not allow discrimination between patients with ADHD in terms of ADHD subtype, age, gender or previous treatment. These caveats must be borne in mind when interpreting the model results.

Conclusions

The main conclusions from this report are as follows:

1. Drug therapy seems to be superior to no drug therapy.
2. No significant differences between the various drugs in terms of efficacy or side effects were found – mainly owing to lack of evidence.
3. The additional benefits from behavioural therapy (in combination with drug therapy) are uncertain.

The main additional feature of the economic model is the consideration of costs. Given the lack of evidence for any differences in effectiveness between the drugs, the model tends to be driven by drug costs, which differ considerably.

Research recommendations

Future trials examining MPH, DEX and ATX should include the assessment of tolerability and safety as a priority. Reporting should be standardised and transparent. Researchers should refer to the CONSORT approach to study design.

Longer term follow-up of individuals participating in trials could further inform policy makers and health professionals. Such data could potentially distinguish between these drugs in a clinically useful way.

In addition, research examining whether somatic complaints are actually related to drug treatment or to the disorder itself would be informative.

Chapter 1

Aim of the review

This review examines the clinical and cost-effectiveness of oral methylphenidate hydrochloride (MPH) (Ritalin®, Equasym®, Equasym XL®, Concerta® XL), dexamfetamine sulphate (DEX) (Dexedrine®) and atomoxetine hydrochloride (ATx) (Strattera®) in children and adolescents (under 18 years of age) diagnosed with attention deficit hyperactivity disorder (ADHD) [including hyperkinetic disorder (HKD)]. It includes an update of the existing National Institute for Health and Clinical Excellence (NICE) Report No. 13.[1]

Chapter 2
Background

Description of underlying health problem

ADHD (including HKD) is defined by the 'core' signs of inattention, hyperactivity and impulsivity, and is characterised by an early onset. The estimated prevalence for ADHD in school-aged children varies widely (e.g. 3–7%), being dependent on a number of variables including the methods of ascertainment, the informants, the population sampled, the diagnostic criteria applied and the sex of the affected individual. For example, prevalence rates may be lower when diagnosed using the International Statistical Classification of Diseases and Related Health Problems (10th edition) (ICD-10) criteria (see below) for hyperkinetic disorder. Data on prevalence in adolescence and adulthood are limited. The disorder is frequently observed in greater numbers of males than females, with ratios ranging from 2:1 to 9:1 depending on subtype and setting.[2,3]

In England and Wales, the prevalence of ADHD in children 6–18 years of age has been estimated to be about 5% (based on mid-1997 estimates).[4] The British Child and Adolescent Mental Health Survey conducted in 1999 examined a sample of 10,438 children and found 2.23% to have ADHD. Of the 5212 males, 3.62% had ADHD compared with 0.85% of the 5226 females in the sample ($p < 0.001$). Overall, 1.41% of the sample was classified as ADHD Combined Type, compared with 0.67% and 0.16% Inattentive and Hyperactive Type, respectively.[5]

Aetiology

Research has indicated that the aetiology of ADHD is of a multifactorial and complex nature. Family, twin and adoption studies consistently implicate the role of genetic factors. Molecular genetic studies have focused on dopamine receptors such as the D4 dopamine receptor gene (DRD4), the mRNA of which appears to play a role in cognitive and emotional functions.

A number of conditions have a very high risk for the presence of ADHD symptoms, including neurofibromatosis Type 1,[6] epilepsy,[7] very low birth weight,[8,9] chronic tic disorders/Tourette's syndrome, developmental coordination disorders[10] and high functioning autism.[11] In addition, numerous biological environmental risk factors have been studied, such as diet, prenatal alcohol and nicotine exposure, some of which appear to account for selected cases. Many studies provide strong evidence for the importance of psychosocial adversity such as severe marital discord; however, these factors tend to emerge as universal predictors of a child's emotional health and adaptive functioning rather than being specific predictors of ADHD. Although there is no single pathophysiological profile of ADHD, neurobiological research suggests that both genetic and environmental factors modify the front-subcortical pathways in the brain that control attention and motor behaviour.[12,13]

Diagnosis

ICD-10, published in 1992,[14] details the diagnosis of **hyperkinetic disorders**. Such disorders, characterised by onset during childhood or adolescence, feature both impaired attention and overactivity evident in more than one situation over a sustained period of time.

According to these guidelines, impaired attention manifests itself in sufferers by premature breaking off from tasks and leaving activities unfinished. Overactivity implies excessive restlessness and is judged in terms of normal expectations for the situation, age and IQ of the individual involved.

Published in 2000, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[2] cites five criteria to be considered in the diagnosis of **Attention deficit/hyperactivity disorder**:

A. At least six symptoms of inattention or hyperactivity/impulsivity should have persisted for at least 6 months to an extent inconsistent with normal development.
B. Some symptoms must have been present before 7 years of age.
C. Resulting impairment should be evident in two or more settings.
D. Impairment should be clinically significant with regard to social, academic or occupational functioning.

E. Symptoms should not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder. Neither should they be better explained by another mental disorder.

The DSM-IV criteria distinguish between three subtypes of attention deficit/hyperactivity disorder according to the predominant symptom pattern for the previous six months: combined type, predominantly inattentive type and predominantly hyperactive–impulsive type.

Choice of diagnostic criteria has important implications in terms of measuring disease prevalence and also making treatment decisions. The ICD-10 criteria are similar to the severe combined type ADHD defined by the DSM-IV criteria. Hence, diagnoses based on the former criteria may be fewer. The two contending approaches continue to be a matter of controversial discussion.[15,16]

The internal validity of the ICD-10 and DSM-IV models is also a focus of research and discussion.[17–24] Studies have been carried out, for example, to compare the impact of application across cultures and age groups. Issues of prevalence, co-morbidity and aetiology, related to internal validity, are highlighted below.

Co-morbidity and associated features

Considerable overlap exists between hyperkinesis and other patterns of disruptive behaviour such as conduct disorder. The ICD-10 diagnostic guidelines consequently distinguish between hyperkinetic conduct disorder and simple disturbance of activity and inattention.[14] The DSM-IV manual estimates that approximately half of clinic-referred children with ADHD also have oppositional defiant disorder (ODD) or conduct disorder (CD).[2]

Common patterns of behaviour and development, insufficient and unnecessary for diagnosis in themselves, have also been noted amongst sufferers:

- disinhibition in social relationships
- recklessness in situations involving some danger
- impulsive flouting of social rules
- cognitive impairment
- specific motor and language developmental delays
- dissocial behaviour such as temper outbursts.

These associated characteristics often result in negative interactions with peers, school authorities and family members and subsequently diminished self-esteem.[2,14]

Current service provision

For the first quarter of 2004, there were 68,000 prescribing items for MPH, at a cost of over £2 million [*Figure 1*; Prescription Pricing Authority (PPA) data cover March 1999 to March 2004 in quarterly periods].

For the first quarter of 2004, there were just under 10,000 prescribing items for DEX, at a cost of just under £80,000 (*Figure 2*; PPA data cover March 1999 to March 2004 in quarterly periods). From December 2001 the cost increased considerably whereas prescribing remained fairly static. The

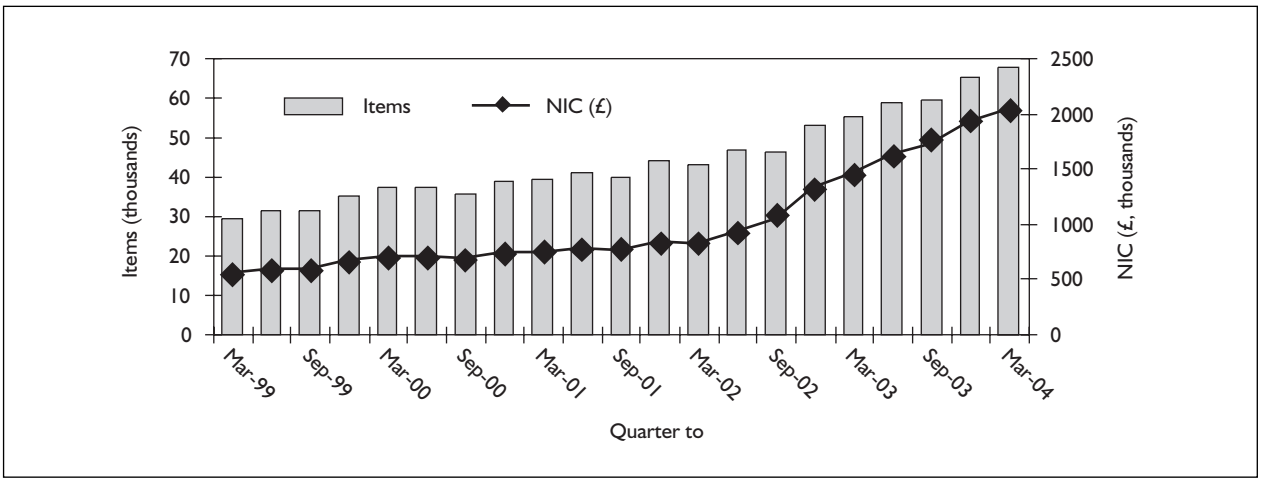

FIGURE 1 *Trends in prescribing of and spending on methylphenidate in general practice in England and Wales. Source: PPA. NIC, net ingredient cost.*

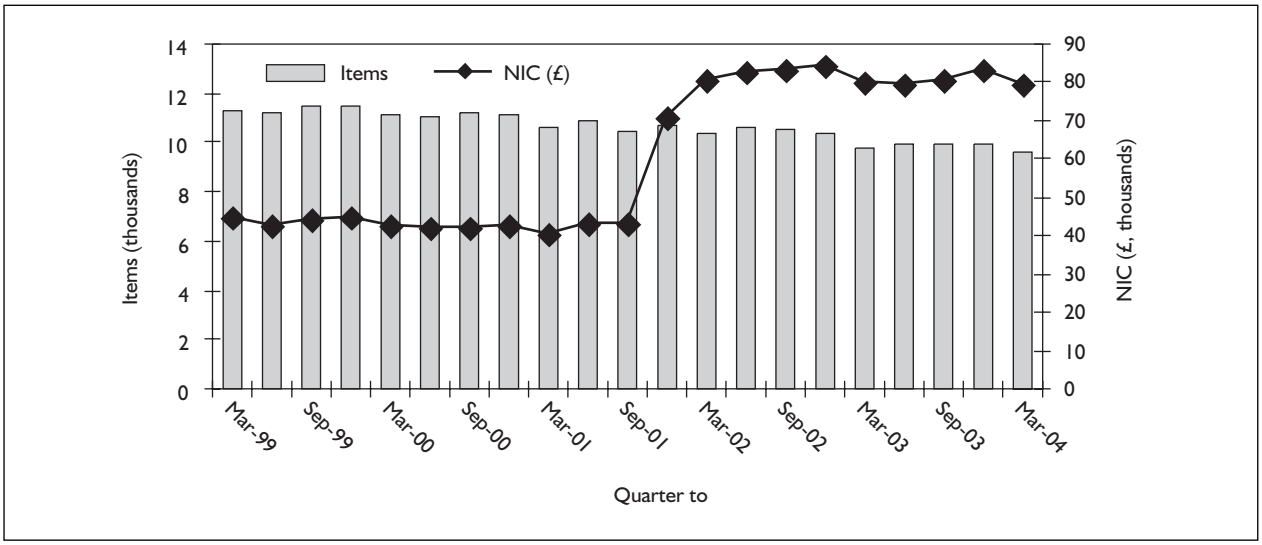

FIGURE 2 *Trends in prescribing of and spending on dexamfetamine in general practice in England and Wales. Source: PPA.*

reason for this is that the majority of the prescribing for dexamfetamine is for the 5-mg tablet (available as the brand Dexedrine) and in October 2001 the price of this product doubled, hence the cost increased.

Health, social and education services will also incur costs for assessment and follow-up of these children. These costs have been estimated at about £23 million for initial specialist assessment (£21.8 million in England and £1.5 million in Wales) and £14 million for follow-up care over 1 year (£13.4 million in England and £0.9 million in Wales). However, some of these costs relate to services that are already in place, and 100% uptake of medication is unlikely. It is also possible that better treatment for children with ADHD could avoid some health, education and social costs in the longer term.

Description of intervention

Methylphenidate hydrochloride[25]

MPH is a mild CNS stimulant with more prominent effects on mental than other motor activities. The mode of therapeutic action is not completely understood, but one key action is the inhibition of the dopamine transporter, with consequent magnification of dopamine-medicated signalling in areas such as frontal lobe and striatum.

Ritalin® (Cephalon UK Ltd), Equasym® (Celltech Pharmaceuticals Ltd), Equasym XL® (Celltech Pharmaceuticals Ltd) and Concerta® XL (Janssen-Cilag Ltd) are each indicated as part of comprehensive treatment programme for ADHD in children (>6 years of age) and adolescents. [Although Tranquilyn® holds a UK Marketing Authorisation (PL 18153/0001-3), its manufacture appears to have been discontinued. The licence holder is Laboratorios Rubio SA.]

Ritalin is available in 10-mg tablets, Equasym is available in 5-, 10- and 20-mg tablets and Concerta XL is available in 18- and 36-mg prolonged-release tablets. A new form of slow-release MPH that may gain license in the UK is Equasym XL. It is to be an addition to the immediate-release 5-, 10- and 20-mg Equasym tablets already established.

Ritalin and Equasym

According to current guidelines, the recommended dose is 0.2–0.7 mg/kg body weight, given twice or three times daily, starting with the lowest and increasing by increments of 5 mg in each dose until a good response is achieved, adverse events appear or the ceiling dose is reached.

Equasym XL

Metadate CD® (Celltech Pharmaceuticals Ltd) is currently licensed in the USA and, if licensed in the UK, it is likely to be known as Equasym XL. Metadate CD is administered once daily in the morning, before breakfast. The recommended starting dose is 20 mg once daily. Dosage may be adjusted in weekly 20-mg increments to a maximum of 60 mg per day. The manufacturers of this drug claim that its effects last through 8 hours.

Concerta XL

Concerta XL is administered orally once daily in the morning and must be swallowed whole with the aid of liquids, and must not be chewed, divided or crushed. Concerta XL may be administered with or without food. Dosage should be individualised according to the needs and responses of the patient. Dosage may be adjusted in 18-mg increments to a maximum of 54 mg per day taken once in the morning. In general, dosage adjustment may proceed at approximately weekly intervals. The manufacturers of this drug claim that its effects last through 12 hours.[26]

Dexamfetamine sulphate (dexamphetamine sulphate)

DEX is a symphathomimetic amine with central stimulant and anorectic activity. It is indicated in narcolepsy. It is also indicated for children with refractory hyperkinetic states under the supervision of a physician specialising in child psychiatry.

Dexedrine® (Celltech Pharmaceuticals Ltd) is available in 5-mg tablets.

The usual starting dosage for children aged 3–5 years is 2.5 mg per day, increased if necessary by 2.5 mg per day at weekly intervals. For children aged ≥ 6 years, the usual starting dose is 5–10 mg per day, increasing if necessary by 5 mg at weekly intervals. The usual upper limit is 20 mg a day although some older children have needed 40 mg or more for optimal response.

Atomoxetine hydrochloride[27]

ATX is reported to be a selective noradrenaline reuptake inhibitor. The precise mechanism by which ATX works on ADHD is not known. It is currently licensed in the USA and the UK under the brand name Strattera® (Eli Lilly & Co. Ltd). The manufacturers claim that it is the first non-stimulant medication approved for the treatment of ADHD in children ≥ 6 years of age. In adolescents who have shown a clear benefit from treatment, and whose symptoms persist into adulthood, treatment may be continued into adulthood. However, starting treatment with Strattera in adults is not appropriate. It is indicated as an integral part of a total treatment programme for patients with ADHD.

Strattera is available in 10-, 18-, 25-, 40- and 60-mg capsules (for oral administration with or without food).

In children and adolescents up to 70 kg body weight, Strattera should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less.

In children and adolescents >70 kg body weight, Strattera should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg administered as stated above. After 2–4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response.

Chapter 3

Methods for reviewing effectiveness and cost-effectiveness

Search strategy

Clinical effectiveness

Details of the search strategies are presented in Appendix 1. They aimed to retrieve papers relating to MPH, DEX and ATX for children with ADHD. The strategy was based on that used in the Agency for Healthcare Research and Quality (AHRQ) report[28] and used a range of free text terms and subject headings for ADHD. In addition, terms were added for methylphenidate, dexamfetamine and atomoxetine, to provide a more focused strategy. No study design filters were added to the searches in order to retrieve a range of study designs, including systematic reviews (SRs), randomised controlled trials (RCTs) and clinically controlled trials (CCTs), economic evaluations and adverse events. A date restriction of 1999 onwards was placed on the methylphenidate searches as this review updates the report produced by Lord and Paisley published in 2000.[4] A date restriction of 1997 onwards was placed on the searches for DEX in order to update the AHRQ report (which included a review of this drug). Research on ATX was searched for from 1981 onwards. Most of the searches were conducted in July 2004. No language restrictions were placed on any of the search strategies.

The following databases were searched for relevant published literature:

- CINAHL
- CENTRAL
- Database of Abstracts of Reviews of Effects (DARE)
- EMBASE
- Health Technology Assessment (HTA) Database
- Health Economic Evaluations Database (HEED)
- MEDLINE
- NHS Economic Evaluation Database (NHS EED)
- PreMEDLINE
- PsycINFO
- Science Citation Index (SCI).

Ongoing and recently completed research was identified from:

- Controlled Clinical Trials
- clinicaltrials.gov
- National Research Register (NRR)
- ReFeR database.

Conference proceedings were identified by:

- ISI Proceedings: Social Sciences and Humanities
- ISI Proceedings: Science and Technology
- Inside Conferences.

Reports, dissertations and other grey literature were identified by:

- Dissertation Abstracts
- System for Information on Grey Literature in Europe (SIGLE).

A number of evidence based websites were searched or browsed, including:

- Agency for Healthcare Research and Quality (AHRQ)
- Health Evidence Bulletins Wales
- Health Services/Technology Assessment Text (HSTAT)
- National Coordinating Centre for Health Technology Assessment
- National Guideline Clearinghouse
- National Institute for Health and Clinical Excellence (NICE) (published appraisals)
- National Horizon Scanning Centre (NHSC)
- Scottish Intercollegiate Guidelines Network (SIGN) Guidelines
- Turning Research Into Practice (TRIP+).

Paper resources to be scanned include the latest Clinical Evidence and the BNF.[29]

Additional specific searches for adverse events related to MPH, DEX and ATX were conducted using TOXLINE. Searches for economic evaluations were conducted using NHS EED and

HEED. These databases were also searched for research relating to the health-related quality of life (HRQoL) of people with ADHD, but who were not necessarily taking any of the three drugs.

The bibliographies of any eligible publication identified from the above sources were checked for additional references. Manufacturer and sponsor submissions made to NICE were reviewed to identify any additional studies.

Cost-effectiveness

In addition to identifying relevant papers retrieved from the clinical effectiveness searches, economic evaluations were identified by searching the following resources (details of the search strategies are presented in Appendix 2):

- Health Economic Evaluations Database (HEED) (Issue: July 2004)
  Searched: 22 July 2004 on CD-ROM
- NHS Economic Evaluation Database (NHS EED)
  Searched: 22 July 2004 on CRD's internal administration database.

Additionally, HRQoL research was sought by searching the following resources:

- CINAHL (1982–June week 2, 2004)
  Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
- Database of Abstracts of Reviews of Effects (DARE)
  Searched 22 June 2004 on CRD's internal administration database
- EMBASE (1980–2004 week 11)
  Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
- Health Economic Evaluations Database (HEED) (Issue: June 2004)
  Searched 22 June 2004 on CD-ROM
- Health Technology Assessment Database (HTA)
  Searched 22 June 2004 on CRD's internal administration database
- MEDLINE (1966–March week 2, 2004)
  Searched: 18 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
- MEDLINE In-process and other non-indexed citations (18 June 2004)
  Searched: 22 June 2004 on OvidWeb at http://gateway1.uk.ovid.com/ovidweb.cgi
- NHS Economic Evaluation Database (NHS EED)
  Searched 22 June 2004 on CRD's internal administration database
- PsycINFO (1967–2004/ June week 1)
  Searched: 23 June 2004 on WebSPIRS via BIDS at http://www.bids.ac.uk/
- Social Science Citation Index (SSCI) (1981–2004)
  Searched: 22 June 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/
- Science Citation Index (SCI) (1981–2004)
  Searched: 22 June 2004 on ISI Web of Knowledge via MIMAS at http://wos.mimas.ac.uk/

Inclusion and exclusion criteria: clinical effectiveness

Two reviewers independently screened all titles and abstracts identified in the updated literature search. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. In addition, full paper copies of relevant studies presented in the NICE, AHRQ and Canadian Coordinating Office for Health Technology and Assessment (CCOHTA)[30] reports were obtained. The decision to include studies was assessed according to criteria presented below. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted.

Study design

Only RCTs examining MPH, DEX or ATX used alone, in combination with each other or in combination with non-drug interventions that were compared with placebo, with one another in head-to-head comparisons or with non-drug interventions were included in the review. Studies that compared MPH, DEX or ATX with other drugs (e.g. Adderall) were included provided that they included a placebo group. This was applied to both efficacy and adverse events data. In addition, SRs were included to examine adverse events data [see the section 'Inclusion and exclusion criteria for systematic reviews: clinical effectiveness' (p. 9)].

To be included, studies had to be at least 3 weeks in duration (3 weeks per treatment arm in parallel studies and 3 weeks in overall trial length for crossover studies). The reason why this cut-off was used is because the literature suggests that 3 weeks is the minimum length of treatment chosen by investigators who are examining clinical outcome. [The literature contains a number of random-allocation comparisons of MPH and placebo based either on single-dose administration or on treatment over a few days. These have been carried out to clarify the mode of action, e.g. the effect of different doses on laboratory tests, rather than as therapeutic trials, so should not be included in assessments of clinical value. The effect of medication on

behaviour is often (not always) apparent immediately, but the impact on the social adjustment of the child may well not be apparent in the first days of therapy. We recognise, however, that even 3 weeks is a short period in which to examine the effect of a drug intended to modify a chronic condition.]

Interventions

MPH (Ritalin, Equasym, Equasym XL, Concerta XL), DEX (Dexedrine) and ATX (Strattera), used alone or as part of a multi-modal treatment programme (involving other drugs and/or non-drug interventions), were included, provided that effectiveness or adverse event data were presented for the three drugs of interest. Non-drug interventions included any type of psychological and behavioural strategies [e.g. cognitive behavioural therapy (CBT), child or parent training, bibliotherapy] and/or nutritional interventions.

Studies that compared MPH, DEX or ATX with other drugs not licensed for ADHD in the UK were excluded from the review, unless the study also included a placebo group. In these studies, data for comparisons between MPH, DEX and ATX and placebo were extracted.

Participants

Participants included children and adolescents <18 years of age diagnosed with ADHD (including HKD). There was no lower age limitation (although there was no lower age limitation for the report, it is noted that MPH is indicated for children >6 years old and ATX is indicated for children ≥ 6 years of age). The diagnosis must have been made in an explicit way, preferably using either the ICD-10 criteria or the DSM-IV criteria.

Studies that included conditions other than ADHD (e.g. Tourette's syndrome) or children with ADHD and mental retardation were only included here if they reported separate analyses for patients with ADHD alone. RCTs excluded from this review that examined children with ADHD and other co-morbid conditions are presented in Appendices 3 and 4.

Outcomes

Given the large number of outcomes presented in the literature, the inclusion criteria were restricted to four broad outcome categories. These efficacy measures are widely used and, after discussions with a clinical expert, were recognised as the most relevant clinical outcomes.

To be included in the review, trials had to report results on one or more of the following:

- core symptoms (including measures of inattention, hyperactivity, impulsivity)
- quality of life (QoL) (clinical global impression or overall severity indices were used as a proxy of QoL)
- adverse effects (including loss of appetite, insomnia, headache, stomach ache and weight loss).

Studies that also reported on educational performance (including various tests of reading, spelling, mathematics, or by accuracy and productivity of seatwork tasks) were also included in the first stage of the screening, but were later excluded if this was the only outcome assessed. Studies that only examined tests of psychological function (e.g. the continuous performance test), measures of depression and/or anxiety or measures of coexistent problems (including poor peer relationships, and conduct/oppositional disorder-related outcomes) were not included in the review. However, if the trial examined these outcomes in addition to one or more of the four presented above, it was noted in data extraction tables.

Studies that presented all results in figures without presenting actual numbers, or only significance values for comparisons, were excluded from the review.

Publication

Studies that met the inclusion criteria above, but were only published as abstracts or as conference presentations, were not included in the review unless a full paper could be obtained that related to the abstract (a list of these excluded publications is presented in Appendix 3).

As there was no language restriction in the search strategy, trials reported in any language were considered for inclusion in the review. However, time limitations resulted in the exclusion of two papers written in Mandarin (see Appendix 3).

Inclusion and exclusion criteria for systematic reviews: clinical effectiveness

To be included, systematic reviews with adverse events data had to:

- provide evidence of a search for primary literature

- analyse safety and/or tolerability as a primary objective
- examine children and/or adolescents with ADHD
- present data by individual drug type: MPH, DEX or ATX.

Of the studies that met our inclusion criteria, we subsequently chose only to assess those with primary studies not already included in our review.

The BNF[29] was used to provide information on the side-effect profiles of MPH, DEX and ATX.

Data extraction strategy: clinical effectiveness

Data relating to both study design and quality were extracted by one reviewer into an Access database and independently checked for accuracy by a second reviewer. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study.

Quality assessment strategy: clinical effectiveness

The quality of the clinical effectiveness studies was assessed using modified criteria based on CRD Report No. 4[31] (see Appendix 5). Each study was assessed by one reviewer and independently checked for agreement with a second reviewer. Disagreements were resolved by consensus and, if necessary, a third reviewer was consulted.

Analysis strategy: clinical effectiveness

Clinical effectiveness data were reported separately for each drug and by the type of comparison. Data for MPH were also analysed separately based on immediate-release or extended-release formulation. For all drugs, the data were examined by dose. The cut-offs used for defining low, medium and high for each type of drug were those presented by Swanson and colleagues.[32] Data for the outcomes of hyperactivity (using any scale that measured hyperactivity specifically), Clinical Global Impression (CGI) (as a proxy of QoL) and adverse events were analysed. Owing to time constraints, information on other core outcomes and academic performance were not analysed; however, this information was extracted and is presented in the data extraction tables (Appendix 12).

Any scale that appeared to have assessed pure hyperactivity was included in the analysis. Results from scales that may incorporate hyperactivity, but also include other symptoms (for example, the Conners' Abbreviated Rating Scale) were not analysed but are included in the data extraction tables (Appendix 12). The type/version of the scale used to assess hyperactivity has been reported as presented in the original papers. Many different scales and versions of the same scales (e.g. the Conners' scales) were used in the trials. Owing to their complexity, no attempt was made to combine results from data using different scales, different versions of a scale or scales which may be the same but have different names.

For crossover studies, the mean and standard deviation (SD) for each outcome were data extracted for end of trial data (i.e. baseline data were not considered). Where possible, we aimed to calculate mean difference and standard errors for crossover studies in order to facilitate meta-analysis where possible.[33] However, owing to the lack of data information needed to calculate mean differences in many of the studies, this was not possible.

For parallel studies, change scores were reported where given, otherwise means and SDs were presented for end of trial data. In addition, mean differences with 95% confidence intervals (CIs) were calculated for each study.

For adverse events, self-ratings were reported when used, otherwise parent reports were utilised. Percentages of participants reporting adverse events were used to calculate numbers of events in each treatment arm. Where actual numbers of participants included in safety analyses were unclear, denominators were based on numbers of participants originally randomised to each treatment arm. Relative risks (RRs) were examined within predefined subgroups (based on drug, dosage and inclusion of a behavioural intervention). Data on weight were also analysed in view of recent concerns regarding the effects of stimulants on growth in children. Mean differences (with 95% CIs) were calculated for each study. Where results were highly variable, possible causes of this were explored in terms of participant age, duration of intervention and method of outcome measurement.

Cost-effectiveness

HRQoL studies were selected if they contained health outcomes data for use in economic evaluations of ADHD. The review of the economic evaluation literature included studies that compared two or more ADHD interventions in terms of their costs and outcomes and where at least one drug intervention was assessed. Economic evaluations could include cost–consequence, cost–utility, cost–effectiveness, cost–minimisation and cost–benefit analyses. Economic evaluations reported as conference proceedings or abstracts were excluded since the data they contain may not be complete. A data extraction form was used to abstract data on all economic evaluations selected in the literature review. The data extraction form used has been used in previous Technology Assessment Reviews.

Each economic evaluation selected for the literature review was quality assessed independently by two health economists based on an economic evaluation checklist.[34] Any discrepancies in quality assessment were resolved through reaching a consensus between the two health economists involved.

In Chapter 5, a systematic review of the HRQoL and cost-effectiveness literature is conducted, followed by a review of the company submissions to NICE. Following this, in Chapter 6, a new model is constructed, drawing on data obtained from the literature review and the company submissions. The methods used to review the literature, construct the new model and analyse the cost-effectiveness data are described in detail in the relevant sections.

Chapter 4

Clinical effectiveness

Quantity and quality of research available

Number of studies identified, included and excluded

In the previous systematic reviews (NICE, AHRQ and CCOHTA), 70 papers were identified that appeared relevant to the current systematic review, and full paper copies were ordered. Of these, 42 papers (describing 40 studies) met the inclusion criteria.

In the updated search, 2515 references were identified (following de-duplication) and screened for relevance. A total of 423 full papers were ordered for more detailed examination, some of which were obtained by checking references of relevant studies (see *Figure 3*). Of these, 20 RCTs and one SR met the inclusion criteria. In addition, four commercial-in-confidence (CIC) papers were included and the Multimodal Treatment Study of ADHD (MTA) trial was assessed. Overall, this gives a total of 66 studies (40 studies from previous SRs, 21 papers from the updated search, four CIC papers and the MTA trial). An additional 52 papers/abstracts related to the trials described in the 66 papers. These were not considered to be fully included, but are referenced in the data extraction tables with the studies to which they relate. Reasons for exclusions are presented for each of the 115 papers from the updated search in Appendix 3 and for each of the 28 papers from the previous reviews in Appendix 4.

Quality of studies

The quality of reporting for each of the included studies is presented in *Table 1*. A key to how poor and good were defined for each question is presented in Appendix 5. No summary score could be tabulated; however, the first two columns of the table can be used to identify immediately studies that reported their study methodology well. It is acknowledged that the quality assessments presented here reflect **only** the quality of reporting of trials.

The majority of included studies poorly reported on study methodology. Only five out of the 60 non-confidential RCTs adequately reported the method used to assign participants to patient groups. Nine out of the 60 non-confidential studies reported that the sequence of allocation was truly random. Most studies were blinded, but none of the included studies reported whether blinding was successful. Eleven out of the 60 non-confidential studies reported to have used an intention-to-treat (ITT) analysis, and 18 out of the 60 non-confidential studies provided a complete description of withdrawals. Of 64 RCTs, 35 were crossover trials and 29 were parallel trials. For most of the crossover trials, the statistical analysis was either not clearly reported or not appropriate; for parallel trials, the quality of the analysis was better reported. **[Confidential information removed from this paragraph]**.

Trials included in the review

An overview of comparisons made in each of the trials is presented in *Table 2* (information from four trials reported as CIC is omitted).

Assessment of effectiveness

As noted above, the clinical effectiveness data are reported separately for each drug (by dose) and by the type of comparison. This was done in order to reproduce accurately the data/results as reported in the original papers. The cut-offs used for defining low, medium and high for each type of drug were those presented by Swanson and colleagues.[32] Data for MPH were also analysed separately based on immediate-release or extended-release formulation.

Where possible, data on hyperactivity specifically are presented in separate tables. The scales used to measure this core symptom are as reported in the trials, hence the level of detail regarding what scale was used may vary.

MPH versus placebo

MPH low dose (≤ 15 mg/day) versus placebo

Twelve studies examined low-dose (≤15 mg/day) immediate-release MPH compared with placebo (*Table 3*, with additional information presented in Appendix 12). Of these, three examined MPH administered once daily and nine examined MPH administered twice or three times daily.

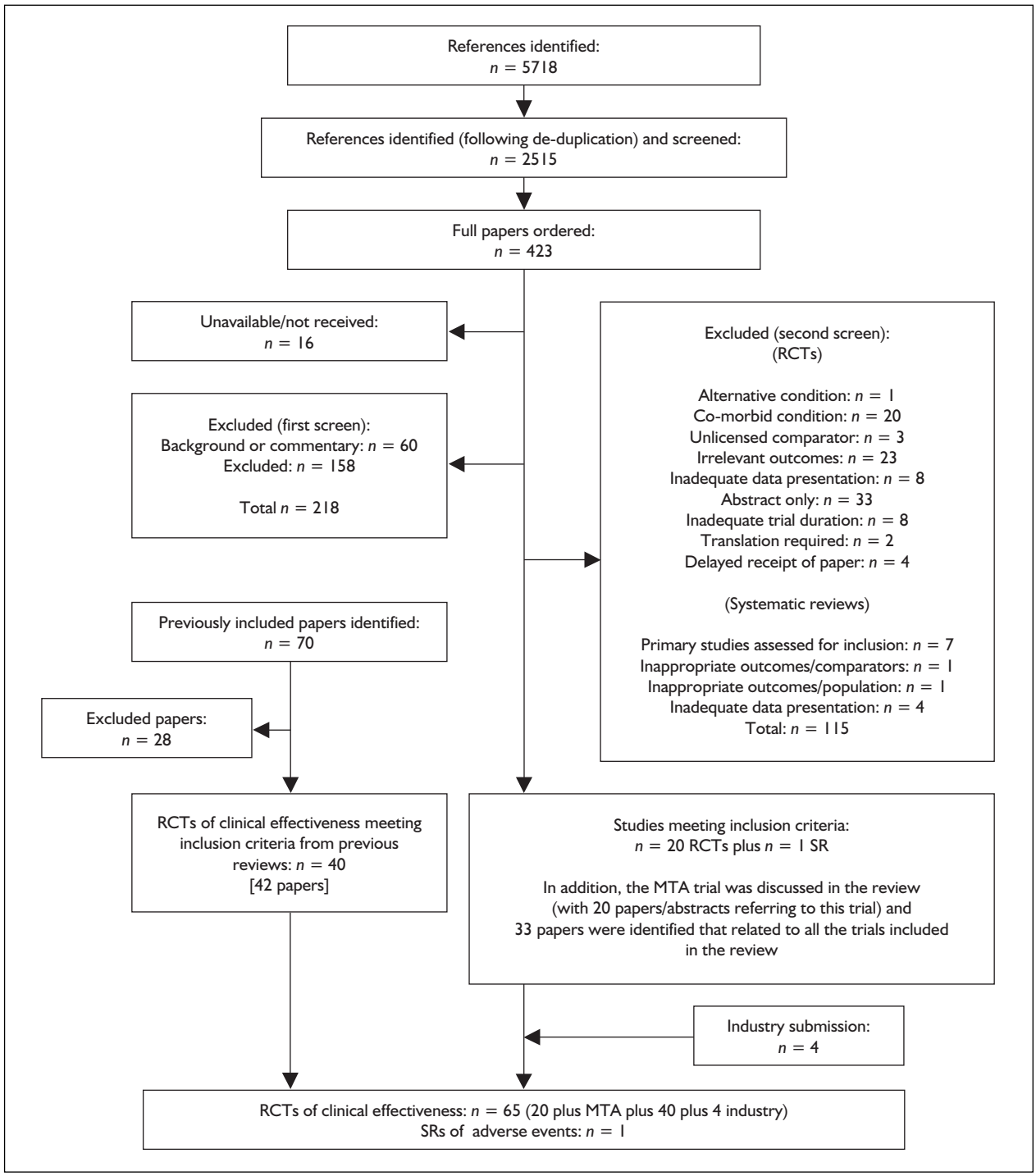

FIGURE 3 *Process of study selection for clinical effectiveness*

MPH administered once daily

Of the studies that examined MPH administered once daily, only one examined hyperactivity (discussed below).[96] The two other studies both used the Abbreviated Conners' Teacher Rating Scale (CTRS) total score to evaluate low-dose MPH.[49,85] In the study by Rapport and colleagues[85] three groups of children were randomised: a low-weight group (22–26 kg), a mid-weight group (27–31 kg) and a high-weight group (32–36 kg). All three MPH low doses (5, 10 and 15 mg/day) resulted in statistically significant improvements compared to placebo for all weight groups ($p < 0.01$). Similarly, in the study by DuPaul and Rapport,[49] all low-dose MPH treatment groups (5, 10 and 15 mg/day) were significantly better than placebo for Abbreviated CTRS total score but the level of significance was not clear.

TABLE 1 *The quality of included studies*

Study	Was the method used to assign participants to the treatment groups really random?	Was the sequence of randomisation concealed?	Was blinding carried out?	Who was blinded?	Was blinding successful?	Was an ITT analysis performed?	Was a complete description of any withdrawals given?	Was the statistical analysis appropriate?	Was an association with industry reported by the authors?
Ahmann, 1993[35]	Poor	Poor	Yes	P/#2	Unclear	No	No	Yes	Yes
Arnold, 1976[36]	Good	Good	Yes	NR	Unclear	Unclear	Unclear	Yes	Yes
Arnold, 1978[37]	Good	Good	Yes	CL/#2	Unclear	Unclear	Unclear	Yes	Yes
Arnold, 1989[38]	Good	Poor	Yes	NR	Unclear	Unclear	Unclear	Unclear	Yes
Barkley, 1990[39]	Poor	Poor	Yes	C/P/T/I	Unclear	Unclear	Yes	Yes?	No
Barkley, 2000[40]	Poor	Poor	Yes	C/P/T/I	Unclear	No	Yes	No	No
Brown, 1985[41]	Poor	Poor	NR	NA	Unclear	NA	NA	Yes	No
Brown, 1986[42]	Poor	Poor	Yes	P/T/I	Unclear	Unclear	Partially	Yes	No
Brown, 1988[43]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	Yes	No
Buitelaar, 1996[44]	Poor	Poor	Yes	NR	Unclear	Yes	NA	Unclear	No
Conners, 1972[45]	Poor	Poor	NR	NA	Unclear	Unclear	No	Yes	No
Conners, 1980[46]	Poor	Poor	Yes	C/P/I	Unclear	Unclear	Unclear	Yes	No
Conrad, 1971[47]	Poor	Poor	Yes	P/T/CL/I	Unclear	Unclear	No	Yes	No
Dopfner, 2003[48]	Poor	Poor	Yes	NR	Unclear	No	Yes	Yes	No
DuPaul, 1993[49]	Poor	Poor	Yes	T/I	Unclear	No	No	Poor	No
Efron, 1997[50]	Poor	Poor	Yes	C/P/T/I	Unclear	Unclear	Unclear	Unclear	No
Elia, 1991[51]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	No	No
Fine, 1993[52]	Poor	Poor	Yes	C/P/T/I	Unclear	NA	NA	No	Yes
Firestone, 1986[53]	Poor	Poor	Yes	P/T/CL	Unclear	Unclear	Partially	Yes?	No
Fischer, 1991[54]	Poor	Poor	Yes	C/P/T/I	Unclear	Unclear	Yes	Unclear	No
Fitzpatrick, 1992[55]	Good	Poor	Yes	#1	Unclear	Unclear	Unclear	Partially	No
Gillberg, 1997[56]	Poor	Poor	Yes	C/P	Unclear	Yes	Partially	Yes	No
Gittelman-Klein, 1976[57]	Poor	Poor	Yes	NR	Unclear	Unclear	Yes	No	Yes
Greenberg, 1972[58]	Poor	Poor	Yes	NR	Unclear	Unclear	Partially	Yes?	Yes
Greenhill, 2002[59]	Poor	Poor	Yes	NR	Unclear	Yes/LOCF	Partially	Yes	Yes
Handen, 1999[60]	Poor	Poor	Yes	#6	Unclear	Unclear	Yes	No	No
Hoeppner, 1997[61]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	No	No
James, 2001[62]	Poor	Good	Yes	NR	Unclear	Unclear	NA	No	Yes
Kelsey, 2004[63]	Poor	Poor	Yes	NR	Unclear	Yes	Yes	Yes	Yes
Kemner, 2004[64]	**[Confidential information removed]**								
Klein, 1997[65]	Poor	Poor	Yes	#4	Unclear	Unclear	Partially	Yes	No
Klorman, 1987[66]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	Poor	No
Klorman, 1990[67]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	No	No
Klorman, 1994[68]	Poor	Poor	Yes	I/#2	Unclear	Unclear	Yes	Unclear	No
Kolko, 1999[69]	Poor	Poor	Yes	#5	Unclear	No	Yes	Unclear	No
Kratochvil, 2002[70]	Poor	Poor	No		NA	Yes/LOCF	Yes	Yes	Yes
Kupietz, 1988[71]	Poor	Poor	Yes	P/T/I	Unclear	Unclear	Partially	Yes	No
Manos, 1999[72]	Poor	Poor	Yes	#3	Unclear	Unclear	NA	No	No
Michelson, 2001[73]	Good	Good	Yes	NR	Unclear	Unclear	Yes	Yes	Yes
Michelson, 2002[74]	Poor	Poor	Yes	C/CL/I	Unclear	Yes/LOCF	Partially	Yes	Yes
Michelson, 2004[75]	Poor	Good	Yes	C/I	Unclear	Yes?	Partially	Yes	Yes
MTA, 1999[76]	Poor	Good	Yes	#7	Unclear	Yes	Partially	Unclear	No
Pelham, 1987[77]	Poor	Poor	Yes	I/#2	Unclear	Unclear	Unclear	Yes	No
Pelham, 1990[78]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	Unclear	No
Pelham, 1993[79]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	Unclear	No
Pelham, 1999[80]	Poor	Poor	Yes	P/T/I/CL	Unclear	Unclear	Yes	Unclear	Yes

continued

TABLE 1 *The quality of included studies (cont'd)*

Study	Was the method used to assign participants to the treatment groups really random?	Was the sequence of randomisation concealed?	Was blinding carried out?	Who was blinded?	Was blinding successful?	Was an ITT analysis performed?	Was a complete description of any withdrawals given?	Was the statistical analysis appropriate?	Was an association with industry reported by the authors?
Pelham, 1999[81]	Poor	Poor	Yes	C/P/T/CL	Unclear	Unclear	Unclear	Yes?	Yes
Pelham, 2001[82]	Poor	Poor	Yes	NR	Unclear	Unclear	Yes	Unclear	Yes
Pliszka, 2000[83]	Poor	Poor	Yes	P/T/CL	Unclear	Yes	Yes	Unclear	Yes
Quinn, 2003[84]	**[Confidential information removed]**								
Rapport, 1989[85]	Poor	Good	Yes	C/P/T/I	Unclear	No	No	Poor	No
Schachar, 1997[86] and Diamond, 1999[87]	Good	Good	Yes	C/P/T/I	Unclear	Unclear	Yes	Yes	No
Smith, 1998[88]	Poor	Poor	Yes	NR	Unclear	Unclear	Yes	Unclear	No
Spencer, 2002[89]	Good	Good	Yes	C/P/I	Unclear	Unclear	Partially	Yes	Yes
Steele, 2004[90]	**[Confidential information removed]**								
Stein, 1996[91]	Poor	Good	Yes	C/P/T/I	Unclear	Unclear	Yes	Yes	No
Stein, 2003[92]	Poor	Poor	Unclear	NR	Unclear	Unclear	Unclear	Unclear	No
Swanson, 2004[32]	Poor	Poor	Yes	NR	Unclear	Yes	No	Good?	Yes
Tervo, 2002[93]	Poor	Poor	Yes	C/P/I	Unclear	No	Unclear	No	No
Weiss, 2004[94]	**[Confidential information removed]**								
Wernicke, 2004[95]	Poor	Poor	Yes	NR	Unclear	Unclear	No	Unclear	Yes
Werry, 1980[96]	Poor	Poor	Yes	NR	Unclear	Unclear	Unclear	Poor	No
Wolraich, 2001[97]	Poor	Poor	Yes	NR	Unclear	Yes/LOCF	Yes	Yes	Yes
Zeiner, 1999[98]	Poor	Poor	Yes	All raters	Unclear	NA	NA	Yes	No

C, children; CL, clinicians/psychiatrists/therapists/counsellors; I, investigators/staff/outcome assessors/clinical assistant; LOCF, last observation carried forward; NA, not applicable; NR, not reported; P, parents/families; T, teachers; #1, some? raters, parents and ?; #2, others unclear; #3, clinicians and parents were not blind to allocated medication, but together with teachers were blind to dosage level; #4, psychologists were blind to all treatment conditions. Psychiatrists and parents were blinded to medication type for those subjects allocated to behavioural therapy arms. Teachers were blind to type of medication, and study design. All classroom observers were blind to study design, and six out of seven were also blind to the type of children under study and the purposes of observation; #5, nurse, programme staff, staff, students, and parents were blind to dosages and schedules; #6, states that 'Preschool staff, patients, laboratory staff were unaware that lower MPH dose preceded higher MPH dose'; 7, classroom observers, peers, laboratory raters, clinicians selecting 'best dose'.

MPH administered two or more times daily

Of the studies that examined MPH administered more than once daily, five examined hyperactivity as a core outcome measure. Results from these studies are presented in *Table 4* by age group and are described below. The remaining four studies presented in *Table 3* did not examine hyperactivity, but did measure other core outcomes (with the exception of Fine and Johnston[52] who reported results for adverse events only). These studies include that of Manos and colleagues[72] where outcome measures included the Abbreviated Symptoms Questionnaire (ASQ) as measured separately by parents and teachers, and the ADHD rating scale (parents). However, Manos and colleagues did not report data separately for low- and medium-dose MPH (see Appendix 12). Hence any results comparing low-dose MPH versus placebo cannot be extracted from this study.

In the study by Barkley and colleagues,[40] five treatment arms were examined including low-dose MPH and a placebo group. The main core outcome examined was ADHD total ratings as evaluated by parents, and teachers (mathematics and English teachers). Overall statistical analyses resulted in no significant differences between the treatment arms.

TABLE 2 *An overview of trials included in the review – and comparators*

Study	Age (years)	IQ	Placebo/st. comm. care/attent. contr.	Non-drug (+ placebo)	MPH low dose	MPH medium dose	MPH high dose	MPH low dose + non-drug	MPH medium dose + non-drug	MPH high dose + non-drug	MPH low dose	MPH-SR medium dose	MPH-SR high dose	MPH-SR low dose + non-drug	MPH-SR medium dose + non-drug	MPH-SR high dose + non-drug	MPH low dose + MPH-SR 20 mg	MPH + thioridazine hydrochloride	DEX low dose	DEX medium dose	DEX high dose	DEX medium dose + non-drug	DEX high dose + non-drug	DEX-TR/ER	DEX-SR + non-drug	ATX L+M	ATX H	Caffeine	Pemoline	Pemoline + non-drug	Imipramine	Adderall	Adderall + non-drug	MAOI + diet	GLA 500 mg + vitamin E	Chlorpromazine	Hydroxyzine	Levoamphetamine	Thioridazine hydrochloride	Pindolol
Ahmann, 1993[35]	5.0–15	NR	×			×	×																																
Arnold, 1976[36]	4.6–12	NR	×			×															×																		
Arnold, 1978[37]	5.0–12	NR				×														×							×											
Arnold, 1989[38]	6.0–12	NR	×				×																															
Barkley, 1990[39]	5.0–13	105	×			×	×																															
Barkley, 2000[40]	12.0–17	104	×			×	×																								2							
Brown, 1985[41]	6.3–11.8	102		×	×			×																														
Brown, 1986[42]	5.7–13.1	97	×	×		×			×																													
Brown, 1988[43]	13–15	93	×		×	×	×																															
Buitelaar, 1996[44]	6.0–13	93	×			×	×																															
Conners, 1972[45]	6.0–12	NR	×																	×																		
Conners, 1980[46]	6.0–11	NR	×			×																																
Conrad, 1971[47]	4.0–6	NR	×	×																			×															
Dopfner, 2003[48]	6.0–16	104	×									×											×															
DuPaul, 1993[49]	6.0–11	NR	×		3	×																																
Efron, 1997[50]	5.0–14.9	99				×															×																	
Elia, 1991[51]	6.0–12	106		×			×																	×														
Fine, 1993[52]	6.0–10	NR	×		×	×																																
Firestone, 1986[53]	5.0–9	NR		×		×			×																													
Fischer, 1991[54]	2.4–17.2	NR	×		×	×																																
Fitzpatrick, 1992[55]	6.9–11.5	114	×		×																																	
Gillberg, 1997[56]	6.0–11	NR	×																			×																
Gittelman-Klein, 1976[57]	6.0–12	NR	×				×																															
Greenberg, 1972[58]	6.5–11	85	×																			×													×			
Greenhill, 2002[59]	5.0–15	NR	×										×																										

continued

TABLE 2 *An overview of trials included in the review – and comparators (cont'd)*

Study	Age (years)	IQ	Placebo/st. comm. care/attent. contr.	Non-drug (+ placebo)	MPH low dose	MPH medium dose	MPH high dose	MPH low dose + non-drug	MPH medium dose + non-drug	MPH high dose + non-drug	MPH-SR low dose	MPH-SR medium dose	MPH-SR high dose	MPH-SR low dose + non-drug	MPH-SR medium dose + non-drug	MPH-SR high dose + non-drug	MPH low dose + MPH-SR 20 mg	MPH + thioridazine hydrochloride	DEX low dose	DEX medium dose	DEX high dose	DEX medium dose + non-drug	DEX high dose + non-drug	DEX-TR/ER	DEX-SR + non-drug	ATX L+M	ATX H	Caffeine	Pemoline	Pemoline + non-drug	Imipramine	Adderall	Adderall + non-drug	MAOI + diet	GLA 500 mg + vitamin E	Chlorpromazine	Hydroxyzine	Levoamphetamine	Thioridazine hydrochloride	Pindolol
Handen, 1999[60]	4.0–5.1	60	×		×	×																																	
Hoeppner, 1997[61]	6.1–18.2	NR	×		×	×	×																																
James, 2001[62]	6.9–12.2	100		×																					×														
Kelsey, 2004[63]	6.0–12	NR	×																							×													
Kemner, 2004[99]																		[Confidential information removed]																					
Klein, 1997[65]	6.0–12	NR		×			×			×																													
Klorman, 1987[66]	12.0–19	101	×				×																																
Klorman, 1990[67]	12.0–18	109	×				×																																
Klorman, 1994[68]	5.6–11.9	109	×			×																																	
Kolko, 1999[69]	7.0–13	NR	×		×	×	×		×	×																													
Kratochvil, 2002[70]	7.0–15	NR					×													×																			
Kupietz, 1988[71]	7.0–13	94			×			2	×																														
Manos, 1999[72]	5.0–17	NR	×		×	2																																	
Michelson, 2001[73]	8.0–18	NR	×																																				
Michelson, 2002[74]	6.0–16	NR	×																																				
Michelson, 2004[75]	6.0–15	NR	×																																				
MTA, 1999[76]	7–9.9	101	×			×			×																														
Pelham, 1987[77]	6.5–11	95		×					×						×																								
Pelham, 1990[78]	8.1–13.2	106		×					×						×										×														
Pelham, 1993[79]	5.4–9.9	111		×			×		×	×																													
Pelham, 1999[80]	5.8–12.7	NR		×					×	×																							2						
Pelham, 1999[81]	6.0–12	110		×				×	2																								3						
Pelham, 2001[82]	6.0–12	105		×					×							×																							
Pliszka, 2000[100]	6.0–11	NR	×			×																									×								

continued

TABLE 2 *An overview of trials included in the review – and comparators (cont'd)*

Study	Age (years)	IQ	Placebo/st. comm. care/attent. contr.	Non-drug (+ placebo)	MPH low dose	MPH medium dose	MPH high dose	MPH low dose + non-drug	MPH medium dose + non-drug	MPH high dose + non-drug	MPH-SR low dose	MPH-SR medium dose	MPH-SR high dose	MPH-SR low dose + non-drug	MPH-SR medium dose + non-drug	MPH-SR high dose + non-drug	MPH low dose + MPH-SR 20 mg	MPH + thioridazine hydrochloride	DEX low dose	DEX medium dose	DEX high dose	DEX medium dose + non-drug	DEX high dose + non-drug	DEX-TR/ER	DEX-SR + non-drug	ATX L+M	ATX H	Caffeine	Pemoline	Pemoline + non-drug	Imipramine	Adderall	Adderall + non-drug	MAOI + diet	GLA 500 mg + vitamin E	Chlorpromazine	Hydroxyzine	Levoamphetamine	Thioridazine hydrochloride	Pindolol
Quinn, 2003[84]			[Confidential information removed]																																				
Rapport, 1989[85]	5.0–15	100	×		3	×																																	
Schachar, 1997[86]	6.0–12	108		×				×																															
Smith, 1998[88]	12.0–17	101		×					×	2																													
Spencer, 2002[89]	7.0–13	105	×																								×												
Steele, 2004[90]			[Confidential information removed]																																				
Stein, 1996[91]	6.0–12	NR	×	×		3																																	
Stein, 2003[92]	5.9–16	107	×	×							×	×	×																										
Swanson, 2004[32]	6.0–12	NR	×	×							2	2	2																										
Tervo, 2002[93]	9.9 (2.9)	NR	×	×		×	×																																
Weiss, 2004[94]			[Confidential information removed]																								×												
Wernicke, 2004[95]	7.0–12	NR	×	×																																			
Werry, 1980[96]	5.5–12.5	NR	×	×		×																									×								
Wolraich, 2001[97]	6.0–12	NR	×	×				×				×																											
Zeiner, 1999[98]	7.0–12	102	×	×			×																																

NR, not reported; SR, single release, ER, extended release.

TABLE 3 *MPH low dose (≤15 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Rapport, 1989[85]	C (5×)	MPH (5 mg/day, o.d.) – 45 MPH (10 mg/day, o.d.) – 45 MPH (15 mg/day, o.d.) – 45	5–12	5	Core: no hyp; Abbreviated CTRS: total score QoL: not reported AE: not reported
DuPaul, 1993[49]	C (5×)	MPH (5 mg/day, o.d.) – 31 MPH (10 mg/day, o.d.) – 31 MPH (15 mg/day, o.d.) – 31	6–11	6	Core: No hyp; Abbreviated CTRS: total score QoL: not reported AE: not reported
Werry, 1980[96]	C (3×)	MPH (0.40 mg/kg, o.d.) – 30	5.5–12.5	4	Core: Conners' Teacher Questionnaire: hyperactivity; Conners' Parent Questionnaire: hyperactivity QoL: CGI (physician) AE: weight
Administered two or more times daily					
Brown, 1988[43]	C (4×)	MPH (8.76 mg/day, b.d.) –11	13–15	8	Core: CPRS: Hyperactivity Index; Conners' Teacher Hyperactivity Index; ACTeRS: hyperactivity QoL: not reported AE: SERS (parents); weight
Fischer, 1991[54]	C (3×)	MPH (0.40 mg/kg/day, b.d.) – 161	2.4–17.2	3	Core: CPRS-R: Hyperactivity Index; CTRS-R: hyperactivity index; CTRS-R: hyperactivity QoL: not reported AE: CPRS-R: psychosomatic; SERS (parents, teachers): number of side-effects, mean severity rating
Fitzpatrick, 1992[55]	C (4×)	MPH (10–15 mg/day, b.d.) – 19	6.9–11.5	8	Core: Conners' Hyperactivity Index (parents and teacher); TOTS: hyperactivity (parents and teachers) QoL: no CGI; comments ratings (parent/teacher) AE: STESS (parents); weight
Fine, 1993[52]	C (3×)	MPH [0.30 mg/kg/day (unclear), b.d.] – 12	6–10	3	Core: not reported QoL: not reported AE: side-effects questionnaire
Hoeppner, 1997[61]	C (3×)	MPH (0.30 mg/kg/day, b.d.) – 50	6.1–18.2	4	Core: CPRS: Hyperactivity Index; CTRS: Hyperactivity Index QoL: not reported AE: not reported

continued

TABLE 3 *MPH low dose (≤15 mg/day) versus placebo (cont'd)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Handen, 1999[60]	C (3×)	MPH (12–15 mg/day, max. 3×) – 11	4–5.1	3	Core: CTRS: Hyperactivity Index; CTRS: hyperactivity QoL: not reported AE: Side Effects Checklist (teachers, parents); mean severity rating 0–6
Manos, 1999[72]	C (4×)	MPH (10 mg/day, b.d.) – 42	5–17	4	Core: no hyp; ASQ (parents and teachers); ARS (parent) QoL: no CGI; composite ratings (clinician) AE: Side Effects Behaviour Monitoring Scale (parents)
Barkley, 2000[40]	C (5×)	MPH (10 mg/day, b.d.) – 38	12–17	5	Core: no hyp; ADHD Total Parent/Teacher rating QoL: not reported AE: number and severity of side-effects (teachers, parents, self)
Tervo, 2002[93]	C (3×)	MPH (0.10 mg/kg/day, b.d.) – 41	M=9.9 (2.9)	3	Core: no hyp; CBCL (parent) QoL: not reported AE: not reported

ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; AE, adverse effects; ARS, ADHD Rating Scale; ASQ, Abbreviated Symptoms Questionnaire; b.d., twice daily; C, crossover trial (number of crossovers); CBCL, Child Behaviour Checklist; CGI, Clinical Global Impression; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; o.d., once daily; P, parallel trial; hyp, hyperactivity; PACS, Parental Account of Childhood Symptoms; SERS, Side Effects Rating Scale.

Tervo and colleagues[93] examined a low-dose MPH group and a placebo group (in addition to a medium-dose MPH group). The main outcome examined was Child Behaviour Checklist (CBCL) as rated by parents. Direct statistical comparisons with placebo were not reported, although the authors found a significant linear response to medication ($p = 0.001$).

Hyperactivity

All of the six studies that examined hyperactivity used a Conners' scale (see *Table 4*). Five of these studies reported results separately for parents and teachers,[43,54,55,61,96] and one reported results for teachers only.[60] One of these studies also assessed hyperactivity using the ADD-H Comprehensive Teacher's Rating Scale (ACTeRS),[43] and another study assessed hyperactivity using the Loney's Time on Task Scale (TOTS).[55]

All of the above studies used a crossover design. They were not combined using meta-analysis because there appeared to be clinical heterogeneity between some of the studies (e.g. the age groups varied) and because certain data were not available that would facilitate meta-analysis of crossover trials. For instance, the significance values for paired analyses were not reported – evidence which is necessary to estimate a mean difference and standard error for each study.

Overall, three studies reported that low-dose MPH was better than placebo,[54,55,61] and three reported no significant difference between the groups.[43,60,96] It is noted, however, that the study by Handen and colleagues[60] was conducted in younger children (4–5 years age) with a low mean IQ (60) and may not be comparable to the other studies.

TABLE 4 *Results for hyperactivity [MPH low-dose (≤ 15 mg/day) versus placebo]*

Study	Scale	MPH low dose: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported)[a]
2–17 years old				
Fischer, 1991[54]	CPRS-R (Hyperactivity Index)	11.7 (6.4)	14.3 (6.8)	S – NR
	CTRS-R (Hyperactivity Index)	9.9 (6.6)	13.7 (7.6)	S – NR
	CTRS-R (hyperactivity)	7.1 (5.5)	9.5 (5.8)	S – NR
4–5 years old				
Handen, 1999[60]	CTRS (hyperactivity)	9.0 (5.1)	14.0 (3.7)	NS
	CTRS (Hyperactivity Index)	11.9 (5.7)	17.4 (6.0)	NS
5–12 years/6–12 years old				
Werry, 1980[96]	Conners' Teacher Questionnaire	2.22 (NR)	2.56 (NR)	NS
	Conners' Parent Questionnaire	1.29 (NR)	1.27 (NR)	NS
Fitzpatrick, 1992[55]		(? Mean, ? SD)	(? Mean, ? SD)	
	Conners' Hyperactivity Index (parents)	0.96 (0.50)	1.75 (0.67)	<0.006
	Conners' Hyperactivity Index (teacher)	0.73 (0.65)	1.36 (0.80)	S – NR
		Mean (SD)	Mean (SD)	
	TOTS (hyperactivity) (parents)	0.20 (0.31)	0.70 (0.48)	S – NR
	TOTS (hyperactivity) (teachers)	0.16 (0.44)	0.36 (0.69)	S – NR
6–18 years old				
Hoeppner, 1997[61]	CPRS (Hyperactivity Index)	7.91 (7.21)	8.40 (6.59)	S – NR
	CTRS (Hyperactivity Index)	8.48 (7.42)	13.54 (8.66)	S – NR
13–15 years old				
Brown, 1988[43]	CPRS-R (Hyperactivity Index)	9.33 (4.32)	12.66 (4.13)	NS
	Conners' Teacher Hyperactivity Index	22.16 (3.12)	24.50 (2.81)	NS
	ACTeRS (hyperactivity)	13.66 (6.97)	8.00 (0.63)	NS

[a] Note that owing to the overall poor reporting of study methodology, *p*-values should be interpreted with caution. Lower scores represent better behavioural outcome.
ACTeRS, ADD/H Comprehensive Teacher Rating Scale; CPRS, Conners' Parent Rating Scale; CPRS-R, Conners' Parent Rating Scale – Revised; CTRS, Conners' Teacher Rating Scale; CTRS-R, Conners' Teacher Rating Scale – Revised; NS, not significant; S – NR: significant (value not reported); TOTS, Loney's Time on Task Scale.

Quality of life
Only one of the 12 studies examined physician-rated GGI (used as a proxy for QoL in this SR). This study, conducted by Werry and colleagues,[96] reported no significant difference between the MPH and placebo groups for this outcome.

Two other studies reported outcomes that could also be used to indicate QoL: Fitzpatrick and colleagues,[55] presented parent and teacher comments ratings and Manos and colleagues[72] reported composite ratings as measured by a clinician (see Appendix 12 for results).

Adverse events
Of the 12 studies comparing low-dose MPH with placebo, only two presented usable data on adverse events.[55,60] The occurrence of headache was not significantly different between treatment arms in either trial [relative risk (RR) = 1.00; 95% CI 0.16 to 6.38; and RR = 3.00; 95% CI 0.14 to 66.53, respectively]. With regard to loss of appetite, neither study detected differences between the treatment arms (RR = 3.00; 95% CI to 0.34 to 26.33; and RR = 5.00; 95% CI 0.69 to 36.13, respectively). Similarly, incidence of stomach ache did not appear to differ between participants assigned to low doses of MPH and those receiving placebo (RR = 3.00; 95% CI 0.13 to 69.31; and RR = 3.00; 95% CI: 0.14 to 66.53). One trial[55] reported the occurrence of insomnia which was not significantly different between treatment arms (RR = 2.67; 95% CI 0.83 to 8.55). Weight data were not adequately reported in any trial.

Summary
In summary, there seems to be variation in the results for low-dose MPH compared with placebo. There were no differences in adverse events for both groups. These studies did not score very well in the quality assessment, and the results should be interpreted with caution.

MPH medium dose (15–30 mg/day) versus placebo
Twenty-one studies examined medium-dose (15–30 mg/day) immediate-release MPH compared with placebo (*Table 5*; with additional information presented in Appendix 12). Two studies examined medium-dose MPH administered once daily and 19 examined MPH administered two or more times daily.

MPH administered once daily
Both Rapport and colleagues[85] and DuPaul and Rapport[49] evaluated the effectiveness of medium-dose MPH administered once daily using the Abbreviated CTRS total score as a main outcome measure. Both studies reported a significant improvement in the treatment group compared with placebo ($p < 0.01$).

MPH administered two or more times daily
Of the 19 studies that examined MPH administered more than once daily, nine measured hyperactivity and will be discussed below. In addition, four studies[35,39,44,52] reported data **only** for adverse events. These are also discussed separately below.

The first of the six remaining studies is that by Manos and colleagues.[72] In this study, two medium doses of MPH were evaluated: 20 and 30 mg/day. However, as reported above, Manos and colleagues did not report data separately for low-dose MPH and the medium doses (see Appendix 12), hence any results comparing medium-dose MPH versus placebo cannot be extracted from this study. In their results, they stated that 'best dose' was better than placebo.

Kolko and colleagues[69] presented results for inattention/overactivity using the Inattention/Overactivity with Aggression (IOWA) CTRS. They reported that medium-dose MPH was better than placebo ($p < 0.0001$). This scale was also used by Pliszka and colleagues,[83] where medium-dose MPH was also observed to improve behaviour compared with placebo ($p < 0.05$), and by Pelham and colleagues,[79] where results showed improvement with treatment (see Appendix 12).

In the study by Barkley and colleagues,[40] five treatment arms were examined, including medium-dose MPH and a placebo group. The main core outcome examined was ADHD total ratings as evaluated by parents and teachers (mathematics and English teachers). Overall statistical analyses resulted in no significant differences between the treatment arms.

Tervo and colleagues 2002[93] also compared a medium-dose MPH group and a placebo group. A main outcome examined was CBCL as rated by parents. Direct statistical comparisons with placebo were not reported, although the authors found a significant linear response to medication ($p = 0.001$).

TABLE 5 *MPH medium dose (15–30 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Rapport, 1989[85]	C (5×)	MPH (20 mg/day, o.d.) – 45	5–12	5	Core: no hyp; ACTeRS: total score QoL: not reported AE: not reported
DuPaul, 1993[49]	C (5×)	MPH (20 mg/day, o.d.) – 31	6–11	6	Core: no hyp; ACTeRS: total score QoL: not reported AE: not reported
Administered two or more times daily					
Conners, 1980[46]	P	MPH (22.0 mg/day, b.d.) – 60	6–11	8	Core: Conners' Parent Questionnaire: hyperactivity; Conners' Teacher Questionnaire: hyperactivity QoL: no CGI; parent global judgements of improvement AE: Physician's Rating Sheet for Side Effects Standardised Form: 50-item checklist (parents); weight
Brown, 1986[42]	P	MPH (20.08 mg/day, b.d.) – 40	5.7–13.1	3 months	Core: CPRS: hyperactivity index; ACTeRs: hyperactivity QoL: not reported AE: not reported
Brown, 1988[43]	C (4×)	MPH (25.1 mg/day, b.d.) – 11	13–15	8	Core: CPRS-R: Hyperactivity Index; Conners' Teacher Hyperactivity Index; ACTeRS: hyperactivity QoL: not reported AE: SERS (parents); weight
Barkley, 1990[39]	C (3×)	MPH (0.60 mg/kg/day, b.d.) – 83	5–13	3	Core: not reported QoL: not reported AE: Stimulant Drug Side Effects Questionnaire: 17-item list
Fischer, 1991[54]	C (3×)	MPH (0.80 mg/kg/day, b.d.) – 161	2.4–17.2	3	Core: CPRS-R: Hyperactivity Index; CTRS-R: Hyperactivity Index; CTRS-R: hyperactivity QoL: not reported AE: CPRS-R: psychosomatic; SERS (parents, teachers): number and severity of side-effects
Ahmann, 1993[35]	C (3×)	MPH (0.90 mg/kg/day, t.d.s.) – 234	5–15	4	Core: not reported QoL: not reported AE: BSEQ

continued

TABLE 5 *MPH medium dose (15–30 mg/day) versus placebo (cont'd)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Fine, 1993[52]	C (3×)	MPH [0.60 mg/kg/day (unclear), b.d.] – 12	6–10	3	Core: not reported QoL: not reported AE: Side Effects Questionnaire
Pelham, 1993[79]	C (3×)	MPH (16.2 mg/day, b.d.) – 31	5.4–9.9	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Klorman, 1994[68]	C (2×)	MPH (22.3 mg/day, b.d.) – 114	5.6–11.9	6	Core: Abbreviated Conners' Hyperactivity Questionnaire (parents and teachers); TOTS: hyperactivity (parents and teachers) QoL: no CGI AE: somatic complaints (parents); mood problems (parents); weight
Buitelaar, 1996[44]	P	MPH (20 mg/day, b.d.) – 32	6–13	4	Core: data presented in graphs cannot be extracted QoL: not reported AE: SSERS (modified version): frequency and severity (parents, psychiatrist)
Stein, 1996[91]	C (4×)	MPH (17.6 mg/day, b.d.) – 25 MPH (26.4 mg/day, t.d.s.) – 25 MPH (17.6–26.4 mg/day 2 or 3× titrated) – 25	6–12	4	Core: CPRS – hyperactivity index; ACTeRS: hyperactivity QoL: not reported AE: SSERS (parents); weight
Hoeppner, 1997[61]	C (3×)	MPH (0.60 mg/kg/day, b.d.) – 50	6.1–18.2	4	Core: CPRS: Hyperactivity Index; CTRS: Hyperactivity Index QoL: not reported AE: not reported
Handen, 1999[60]	C (3×)	MPH (25–30 mg/day, max. 3×) – 11	4–5.1	3	Core: CTRS: Hyperactivity Index; CTRS: hyperactivity QoL: not reported AE: Side Effects Checklist (teachers, parents); mean severity rating 0–6
Kolko, 1999[69]	C (4×)	MPH (0.60 mg/kg/day, b.d.) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity. QoL: not reported AE: SSERS
Manos, 1999[72]	C (4×)	MPH (20 mg/day, b.d.) – 42 MPH (30 mg/day, b.d.) – 42	5–17	4	Core: no hyp; ASQ (parents) (teachers); ARS (parent) QoL: no CGI; composite ratings (clinician) AE: SE/BMS (parents)

continued

TABLE 5 *MPH medium dose (15–30 mg/day) versus placebo (cont'd)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Zeiner, 1999[98]	C (2×)	MPH (22.4 mg/day, b.d. or t.d.s.) – 36	7–12	6	Core: CTRS: hyperactivity; PACS: hyperactivity QoL: not reported AE: not reported
Pliszka, 2000[83]	P	MPH (25.2 mg/day, b.d. or t.d.s.) – 58	6–11	3	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: CGI (improvement); Conners' Global Index (parent) AE: Multi-Modality Treatment of ADHD Side Effects Scale; weight
Barkley, 2000[40]	C (5×)	MPH (20 mg/day, b.d.) – 38	12–17	5	Core: no hyp; ADHD Total Parent/Teacher rating QoL: not reported AE: number and severity of side-effects (teacher, parents, self)
Tervo, 2002[93]	C (3×)	MPH (0.60 mg/kg/day, b.d.) – 41	M = 9.9 (2.9)	3	Core: no hyp; CBCL (parent) QoL: not reported AE: not reported

ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; ARS, ADHD Rating Scale; ASQ, Abbreviated Symptoms Questionnaire; b.d., twice daily; BSEQ, Barkley Side Effects Questionnaire; C, crossover trial (number of crossovers); CBCL, Child Behaviour Checklist; CGI, Clinical Global Impression; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; IOWA, Inattention/Overactivity with Aggression; o.d., once daily; P, parallel trial; PACS, Parental Account of Childhood Symptoms; SE/BMS, Side Effects Behaviour Monitoring Scale; SERS, Side Effects Rating Scale; SSERS, Stimulant Drug Side Effects Rating Scale; t.d.s., three times daily.

Hyperactivity

All nine studies that examined hyperactivity used a Conners' scale. Six used the Conners' Hyperactivity Index as an outcome measure – three of which reported results for both parents and teachers,[43,54,61] one that reported results for teachers only[60] and two that reported results for parents only.[42,91] In addition to these studies, two reported measuring hyperactivity for parents and teachers using a Conners' questionnaire,[46,68] and one measured hyperactivity only using the CTRS.[98] Five of the studies also measured hyperactivity using additional scales.[42,43,68,91,98]

Table 6 presents the means and SD for the results of these studies (where reported). Two of the studies used a parallel design.[42,46] As with low-dose placebo, none of the studies could be combined because of clinical heterogeneity (e.g. age), and/or because the necessary data were not available to facilitate a meta-analysis of the crossover studies. Two studies that could have been combined (by Klorman and colleagues[68] and Conners and Taylor[46]) used different study designs. *Table 6* shows that most of the studies reported significant improvements for medium-dose MPH compared with placebo. When assessing hyperactivity using the Conners' scales, four of the studies reported some tests with no significant changes, most of which were measures of hyperactivity as assessed by the parents.[42,43,91]

Quality of life

Only one of these 21 studies examined CGI (considered to be a proxy for QoL in this SR). Pliszka and colleagues[83] assessed the effectiveness of medium-dose MPH compared with placebo using the Clinical Global Impression improvement subscale (CGS-I) and also the Conners Global Index (see Appendix 12). They observed a significant difference between the treatment group and placebo group at 3 weeks ($p < 0.05$), favouring the treatment group [mean (SD): MPH group 2.35 (0.81) and placebo group 3.22 (1.44)]. They did not, however, find any significant differences between groups using the Conners' Global Index as assessed by the parents.

Other scales could also be used as an indicator of QoL. For example, Conners and Taylor[46] assessed parent global judgements of improvement (how serious a problem does your child have?: no/minor/serious problem). After 8 weeks, 27.8% of children in the MPH group were deemed to have a 'serious problem' compared with 50% in the placebo group.

Adverse events

Of 21 studies comparing a medium dose of MPH with placebo, eight reported data which were informative to the analysis of adverse events. The study by Stein and colleagues[91] examined the effectiveness of a medium dose of MPH administered twice daily, three times daily or by titration. Two trials detected a significantly higher occurrence of headache during the MPH phase, with RRs of 1.43 and 2.33, respectively (*Figure 4*).

Participants in four of the five crossover trials reporting loss of appetite displayed a higher incidence of this outcome when assigned to a medium dose of MPH. RRs ranged from 2.00 to 3.86 (*Figure 5*). The direction of effect in Handen[60] was similar, but not significant. This may be related to differences in the ages of participants; Handen 1999[60] examined children of preschool age whereas the other studies examined children 5–13 years old.

A significantly higher incidence of stomach ache during the MPH treatment phase was found in two crossover trials, with RRs of 1.84 and 2.13, respectively (*Figure 6*).

One parallel trial and three crossover trials detected significant differences in the occurrence of insomnia between treatment arms, with RRs ranging from 1.55 to 2.73 (*Figure 7*). Greater proportions of participants suffered from this adverse event when assigned to the active drug.

Only one trial presented informative data on participants' weight.[83] No significant differences in mean weight change were detected between treatment groups (mean difference = –0.70; 95% CI –6.16 to 4.76).

Summary

Generally, the majority of studies that examined hyperactivity reported that medium-dose MPH was beneficial compared with placebo. Only one study evaluated the CGI-I subscale.[83] In this study, the authors reported that behaviour was statistically improved with medium-dose MPH compared with placebo. Where data on adverse events were available, medium-dose MPH was consistently associated with higher incidences of headache, loss of appetite, stomach ache and insomnia. It is noted that, in general, the studies did not score very well in the quality assessement, and the results should be interpreted with caution.

MPH high dose (>30 mg/day) versus placebo

Ten studies examined high-dose (>30 mg/day)

TABLE 6 *Results for hyperactivity [MPH medium dose (15–30 mg/day) versus placebo]*

Study	Scale	MPH medium dose: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported) or mean difference[a]
2–17 years				
Fischer, 1991[54]	CPRS-R (Hyperactivity Index)	11.1 (6.7)	14.3 (6.8)	S – NR
	CTRS-R (Hyperactivity Index)	8.4 (6.3)	13.7 (7.6)	S – NR
	CTRS-R (hyperactivity)	6.0 (4.9)	9.5 (5.8)	S – NR
4–5 years				
Handen, 1999[60]	CTRS (hyperactivity)	6.2 (3.4)	14.0 (3.7)	<0.05
	CTRS (Hyperactivity Index)	9.2 (3.8)	17.4 (6.0)	<0.05
5–11 years/5–13 years				
Klorman, 1994[68]	Abbreviated Conners' Hyperactivity Questionnaire:			
	Parents	0.99 (0.60)	1.41 (0.60)	<0.01
	Teachers	0.56 (0.42)	1.09 (0.52)	<0.01
	TOTS (hyperactivity) (parents)	–0.44 (0.51)	–0.11 (0.48)	<0.01
	TOTS (hyperactivity) (teachers)	–1.04 (0.43)	–0.61 (0.45)	<0.01
Brown, 1986[42]				MD (95% CI)
	CPRS (Hyperactivity Index)	15.88 (6.36)	17.25 (7.50)	–0.24 (–4.61 to 4.13)
	ACTeRs (hyperactivity)	14.25 (5.6)	17.50 (4.41)	4.12 (–7.84 to –0.40)
6–11 years/6–12 years				
Conners, 1980[46]				MD (95% CI)
	Conners' Parent Questionnaire (hyperactivity)	0.46 (0.23)	0.75 (0.36)	–0.30 (–0.46 to –0.14)
	Conners' Teacher Questionnaire (hyperactivity)	1.28 (0.67)	1.45 (0.63)	–0.51 (–0.75 to –0.27)
Stein, 1996[91]	CPRS (Hyperactivity Index)	titration: 11.4 (4.0) b.i.d.: 9.7 (5.8) t.i.d.: 9.2 (7.5)	11.7 (6.4)	NS
	ACTeRS (hyperactivity)	titration: 16.3 (4.6) b.i.d.: 15.5 (4.8) t.i.d.: 13.5 (4.8)	16.3 (5.7)	NS
6–18 years				
Hoeppner, 1997[61]	CPRS (Hyperactivity Index)	7.13 (6.37)	8.40 (6.59)	S – NR
	CTRS (Hyperactivity Index)	8.20 (6.85)	13.54 (8.66)	S – NR
7–12 years				
Zeiner, 1999[98]	CTRS (hyperactivity)	8.83 (6.49)	14.69 (6.17)	<0.0001
	PACS (hyperactivity)	3.08 (3.70)	5.25 (5.01)	<0.05

continued

TABLE 6 *Results for hyperactivity [MPH medium dose (15–30 mg/day) versus placebo]*

Study	Scale	MPH medium dose: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported) or mean difference[a]
13–15 years				
Brown, 1988[43]	CPRS-R (Hyperactivity Index)	9.00 (3.16)	12.66 (4.13)	NS
	Conners' Teacher Hyperactivity Index	18.33 (3.07)	24.50 (2.81)	<0.05
	ACTeRS (hyperactivity)	9.50 (5.04)	8.00 (0.63)	NS

[a] Note that owing to the overall poor reporting of study methodology, *p*-values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
ACTeRS, ADD-H Comprehensive Teacher Rating Scale; CPRS, Conners' Parent Rating Scale; CPRS-R, Conners' Parent Rating Scale – Revised; CTRS, Conners' Teacher Rating Scale; CTRS-R, Conners' Teacher Rating Scale – Revised; MD, mean difference; NS, not significant; PACS, Parental Account of Childhood Symptoms; S – NR, significant (value not reported).

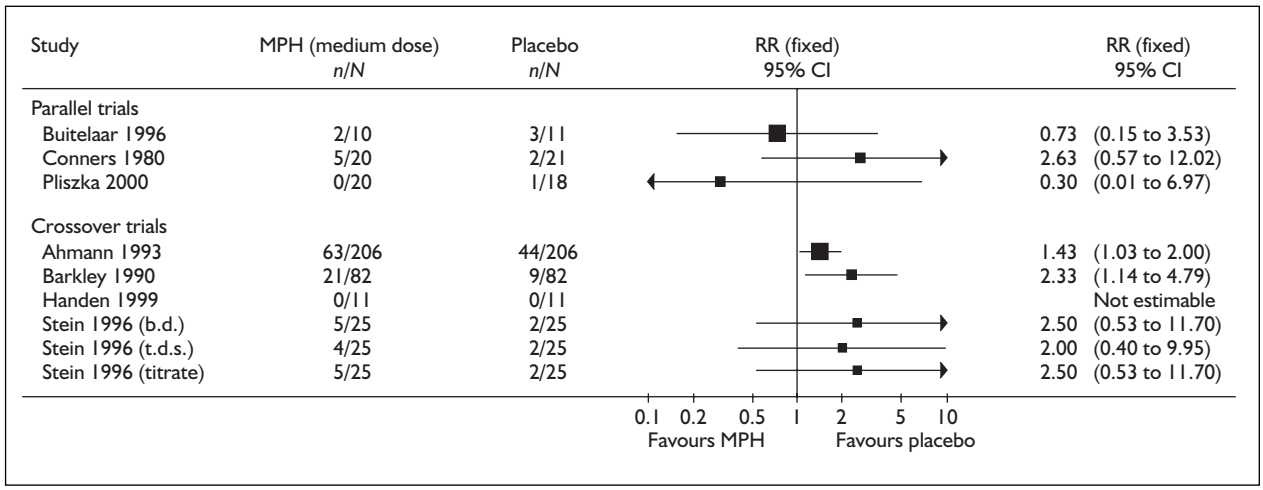

FIGURE 4 *Relative risks of headache: MPH (medium dose) versus placebo*

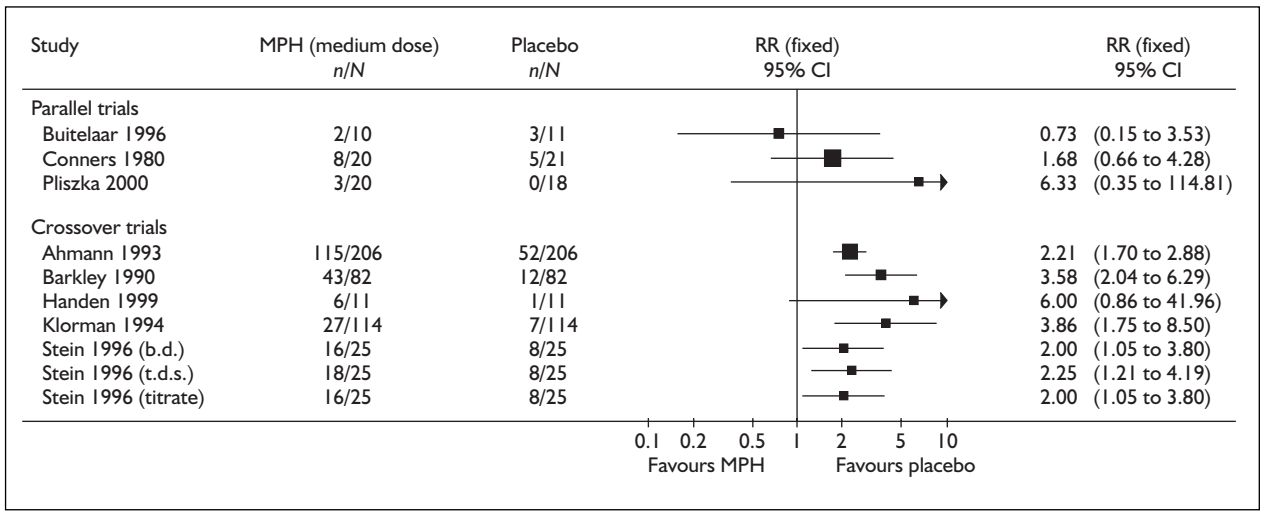

FIGURE 5 *Relative risks of loss of appetite: MPH (medium dose) versus placebo*

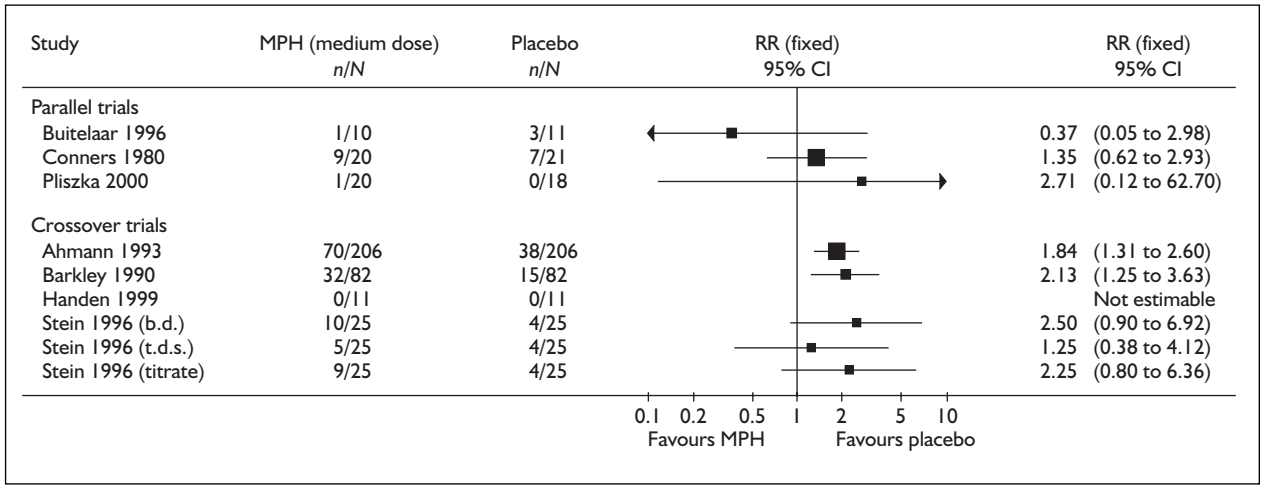

FIGURE 6 *Relative risks of stomach ache: MPH (medium dose) versus placebo*

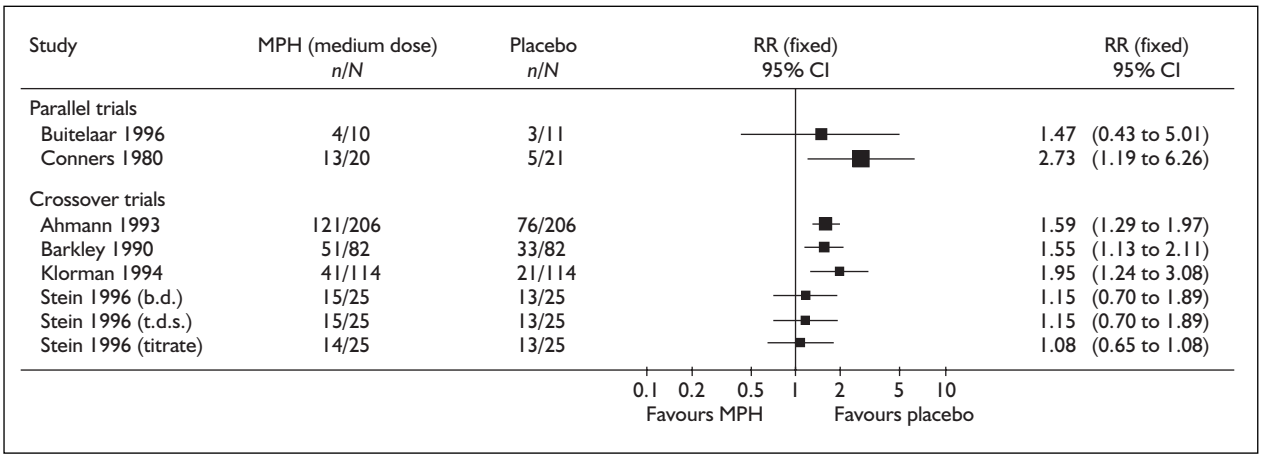

FIGURE 7 *Relative risks of insomnia: MPH (medium dose) versus placebo*

immediate-release MPH compared with placebo (*Table 7*; with additional information presented in Appendix 12). All of these studies examined high-dose MPH administered more than once daily.

Of the studies that examined high-dose MPH and placebo, two examined hyperactivity[43,67] and one evaluated hyperactivity/impulsivity using the SNAP-IV scale (a variation of the Conners' scales). These studies will be discussed separately below. Three studies presented results for adverse events only,[35,39,57] and these will also be presented below.

Two of the remaining studies examined inattention/overactivity using an IOWA CTRS as one of the main core outcomes: Kolko and colleagues[69] observed that high-dose MPH was better than placebo ($p < 0.0001$). Pelham and colleagues[79] reported that behaviour improved with treatment, but did not present direct statistical comparisons (see Appendix 12).

[Confidential information removed].

Hyperactivity

Of the three studies that examined hyperactivity, one did not report enough data to be included in *Table 8*.[67] One of the remaining studies used a crossover design[43] and the other was a parallel study.[97] The studies used different Conners' scales, but both reported results for parents and teachers. The study by Brown and Sexson[43] also examined hyperactivity using the ACTeRS. Given the different outcome scales, study designs and age groups, data from these two studies were not pooled.

Results from the two studies show some variability (*Table 8*). Of the two results that were not found to be significant, one used a scale that was assessed by parents and the other used a scale assessed by teachers.

Quality of life

Wolraich and colleagues[97] examined CGI and reported that 47.2% of participants on immediate-release high-dose MPH were 'much or very much improved' at the end of the study compared with 16.7% of participants in the placebo group (no significance value was reported).

[Confidential information removed].

It is noted that Klorman and colleagues[66,67] also reported on ratings of global outcome (results presented in Appendix 12) – data that could also be used to assess QoL but were not considered to be a primary outcome measure in this SR.

Adverse events

Of 10 trials comparing a high dose of MPH with placebo, seven presented usable data on adverse events (see *Table 7*). The occurrence of headache was significantly higher in the treatment group only in Ahmann and colleagues[35] (RR = 1.89, 95% CI 1.34 to 2.68) (*Figure 8*).

One parallel trial found significantly higher proportions of participants suffering from loss of appetite in the treatment group, with an RR of 22.54 (95% CI 3.18 to 159.56). Three crossover trials also detected higher proportions in the treatment groups with RRs of between 2.44 and 4.67 (*Figure 9*).

Two crossover trials reporting occurrence of stomach ache detected significant differences between the treatment and placebo groups; RRs of 2.11 and 1.93 are reported (*Figure 10*). Both

TABLE 7 *MPH high dose (>30 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Gittelman-Klein, 1976[57]	P	MPH (max. 60 mg/day, b.d.) – 166	6–12	12	Core: no core symptoms reported QoL: not reported AE: side effects standardised form: severity and consistency
Klorman, 1987[66]	C (2×)	MPH (25–40 mg/day, t.d.s.) – 19	12–19	6	Core: no hyp; Abbreviated Conners' Questionnaire QoL: no CGI; Loney and Ordona Scale: response (patients and parents) AE: STESS (based on interview with parent and patient)
Brown, 1988[43]	C (4×)	MPH (42.56 mg/day, b.d.) –11	13–15	8	Core: CPRS: Hyperactivity Index; Conners' Teacher Hyperactivity Index; ACTeRS: hyperactivity QoL: not reported AE: SERS (parents); weight
Barkley, 1990[39]	C (3×)	MPH (1.0 mg/kg/day, b.d.) – 83	5–13	3	Core: not reported QoL: not reported AE: Stimulant Drug Side Effects Questionnaire: 17-item list
Klorman, 1990[67]	C (2×)	MPH (35.21 mg/day, t.d.) – 48	12–18	6	Core: Abbreviated Conners' Hyperactivity Questionnaire (parents, teachers); IOWA inattention/overactivity scale (parents, teachers); TOTS: hyperactivity and attention scales (parents, teachers) QoL: no CGI; ratings of global outcome (parents/patients) AE: STESS (patients, parents); Nowlis Mood Scale: fatigue (patients); weight
Pelham, 1993[79]	C (3×)	MPH (32 mg/day, b.d.) – 31	5.4–9.9	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Ahmann, 1993[35]	C (3×)	MPH (1.5 mg/kg/day, t.d.) – 234	5–15	4	Core: not reported QoL: not reported AE: BSEQ
Kolko, 1999[69]	C (4×)	MPH (1.2 mg/kg/day, b.d.) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: SSERS
Wolraich, 2001[97]	P	MPH (15, 30 or 45 mg/day, t.d.) – 312	6–12	4	Core: SNAP-IV Hyperactivity/Impulsivity (teacher rated) (parent rated) QoL: CGI (investigator rated) AE: solicited and spontaneous reports: focus on sleep quality, tics and appetite (parent)
Quinn, 2003[84]	**[Confidential information removed]**				

ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; b.d., twice daily; BSEQ, Barkley Side Effects Questionnaire; C, crossover trial (number of crossovers); CGI, Clinical Global Impression; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; P, parallel trial; SNAP, Swanson, Nolan and Pelham (scale); SSERS, Stimulant Drug Side Effects Rating Scale; t.d.s., three times daily.

TABLE 8 *Results for hyperactivity [MPH High dose (>30 mg/day) versus placebo]*

Study	Scale	MPH high dose: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported) or mean difference[a]
6–12 years				
Wolraich, 2001[97]				MD (95%CI)
	SNAP-IV Hyperactivity/Impulsivity (teacher)	0.93 (0.79)	1.57 (0.89)	–1.26 (–1.44 to –1.08)
	SNAP-IV Hyperactive/Impulsivity (parent)	1.10 (0.69)	1.83 (0.89)	–0.58 (–0.73 to –0.43)
13–15 years				
Brown, 1988[43]	CPRS (Hyperactivity Index)	9.33 (2.06)	12.66 (4.13)	NS
	Conners' Teacher Hyperactivity Index	17.33 (3.72)	24.50 (2.81)	<0.05
	ACTeRS (hyperactivity)	10.00 (6.69)	8.00 (0.63)	NS

[a] Note that owing to the overall poor reporting of study methodology, the *p*-values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
ACTeRS: ADD-H Comprehensive Teacher Rating Scale; CPRS, Conners' Parent Rating Scale; MD, mean difference; Nolan and Pelham (scale); NS, not significant; SNAP, Swanson.

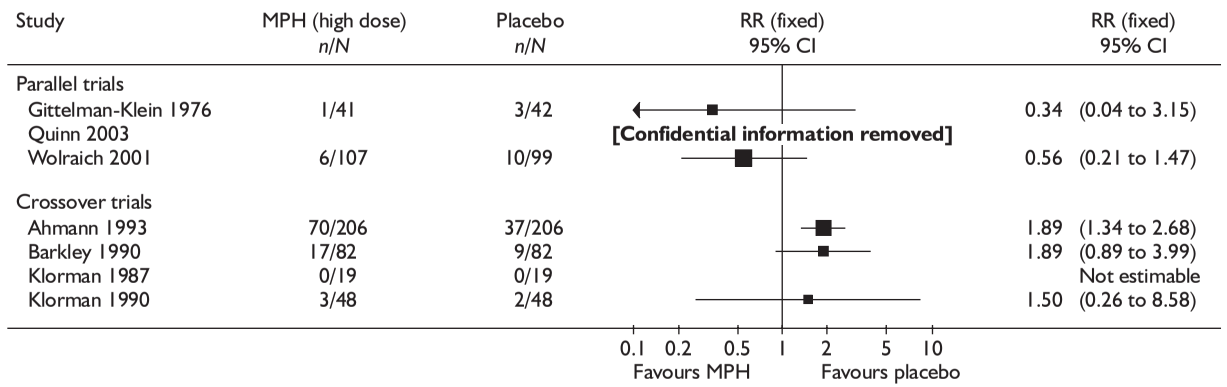

FIGURE 8 *Relative risks of headache: MPH (high dose) versus placebo*

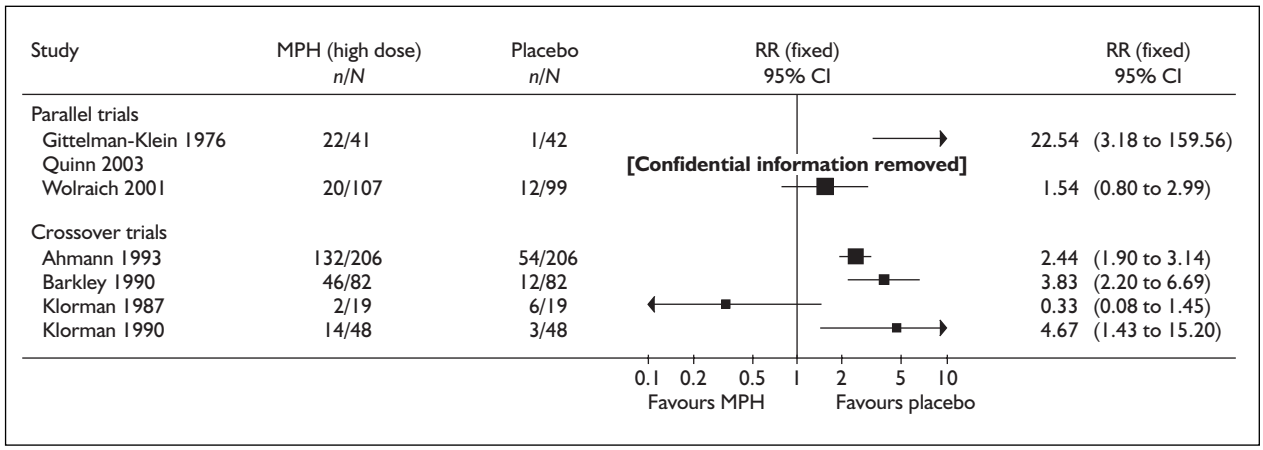

FIGURE 9 *Relative risks of loss of appetite: MPH (high dose) versus placebo*

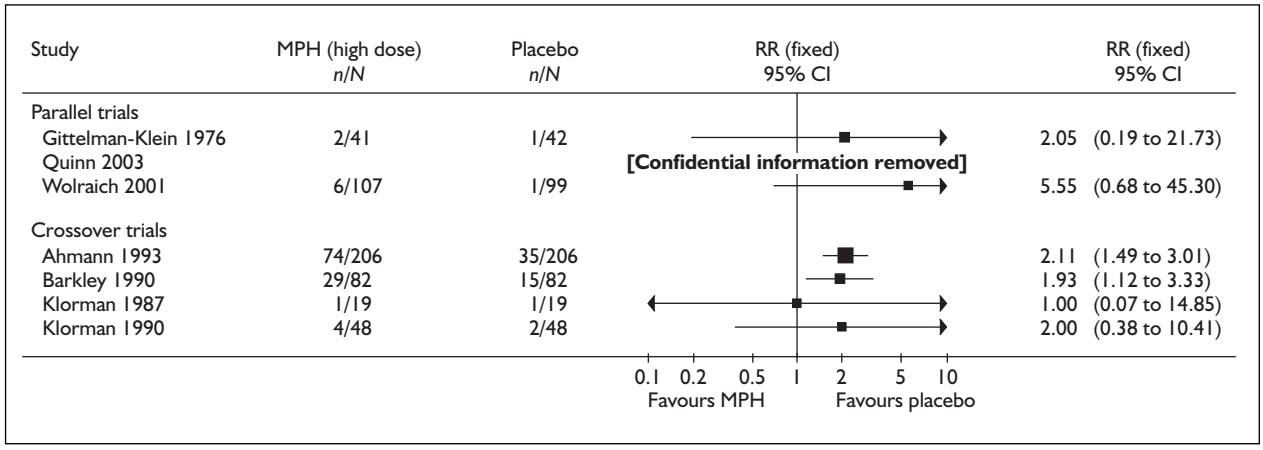

FIGURE 10 *Relative risks of stomach ache: MPH (high dose) versus placebo*

studies included participants spanning a wide age range: 5–13 and 5–15 years, respectively.

One parallel and two crossover trials detected a significantly higher incidence of insomnia in the treatment groups, with the greatest RR in the parallel study (4.10) compared with RRs of 1.51 and 1.70 in the crossover trials (*Figure 11*).

[Confidential information removed].

Summary

Only two studies reported detailed data on hyperactivity and there was variability in the results. The one non-confidential study that reported data on CGI reported improved behaviour in the high-dose MPH group compared with placebo **[Confidential information removed]**. Adverse event data showed that high-dose MPH seems to be associated with higher incidences of headaches, loss of appetite, stomach ache and insomnia, although not all differences were significant. Most of these studies did not score very well in the quality assessment and their results should be interpreted with caution.

[Confidential information removed].

MPH low dose (≤15 mg/day) plus non-drug intervention versus placebo

No studies reported on low-dose (≤15 mg/day) immediate-release MPH plus a non-drug intervention versus placebo.

MPH medium dose (15–30 mg/day) plus non-drug intervention versus placebo

Three studies examined medium-dose (15–30 mg/day) immediate-release MPH plus non-drug intervention compared with placebo (*Table 9*; with additional information presented in

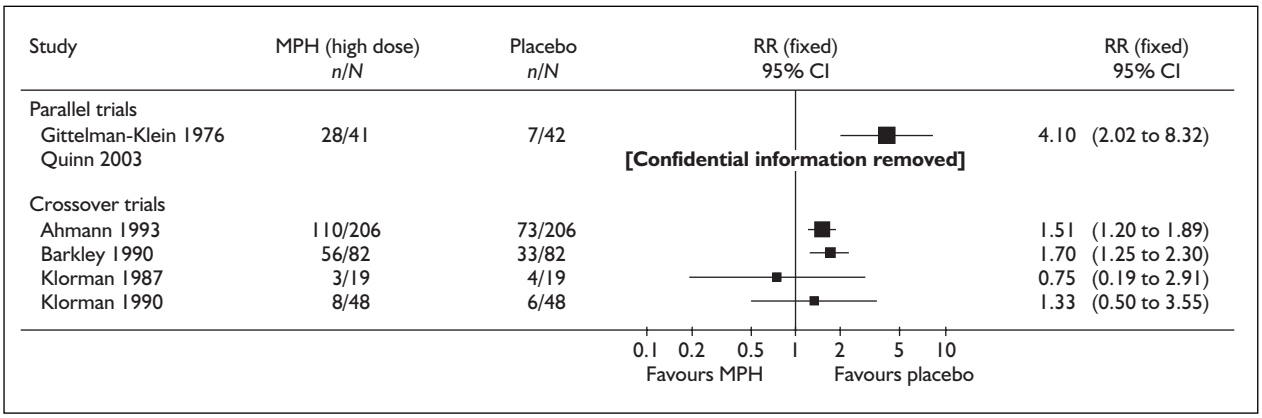

FIGURE 11 *Relative risks of insomnia: MPH (high dose) versus placebo*

Appendix 12). All of the studies examined medium-dose MPH administered more than once daily.

Only one of these studies evaluated MPH treatment plus non-drug intervention using hyperactivity as an outcome variable (*Table 10*).[42] In this parallel study, the non-drug intervention was cognitive therapy. Statistical comparisons between the treatment arms for the (CPRS) or ACTeRs were not clearly reported by the authors; however, mean differences (MDs) and 95% CIs show no significant differences between the groups.

Rating scale
The remaining two studies evaluated medium-dose MPH plus non-drug treatment by measuring inattention/overactivity (as one of the core outcomes) using the IOWA Conners' Rating Scales (IOWA-C).[69,79] Both studies examined MPH plus a behavioural modification intervention, and both reported that combined treatment was better than placebo; however, the statistical results were not clearly presented (see Appendix 12).

Adverse events
None of the trials presented informative adverse event data.

Summary
Only one study evaluated the effectiveness of MPH plus a non-drug intervention compared with placebo using hyperactivity as an outcome,[42] and the results from these comparisons were not significant. None of the studies evaluated CGI.

MPH high dose (>30 mg/day) plus non-drug intervention versus placebo
Two studies evaluated high-dose (>30 mg/day) immediate-release MPH plus non-drug intervention compared with placebo (*Table 11*; with additional information presented in Appendix 12).

Both studies in this category used the IOWA-C to evaluate inattention/overactivity. As presented in *Table 11*, both examined MPH plus a behavioural modification intervention and a placebo group. Both reported that the MPH plus non-intervention group differed from the placebo group; however, direct statistical comparisons were not clearly reported (see Appendix 12).

Adverse events
None of the trials presented informative adverse event data.

Summary
No studies in this category examined hyperactivity or CGI or reported informative adverse event data.

ER-MPH low dose (≤20 mg/day) versus placebo
Two studies examined low-dose (≤ 20 mg/day) extended-release MPH (ER-MPH) compared with placebo (*Table 12*; with additional information presented in Appendix 12). Both studies examined low-dose MPH administered once daily.

Only one of these studies measured hyperactivity as an outcome.[55] Using the Conners' Hyperactivity Index, this crossover study reported that low-dose ER-MPH resulted in improved behaviour compared with placebo, when assessed by both parents and teachers (*Table 13*). The other study in this category measured other behavioural outcomes using scales such as the ADHD Rating Scale IV.[92] Details from these results are presented in Appendix 12.

TABLE 9 *MPH medium dose (15–30 mg/day) plus non-drug intervention versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Brown, 1986[42]	P	MPH (20.08 mg/day, b.d.) – 40	5.7–13.1	3 months	Core: CPRS: Hyperactivity Index; ACTeRs: hyperactivity QoL: not reported AE: not reported.
Pelham, 1993[79]	C (3×)	MPH (16.2 mg/day, b.d.) – 31	5.4–9.9	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Kolko, 1999[69]	C (4×)	MPH (0.60 mg/kg/day, b.d.) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: SSERS

ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; C, crossover trial (number of crossovers); CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; P, parallel trial; SSERS, Stimulant Drug Side Effects Rating Scale.

TABLE 10 *Results for hyperactivity [MPH medium dose (15–30 mg/day) plus non-drug intervention versus placebo]*

Study	Scale	MPH medium dose + non-drug: mean (SD)	Placebo: mean (SD)	Mean difference
5–13 years				
Brown, 1986[42]				MD (95% CI)
	CPRS (Hyperactivity Index)	13.78 (8.14)	17.25 (7.50)	–0.31 (–4.47 to 3.85)
	ACTeRs (hyperactivity)	19.60 (2.63)	17.50 (4.41)	0.68 (–1.89 to 3.25)

Lower scores represent a better behavioural outcome.
ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; CPRS, Conners' Parent Rating Scale.

TABLE 11 *MPH high dose (>30 mg/day) plus non-drug intervention versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Pelham, 1993[79]	C (3×)	MPH (32 mg/day, b.d.) – 31	5.4–9.9	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Kolko, 1999[69]	C (4×)	MPH (1.2 mg/kg/day, b.d.) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: SSERS
C, crossover trial (number of crossovers); CTRS. Conners' Teacher Rating Scale; SSERS, Stimulant Drug Side Effects Rating Scale.					

TABLE 12 *ER-MPH low dose (≤20 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Fitzpatrick, 1992[55]	C (4×)	Sustained-release MPH (slow-release Ritalin, SR-20) (20 mg/day, o.d.) – 19	6.9–11.5	8	Core: Conners' Hyperactivity Index (parents and teacher) QoL: no CGI; comments ratings (parent and teacher) AE: STESS (parents); weight
Stein, 2003[92]	C (4×)	OROS MPH (Concerta) (18 mg/day, o.d.) – 47	5.9–16	4	Core: no hyp; ADHD Rating Scale IV (parents) QoL: CGI AE: SERS (parents)
C, crossover trial (number of crossovers); CGI, Clinical Global Impression; SERS, Side Effects Rating Scale; STESS, Subject's Treatment Emergent Symptom Scale.					

TABLE 13 *Results for hyperactivity [ER-MPH low dose (≤ 20 mg/day) versus placebo]*

Study	Scale	ER-MPH low dose: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported)[a]
6–11 years				
Fitzpatrick, 1992[55]	Conners' Hyperactivity Index			
	(parents)	0.98 (0.72)	1.75 (0.67)	<0.006
	(teachers)	0.77 (0.63)	1.36 (0.80)	<0.006

[a] Note that owing to the overall poor reporting of study methodology, the *p*-values should be interpreted with caution. Lower scores represent a better behavioural outcome.

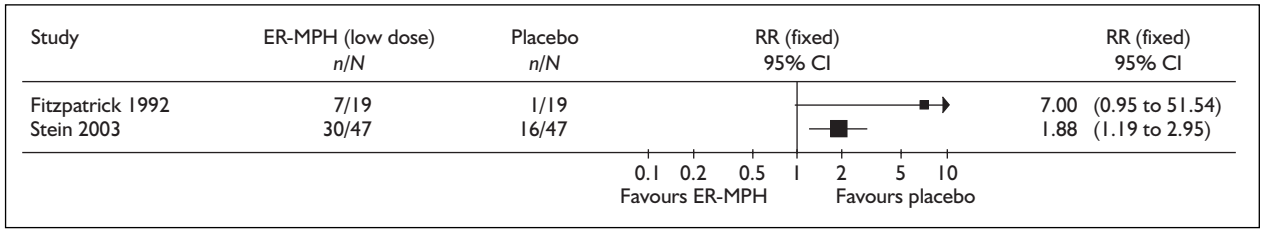

FIGURE 12 *Relative risks of loss of appetite: ER-MPH (low dose) versus placebo*

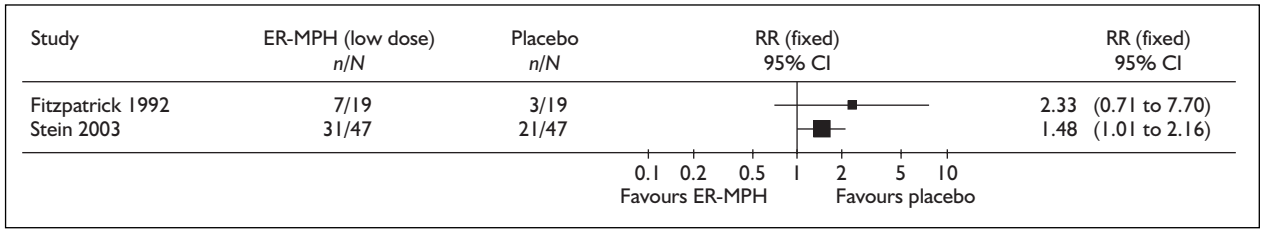

FIGURE 13 *Relative risks of insomnia: ER-MPH (low dose) versus placebo*

Quality of life

Stein and colleagues[92] reported results for CGI severity scores. They observed that overall impairment decreased with increasing doses of MPH ($p < 0.001$). Results were presented separately for children with inattentive and combined subtypes, and are presented in Appendix 12.

Adverse events

Both studies reported data on adverse events. Neither study detected differences in the incidence of headache or stomach ache between treatment arms. A significantly higher number of participants suffered from decreased appetite when assigned to a low dose of ER-MPH in one study;[92] similar results were observed with regard to incidence of insomnia (*Figures 12* and *13*).

Neither study adequately reported data on the weight of participants.

Summary

The study that assessed hyperactivity reported that low-dose ER-MPH was better than placebo.[55] The other study assessed CGI, but direct statistical comparisons between low dose ER-MPH and placebo were not reported, although there was a trend towards improvement with drug treatment. Both studies showed differences between groups for loss of appetite and insomnia, but not for headache or stomach ache. The studies did not score very well in the quality assessment, and although the study by Fitzpatrick and colleagues[55] scored slightly better, the results should be treated with caution.

ER-MPH medium dose (20–40 mg/day) versus placebo

Six studies examined medium-dose (20–40 mg/day) ER-MPH compared with placebo (*Table 14*; with additional information presented in Appendix 12). All of the studies examined

TABLE 14 *ER-MPH medium dose (20–40 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Wolraich, 2001[97]	P	OROS MPH (Concerta) (18, 36 or 54 mg/day, o.d.) – 312	6–12	4	Core: SNAP-IV: hyperactivity/impulsivity (parent, teacher) QoL: CGI improvement (investigators) AE: solicited and spontaneous reports: focus on sleep quality, tics and appetite (parent)
Greenhill, 2002[59]	P	MPH-Modified Release (Metadate CD) (mean 40.7 mg/day, o.d.) – 321	5–15	3	Core: not reported QoL: CGI (teacher; parent); CGI improvement ratings AE: Teacher and Parent Side-Effect Questionnaires
Quinn, 2003[84]			**[Confidential information removed]**		
Dopfner, 2003[48]	P	MPH-Retard (Medikinet) (20–60 mg/day, o.d.) – 85	6–16	4	Core: no hyp; Peer Assessment for Hyperkinetic Disorders (teachers); effectiveness scale (parents, physicians) QoL: not reported AE: no specific scale reported
Stein, 2003[92]	C (4×)	OROS MPH (Concerta) (36 mg/day, o.d.) – 47	5.9–16	4	Core: no hyp; ADHD Rating Scale IV (parents)/ACTeRS QoL: CGI AE: SERS (parents)
Swanson, 2004[32]	C (3×)	OROS MPH (Concerta) (18, 36 or 54 mg/day, o.d.) – 184 MPH-Modified Release (Metadate CD) (20, 40 or 60 mg/day, o.d.) –184	6–12	3	Core: no hyp; SKAMP: deportment; attention (measured by two trained observers) QoL: not reported AE: side-effects on the Barkley Scale

C, crossover trial (number of crossovers); CGI, Clinical Global Improvement; P, parallel trial; SKAMP, Swanson, Kotkin Agler, M-Flynn, Pelham (scale); SNAP, Swanson, Nolan and Pelham (scale).

medium-dose MPH administered once daily. Four studies were parallel in design and two used a crossover design. Although participants in Swanson and colleagues' trial[32] were assigned to varying dosages of ER-MPH according to pre-existing requirements, data were presented by type of treatment only (Metadate MPH, Concerta MPH or placebo); hence it is included in the medium-dose category. Similarly, data were presented across varying dosages in the trials of Wolraich and colleagues[97] and Quinn.[84]

Most of the studies did not report results for hyperactivity, but did measure other core outcomes including **[Confidential information removed]**, the ADHD Rating Scale[92] and the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP Scale).[32] In addition, Dopfner and colleagues[48] used the Peer Assessment for Hyperkinetic Disorders as assessed by teachers, and a five-point effectiveness scale as assessed by parents, and also by physicians.

[Confidential information removed].

The statistical results from the other studies were less clearly presented (see Appendix 12), although Stein and colleagues[92] reported that as the ER-MPH dose was increased from 0 to 54 mg, parent-rated ADHD symptoms decreased in a linear manner ($p < 0.001$).

Hyperactivity

One study measured hyperactivity/impulsivity using the Swanson, Nolan and Pelham (SNAP) IV Scale (a variation of the Conners' scales).[97] Wolraich and colleagues[97] observed significant improvements in the ER-MPH group compared with the placebo group (*Table 15*). This result was consistent when rated by teachers and parents.

Quality of life

Four studies in this category reported on CGI. Wolraich and colleagues[97] reported that 46.7% of participants on medium-dose ER-MPH were 'much or very much improved' at the end of the study compared with 16.7% of participants in the placebo group (no significance value was reported). Greenhill and colleagues[59] observed that 81% assigned to active drug were significantly improved compared with 50% in the placebo group ($p < 0.001$).

[Confidential information removed].

Finally, Stein and colleagues[92] reported CGI severity scores in children with ADHD inattentive subtype and combined subtype. The results increased with medication dose, and were better than placebo; however, direct statistical comparisons were not reported.

Adverse events

Five of the six studies reported usable data regarding adverse events. Differences between participants in the incidence of headache were not detected in four of these trials. **[Confidential information removed]**.

Participants in the trials of Stein and colleagues[92] and Greenhill and colleagues[59] suffered from significantly decreased appetite when assigned to the extended-release form of MPH. Those assigned to the Concerta form of MPH in Swanson and colleagues' trial[32] also suffered from significantly decreased appetite (*Figure 14*).

One crossover trial[92] reported higher numbers of participants suffering from stomach ache during the ER-MPH phase compared with placebo (RR = 2.09; 95% CI 1.15 to 3.79). The other three non-confidential trials did not find significantly different frequencies between treatment arms. Of the three trials reporting incidence of insomnia,[32,59,84,92] no trial detected significant differences between participants assigned to ER-MPH compared with placebo. No trial in this comparison group reported data on weight.

TABLE 15 *Results for hyperactivity [ER-MPH medium dose (20–40 mg/day) versus placebo]*

Study	Scale	ER-MPH medium dose: mean (SD)	Placebo: mean (SD)	Mean difference
6–12 years				
Wolraich, 2001[97]	SNAP-IV			
	(hyperactivity/impulsivity)			MD (95%CI)
	(teacher)	0.96 (0.79)	1.57 (0.89)	–1.21 (–1.40 to –1.02)
	(parent)	1.11 (0.65)	1.83 (0.89)	–0.75 (–0.89 to –0.61)
Lower scores represent a better behavioural outcome.				

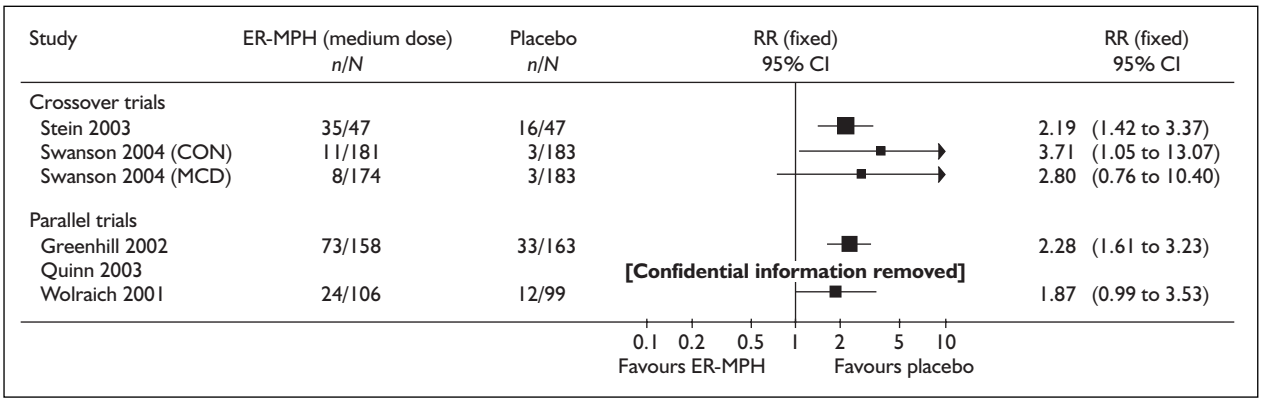

FIGURE 14 *Relative risks of loss of appetite: ER-MPH (medium dose) versus placebo*

TABLE 16 *ER-MPH high dose (>40 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Stein, 2003[92]	C (4×)	OROS MPH (Concerta) (54 mg/day, o.d.) – 47	5.9–16	4	Core: no hyp; ADHD Rating Scale IV (parents)/ACTeRS QoL: CGI AE: side-effect rating scale (parents)

ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; AE, adverse events; C, crossover trial (number of crossovers); CGI, Clinical Global Impression.

Summary

Only one study examined hyperactivity/impulsivity using the SNAP-IV scale and reported significant improvements in the ER-MPH group compared with the placebo group when assessed by teachers and parents.[97] Four studies reported results for CGI, two of which did not report direct statistical comparisons between treatment and placebo.[92,97] One study reported a significant improvement in the treatment group compared with placebo.[59] **[Confidential information removed]**. Adverse events data showed that medium dose ER-MPH seems to be associated with a higher incidence of decreased appetite. Most of these studies did not score very well in the quality assessment and their results should be interpreted with caution. **[Confidential information removed]**.

ER-MPH high dose (>40 mg/day) versus placebo

Only one study examined high-dose (>40 mg/day) ER-MPH compared to placebo (*Table 16*; with additional information presented in Appendix 12). No hyperactivity outcomes were reported, although the study did report on CGI and adverse events. Although no direct statistical comparisons were made with placebo, Stein and colleagues[92] reported that overall impairment, as measured by CGI severity scores, decreased with increasing dose of MPH ($p < 0.001$).

[Confidential information removed].

Adverse events

Participants suffered from a significantly higher incidence of decreased appetite and insomnia during the ER-MPH phase compared with placebo (RR = 2.31; 95% CI 1.51 to 3.54 and RR = 1.62; 95% CI 1.13 to 2.33, respectively). No significant differences in the incidence of headache or stomach ache were detected. Data on weight were not given.

Summary

The one study included in this category reported results for CGI only. The authors reported that overall impairment decreased with increasing dose of ER-MPH. In addition, they reported a significant decrease in appetite and increased insomnia with treatment. However, this study did not score very well in the quality assessment, and the results should be treated with caution.

TABLE 17 *MPH low dose (≤15 mg/day) versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (months)	Core outcomes
Administered two or more times daily					
Brown, 1985[41]	P	MPH (5–15 mg/day, b.d.) vs cognitive training (12 weeks, 24 sessions) – 30	6.3–11.8	6	Core: no hyp; CPRS; ACTRS QoL: not reported AE: not reported
ACTRS, Abbreviated Conners' Teacher Rating Scale; CPRS, Conners' Parent Rating Scale; P, Parallel trial.					

TABLE 18 *MPH medium dose (15–30 mg/day) versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Brown, 1986[42]	P	MPH (20.08 mg/day, b.d.) vs cognitive therapy (11 weeks, 22 sessions) – 40	5.7–13.1	3 months	Core: CPRS: Hyperactivity Index; ACTeRS: hyperactivity AE: not reported
Firestone, 1986[53]	P	MPH (22.0 mg/day, b.d.) vs parent training (3 months) – 134	5–9	3 months	Core: CTRS: Hyperactivity Index QoL: not reported AE: not reported
Pelham, 1993[79]	C (3×)	MPH (16.2 mg/day, b.d.) vs behavioural modification intervention (STP, 8 weeks) – 31	5.4–9.9	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Kolko, 1999[69]	C (4×)	MPH (1.2 mg/kg/day, b.d.) vs behavioural modification (6 weeks) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: no details reported
ACTeRS, ADD-H Comprehensive Teachers' Rating Scale; C, crossover trial (number of crossovers); CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; P, parallel trial.					

MPH versus non-drug intervention

MPH low dose (≤15 mg/day) versus non-drug intervention

Only Brown and colleagues[41] evaluated low-dose (≤15 mg/day) immediate-release MPH compared with a non-drug intervention (cognitive training) (*Table 17*; with additional information in Appendix 12). In this study, hyperactivity was not evaluated, although the authors measured overall behaviour using the CPRS and the Abbreviated CTRS. Results from comparisons between treatment groups were not clearly presented in this study.

Summary

No studies in this category examined hyperactivity, CGI or adverse events.

MPH medium dose (15–30 mg/day) versus non-drug intervention

Four studies examined medium-dose (15–30 mg/day) immediate-release MPH compared with a non-drug intervention (*Table 18*; with additional information presented in Appendix 12). All studies examined MPH administered two or more times daily.

Only two of the studies measured hyperactivity (*Table 19*). Firestone and colleagues[53] observed that medium-dose MPH was significantly better than parent training. This involved sessions and group meetings on child management and learning how to cooperate efficiently with school personnel. In the study by Brown and colleagues,[42] results from comparisons between the

TABLE 19 *Results for hyperactivity [MPH medium dose (15–30 mg/day) versus non-drug intervention]*

Study	Scale	MPH medium dose: mean (SD)	Non-drug: mean (SD)	Mean difference
5–9 years				
Firestone, 1986[53]				MD (95% CI)
	CTRS (Hyperactivity Index)	0.91 (0.58)	1.37 (0.57)	–0.49 (–0.65 to –0.33)
5–13 years				
Brown, 1986[42]				MD (95% CI)
	CPRS (Hyperactivity Index)	15.88 (6.36)	21.10 (5.65)	–5.27 (–9.72 to –0.82)
	ACTeRS (hyperactivity)	14.25 (5.60)	19.60 (2.63)	–4.80 (–7.86 to –1.74)

Lower scores represent a better behavioural outcome.
CTRS, Conners' Teacher Rating Scale; CPRS, Conners' Parent Rating Scale; ACTeRS, ADD-H Comprehensive Teachers' Rating Scale.

MPH group and those receiving cognitive therapy were not clearly presented; however, calculated MD and 95% CI values demonstrate significant differences.

The two remaining studies measured inattention/overactivity using the IOWA CTRS as a main outcome variable.[69,79] However, direct statistical comparisons between medium-dose MPH and behaviour modification were not clearly presented (see Appendix 12).

Adverse events
No study reported adequate data on adverse events.

Summary
Both studies that compared medium-dose MPH (with either parent training or cognitive therapy) demonstrated a significant difference in favour of MPH. None of the studies examined CGI. The studies did not score very well in the quality assessment, and the results should be interpreted with caution.

MPH high dose (>30 mg/day) versus non-drug intervention

Three studies examined high-dose (>30 mg/day) immediate-release MPH compared with a non-drug intervention (*Table 20*; with additional information presented in Appendix 12). All studies examined MPH administered two or more times daily.

The two other studies measured inattention/overactivity using the IOWA CTRS as a main outcome variable.[69,79] Statistical significance of comparisons between high-dose MPH compared with behaviour modification was not reported in these studies (see Appendix 12).

One study measured hyperactivity using three different measures (*Table 21*). Klein and Abikoff[65] compared high-dose MPH with a behavioural therapy that involved parent and teacher education. They observed that the behaviour of the children was better in the MPH group compared with non-drug therapy when evaluated using the CTRS, but not when evaluated by parents using either the CPRS or the Home Hyperactivity Scale. However, when the MD and CIs are calculated, these results are significant.

In addition, Klein and Abikoff[65] assessed CGI. When evaluated by psychiatrists, 79% in the MPH group compared with 50% in the non-drug group improved after 8 weeks of treatment.

Adverse events
No study reported adequate data on adverse events.

Summary
Only one study examined high-dose MPH compared with a non-drug intervention (parent and teacher education) using hyperactivity as an outcome,[65] with significant effects in favour of the drug treatment group. This study also examined CGI, and found a higher percentage of improved children in the MPH group compared with the non-drug intervention group. This study did not score very well in the quality assessment, and the results should be interpreted with caution.

MPH low dose (≤15 mg/day) plus non-drug intervention versus non-drug intervention

Three studies examined low-dose (≤15 mg/day) immediate-release MPH plus non-drug intervention compared with a non-drug intervention (*Table 22*; with additional information presented in Appendix 12). Two studies

TABLE 20 *MPH high dose (>30 mg/day) versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Pelham, 1993[79]	C (3×)	MPH (32 mg/day, b.d.) vs behavioural modification intervention (STP, 8 weeks) – 31	5.4–9.9	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Klein, 1997[65]	P	MPH (1.55 mg/kg/day, b.d.) vs behavioural intervention + parent and teacher education (4 weeks) – 86	6–12	12	Core: CTRS and CPRS: hyperactivity; Home Hyperactivity Scale (parents) QoL: CGI (teacher/mothers/psychiatrists) AE: not reported
Kolko, 1999[69]	C (4×)	MPH (1.2 mg/kg/day, b.d.) vs behavioural modification (6 weeks) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: no details reported

C, crossover trial (number of crossovers); CGI, Clinical Global Improvement; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; P, parallel trial; STP, Summer Treatment Programme.

TABLE 21 *Results for hyperactivity [MPH high dose (>30 mg/day) versus non-drug intervention]*

Study	Scale	MPH high dose: mean (SD)	Non-drug: mean (SD)	*p*-Value (if reported)[a]
6–12 years				
Klein, 1997[65]				MD (95% CI)
	CTRS (hyperactivity)	1.1 (0.4)	1.5 (0.6)	0.01 –0.60 (–0.76 to –0.44)
	CPRS (hyperactivity)	0.7 (0.5)	0.8 (0.4)	NS –0.20 (–0.32 to –0.08)
	Home Hyperactivity Scale (parents)	2.1 (0.46)	2.4 (0.86)	NS –0.60 (–0.92 to –0.28)

[a] Note that owing to the overall poor reporting of study methodology, the *p*-values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; NS, not significant; MD, mean difference.

TABLE 22 *MPH low dose (≤ 15 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Kupietz, 1988[71]	P	MPH (0.3 mg/kg, o.d.) vs one-to-one reading therapy (6 months) – 58 MPH (0.5 mg/kg, o.d.) vs one-to-one reading therapy (6 months) – 58	7–13	6 months	Core: CTRS: hyperactivity QoL: not reported AE: not reported
Pelham, 1999[81]	C (7×)	MPH (0.3 mg/kg/day, o.d.) vs behavioural programme – 21	6–12	6	Core: no hyp; IOWA-C: inattention/overactivity (teachers and parents) QoL: not reported AE: Pittsburgh Side Effect Rating Scale (counsellors, teachers, parents)
Administered two or more times daily					
Brown, 1985[41]	P	MPH (5–15 mg/day, b.d.) vs cognitive training (12 weeks, 24 sessions) – 30	6.3–11.8	6 months	Core: no hyp; CPRS; ACTRS QoL: not reported AE: not reported

ACTRS, Abbreviated Conners' Teacher Rating Scale; C, crossover trial (number of crossovers); CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; P, parallel trial.

TABLE 23 *Results for hyperactivity MPH low dose (≤ 15 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Scale	MPH low dose + non-drug: mean (SD)	Non-drug: mean (SD)	Mean difference
7–13 years				
Kupietz, 1988[71]	CTRS (hyperactivity)	0.3 mg/kg: 2.21 (0.53) 0.5 mg/kg: 2.04 (0.43)	2.89 (0.69)	MD (95% CI) –0.47 (–0.84 to –0.10) –0.76 (–1.06 to –0.46)

Lower scores represent a better behavioural outcome.
CTRS, Conners' Teacher Rating Scale.

examined MPH administered once daily and one examined MPH given two or more times daily.

Only Kupietz and colleagues[71] evaluated hyperactivity as an outcome measure using the CTRS (*Table 23*). In this parallel study, the non-drug intervention involved a one-to-one reading therapy programme during weeks 3–14 and weeks 16–27 of the study. While the results of these analyses are not clearly reported, the MD and 95% CI values show significant differences in favour of combined treatment.

Pelham and colleagues[81] did not report on hyperactivity or QoL outcomes, but did assess inattention/overactivity (using the IOWA Conners' Rating Scale as assessed by teachers and parents), and also other core outcomes (see Appendix 12). They reported that once-daily low-dose MPH (plus non-drug intervention) was better for inattention/overactivity than non-drug intervention ($p < 0.05$).

Brown and colleagues[41] examined MPH plus cognitive training compared with cognitive training alone. Outcome measures assessed included the CPRS and the Abbreviated CTRS. It appears that MPH plus cognitive training was more beneficial than cognitive training alone, although the significance of these comparisons was not clear.

Adverse events
One study presented data on adverse events.[81] Incidence of headache, stomach ache, insomnia and appetite loss did not differ significantly between treatment groups. Data on weight were not reported.

Summary
Only one study examined hyperactivity as an outcome measure,[71] with significant results in favour of combined treatment. No studies examined CGI. Another study examined adverse events,[81] but reported no differences between the treatment groups. The studies did not score very well in the quality assessment, and any results should be interpreted with caution.

MPH medium dose (15–30 mg/day) plus non-drug intervention versus non-drug intervention

Eleven studies evaluated medium-dose (15–30 mg/day) immediate-release MPH plus non-drug intervention compared with a non-drug intervention (*Table 24*; with additional information in Appendix 12). One of the studies examined medium-dose MPH administered once daily and 10 examined MPH administered two or more times daily.

Hyperactivity
Three studies reported on hyperactivity as an outcome, all of which used a Conners' scale (*Table 25*).[42,53,71] Brown and colleagues[42] also evaluated hyperactivity using the ACTeRS. Although all were parallel studies, the different types of Conners' scales (two reported results for teachers and one reported result for parents) and the lack of detailed statistical information precluded the studies from being combined in a meta-analysis.

Firestone and colleagues[53] reported that MPH plus parent training was superior to parent training alone. Similarly, Kupietz and colleagues[71] reported that MPH plus one-to-one reading therapy was significantly better than one-to-one therapy without medication. Brown and colleagues[42] did not present clear results for comparisons between MPH plus cognitive therapy compared with cognitive therapy; however, the MD and 95% CI values demonstrate significant differences in favour of combined treatment.

Two of the remaining eight studies measured overall behaviour using the Abbreviated CTRS,[77,78] and six evaluated inattention/overactivity using a IOWA Rating Scale.[69,79–82,88] A number of these studies were conducted by Pelham and colleagues and involved behaviour modification that took place over a Summer Treatment Programme (STP).[77–81] The results from direct comparisons between treatment groups were not always clearly presented in these studies (see Appendix 12 for more detail). One study by Pelham and colleagues[82] was conducted at home and in a Saturday school. In this study, MPH plus a behavioural programme was significantly better than the behavioural programme alone ($p < 0.001$).

Similarly, Smith and colleagues[88] evaluated medium-dose MPH plus behavioural treatment compared with behavioural treatment alone. They reported that a significant difference was observed between all comparisons at the $p < 0.05$ level, but no further detail was given. Lastly, in the study by Kolko and colleagues,[69] medium-dose MPH plus behaviour modification was reported to be better for scores on inattention/overactivity than behaviour modification alone (see Appendix 12).

Quality of life
No studies reported data on CGI. Pelham and colleagues[82] assessed global effectiveness as

TABLE 24 *MPH medium dose (15–30 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Kupietz, 1988[71]	P	MPH (0.7 mg/kg, o.d.) vs one-to-one reading therapy (6 months) – 58	7–13	6 months	Core: CTRS: hyperactivity QoL: not reported AE: not reported
Administered two or more times daily					
Brown, 1986[42]	P	MPH (20.08 mg/day, b.d.) vs cognitive therapy (11 weeks, 22 sessions) – 40	5.7–13.1	3 months	Core: CPRS: hyperactivity Index; ACTeRs: hyperactivity QoL: not reported AE: not reported
Firestone, 1986[53]	P	MPH (22 mg/day, b.d.) vs parent training (3 months) – 134	5–9	3 months	Core: CTRS: Hyperactivity Index QoL: not reported AE: not reported
Pelham, 1987[77]	C (3×)	MPH (20 mg/day, b.d.) vs behaviour modification (STP, 7 weeks) – 13	6.5–11	7	Core: no hyp; Abbreviated CTRS QoL: not reported AE: Side Effects Checklists (parents, teachers, counsellors)
Pelham, 1990[78]	C (5×)	MPH (20 mg/day, b.d.) vs behaviour modification (STP, 8 weeks) – 22	8.1–13.2	8	Core: no hyp; Abbreviated CTRS QoL: not reported AE: Side Effects Checklists (parents, teachers, counsellors)
Pelham, 1993[79]	C (3×)	MPH (16.2 mg/day, b.d.) vs behaviour modification (STP, 8 weeks) – 31	5.4–9.9	8	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Smith, 1998[88]	C (4×)	MPH (25 mg/day, t.d.s.) vs behavioural treatment (STP, 8 weeks) – 49	12–17	8	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: side-effects rating from 0 (not troubling) to 3 (severe) (counsellor, parents)
Pelham, 1999[81]	C (7×)	MPH (0.75 mg/kg/day, t.d.s,) – 21 MPH (0.90 mg/kg/day, t.d.s.) – 21	6–12	6	Core: no hyp; IOWA-C: inattention/overactivity (teachers and parents) QoL: not reported AE: Pittsburgh Side Effect Rating Scale (counsellors, teachers, parents)
Pelham, 1999[80]	C (5×)	MPH (20 mg/day, b.d.) – 26	5.8–12.7	6	Core: no hyp; IOWA-C: inattention/overactivity (teachers and parents) QoL: not reported AE: Side Effects Checklists (teachers, counsellors, parents)

continued

TABLE 24 *MPH medium dose (15–30 mg/day) plus non-drug intervention versus non-drug intervention (cont'd)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Kolko, 1999[69]	C (4×)	MPH (0.60 mg/kg/day, b.d.) vs behaviour modification (STP, 3 weeks) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: SSERS
Pelham, 2001[82]	C (3×)	MPH (15, 30 or 45 mg/day, t.d.s.) vs parent training, teacher consultation and point systems (3 weeks) – 70	6–12	3	Core: no hyp; IOWA-C: inattention/overactivity (teachers and parents) QoL: no CGI; global effectiveness (parent/teacher) AE: questions regarding adverse events, sleep quality, appetite and tics (parents) Spontaneous reports of adverse events

C, crossover trial (number of crossovers); CGI, Clinical Global Impression; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; P, parallel trial; STP, Summer Treatment Programme.

TABLE 25 *Results for hyperactivity [MPH medium dose (15–30 mg/day) plus non-drug intervention versus non-drug intervention]*

Study	Scale	MPH medium dose + non-drug: mean (SD)	Non-drug: mean (SD)	Mean difference
5–9 years				
Firestone, 1986[53]				MD (95% CI)
	CTRS (Hyperactivity Index)	0.89 (0.49)	1.37 (0.57)	–0.40 (–0.56 to –0.24)
5–13 years				
Brown, 1986[42]	CPRS (Hyperactivity Index)	13.78 (8.14)	21.10 (5.65)	–5.34 (–9.58 to –1.10)
	ACTeRS (hyperactivity)	14.33 (4.66)	19.60 (2.63)	–2.58 (–5.09 to –0.07)
7–13 years				
Kupietz, 1988[71]	CTRS (hyperactivity)	2.03 (0.64)	2.89 (0.69)	–0.64 (–0.93 to –0.35)

Lower scores represent a better behavioural outcome.
ACTeRS, ADD-H Comprehensive Teacher Rating Scale; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale.

assessed by parents and teachers. In this study, the non-drug intervention involved a behavioural programme incorporating parent training, teacher consultation and a point system. They observed significant differences in favour of the MPH plus non-drug intervention group ($p < 0.001$ for both parent and teacher ratings).

Adverse events
Of the 11 trials, six contributed data to the analysis of adverse events. Pelham[81] examined the tolerability of two medium doses of MPH, 0.75 and 0.90 mg/kg/day. No significant differences in the incidence of headache,[80–82,88] stomach ache[80–82,88] or insomnia[77,78,80–82,88] were detected between treatment phases in any trial reporting these outcomes. Participants in the Pelham[82] trial displayed significantly reduced appetite in the MPH treatment phase compared with the placebo phase (RR = 5.67; 95% CI 1.74 to 18.48). None of the other three trials[80,81,88] reporting this outcome detected differences in incidence. No study reported data on weight.

Summary
MPH plus non-drug interventions (one-to-one reading therapy, parent training and cognitive therapy) were found to be better than the non-drug intervention alone. None of the studies in this category evaluated CGI as a core outcome. No significant differences in the incidence of headache, stomach ache or insomnia were reported between treatment groups, although one study reported significantly reduced appetite in the MPH group. Overall, these studies did not score very well in the quality assessment, and any results should be interpreted with caution.

MPH high dose (>30 mg/day) plus non-drug intervention versus non-drug intervention

Seven trials (presented in eight papers) evaluated high-dose (>30 mg/day) immediate-release MPH plus non-drug intervention compared with a non-drug intervention (*Table 26*; with additional information in Appendix 12). All of these studies examined MPH administered two or more times daily.

The majority of studies in this category did not assess hyperactivity, but examined inattention/overactivity using a Conners' scale as a main outcome measure.[69,79,80,88] The results of comparisons between treatment groups were not clearly presented in most of these studies.

Hyperactivity
Three of the studies reported results on hyperactivity,[51,65,86] but one of them presented data in graphs only and was not included in *Table 27*.[51] The remaining two studies both assessed hyperactivity using Conners' scales and also other measures. In Schachar and colleagues' study,[86] the non-drug intervention was parent training or support, and in the Klein and Abikoff[65] study, the non-drug intervention involved parent and teacher education. These parallel studies both reported significant differences in favour of MPH plus non-drug intervention compared with non-drug intervention when assessed by teachers, but not when assessed by parents.

Quality of life
Elia and colleagues[51] assessed CGI as assessed by physicians. They reported that children receiving MPH plus a behaviour modification programme and a low monoamine diet had better behaviour than children in the non-drug intervention group ($p < 0.05$). In addition, Klein and Abikoff[65] evaluated Clinical Global Improvement as assessed by teachers, mothers and psychiatrists. After 8 weeks of treatment, the physicians rated 97% of children in the MPH plus parent and teacher education group to be improved compared with 50% in the non-drug intervention group.

Adverse events
Of the seven trials comparing a high dose of MPH plus a non-drug intervention with a non-drug intervention alone, three informed analysis of adverse events. Smith and colleagues[88] examined the tolerability of two high doses of MPH combined with a non-drug intervention – 50 and 75 mg daily. No differences in the incidence of headache[80,88] or stomach ache[80,88] were detected. Participants in Elia and colleagues' trial[51] suffered from loss of appetite and insomnia to a significantly greater extent in the MPH treatment phase of the trial (RR = 83.00; 95% CI 5.25 to 1311.65 and RR = 2.92; 95% CI 1.80 to 4.75, respectively). The remaining two trials did not detect differences in the incidence of insomnia or reduced appetite. Heterogeneity of results did not appear to be explained by participant age, outcome measurement or trial duration. Data on weight were not presented in any of the trials in this comparison group.

Summary
Two studies presented results for hyperactivity using different scales, including those of Conners.[65,86] In these studies, the non-drug interventions were parent training or support, and parent and teacher education, respectively. For both studies, the results were generally significant

TABLE 26 *MPH high dose (>30 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Elia, 1991[51]	C (3×)	MPH (25–90 mg/day, b.d.) vs behaviour modification + diet (9 weeks) – 48	6–12	9	Core: results presented in graphs only QoL: CGI (physician); C-GAS AE: STESS (physician, parents) Children's Psychiatric Rating Scale: nervous mannerisms, obsessive thinking
Pelham, 1993[79]	C (3×)	MPH (32 mg/day, b.d.) vs behavioural modification (STP, 8 weeks) – 31	5.4–9.9	8	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: not reported
Schachar, 1997[86] and Diamond, 1999[87]	P	MPH (31.4 mg/day, b.d.) vs parent training or parent support (4 months) – 91	6–12	4 months	Core: IOWA-C: hyperactivity (parent); IOWA-C: hyperactivity–inattentiveness (teacher); TIP: hyperactivity–impulsiveness (teacher and parent) QoL: not reported AE: Barkley 10-point scale: physiological, affective, overfocus, tics (parents, teachers)
Klein, 1997[65]	P	MPH (1.48 mg/kg/day, b.d.?) vs BI + parent and teacher education (4 weeks) – 86	6–12	12	Core: CTRS/CPRS: hyperactivity; Home Hyperactivity Scale (parents) QoL: CGI (teacher/mothers/psychiatrists) AE: not reported
Smith, 1998[88]	C (4×)	MPH (50 mg/day, t.d.s.) vs behavioural treatment (STP, 8 weeks) – 49 MPH (75 mg/day MPH) behavioural treatment (STP, 8 weeks) – 49	12–17	8	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: side-effects rating from 0 (not troubling) to 3 (severe) (counsellor, parents)
Kolko, 1999[69]	C (4×)	MPH (1.2 mg/kg/day, b.d.) vs behaviour modification (STP, 3 weeks) – 22	7–13	6	Core: no hyp; IOWA CTRS: inattention/overactivity QoL: not reported AE: SSERS
Pelham, 1999[80]	C (5×)	MPH (35 mg/day, b.d.) – 26	5.8–12.7	6	Core: no hyp; IOWA-C: inattention/overactivity (teachers and parents) QoL: not reported AE: Side Effects Checklist (teachers, counsellors, parents)

C, crossover trial (number of crossovers); C-GAS, Children's Global Assessment Scale; CGI, Clinical Global Impression; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; IOWA-C, IOWA Conners' Rating Scale; P, parallel trial; SSERS, Stimulant Drug Side Effects Rating Scale; TIP, Telephone Interview Probe.

TABLE 27 *Results for hyperactivity [MPH high dose (>30 mg/day) plus non-drug intervention versus non-drug intervention]*

Study	Scale	MPH high dose + non-drug: mean (SD)	Non-drug: mean (SD)	Mean difference
6–12 years				
Schachar, 1997[86]				MD (95% CI)
	IOWA-C (hyperactivity) (parents)	1.2 (0.7)	1.3 (0.7)	–0.10 (–0.33 to 0.13)
	IOWA-C (hyperactivity–inattentiveness) (teachers)	0.9 (0.7)	1.7 (0.7)	–0.80 (–1.05 to –0.55)
	TIP (hyperactivity–impulsiveness) (teachers)	0.8 (0.7)	1.3 (1.1)	–0.90 (–1.29 to –0.51)
	TIP (hyperactivity–impulsiveness) (parents)	1.2 (1.1)	0.9 (0.9)	0.20 (–0.22 to 0.62)
Klein, 1997[65]	CTRS (hyperactivity)	0.8 (0.4)	1.5 (0.6)	–0.70 (–0.84 to –0.56)
	CPRS (hyperactivity)	0.6 (0.3)	0.8 (0.4)	0.20 (0.11 to 0.29)
	Home Hyperactivity Scale (parents)	1.8 (0.51)	2.4 (0.86)	0.20 (–0.15 to 0.55)

Lower scores represent a better behavioural outcome.
CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; TIP, Telephone Interview Probe.

TABLE 28 *ER-MPH low dose (≤ 20 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Pelham, 1987[77]	C (3×)	Sustained-release MPH (Slow Release Ritalin, SR-20) (20 mg/day, o.d.) vs behaviour modification (STP, 7 weeks) – 13	6.5–11	7	Core: no hyp; Abbreviated Conners' Rating Scale (teacher rating) QoL: not reported AE: Side Effects Checklists (parents, teachers, counsellors)
Pelham, 1990[78]	C (5×)	Sustained-release MPH (Slow Release Ritalin, SR-20) (20 mg/day, o.d.) vs behaviour modification (STP, 8 weeks) – 22	8.1–13.2	8	Core: no hyp; Abbreviated Conners' Rating Scale (teachers and counsellors) QoL: not reported AE: Side Effects Checklists (parents, teachers, counsellors)

C, crossover trial (number of crossovers); STP, Summer Treatment Programme.

(in favour of the MPH group) when assessed by teachers and non-significant when assessed by parents. One study reported results for CGI[51] and one measured Clinical Global Improvement.[65] Both studies reported that children receiving MPH in addition to a behavioural modification programme, or parent and teacher education, showed improvement compared with children receiving only non-drug treatments. Regarding adverse events, no differences were observed between treatment groups for headache or stomach ache. One study reported a higher incidence of loss of appetite and insomnia in the MPH group, whereas the other two did not. However, these studies did not score very well in the quality assessment, and any results should be interpreted with caution.

ER-MPH low dose (≤20 mg/day) plus non-drug intervention versus non-drug intervention

Two studies evaluated low-dose (≤ 20 mg/day) ER-MPH plus non-drug intervention compared with a non-drug intervention (*Table 28*; with additional information in Appendix 12).[77,78] Both studies were crossover trials conducted by Pelham and colleagues that examined the effectiveness of ER-MPH in association with a behaviour modification programme. Neither reported hyperactivity as a core outcome measure, but both measured behaviour using the Abbreviated Conners' Rating Scale as measured by teachers (and counsellors). Only one significant result was reported: Pelham and colleagues[78] found behaviour was improved in children receiving ER-MPH plus behaviour modification in comparison with children receiving only behaviour modification ($p < 0.05$) when assessed by counsellors.

Adverse events

Neither study displayed significant differences between treatments in the incidence of insomnia. Data regarding other adverse events or weight were not adequately reported to be included in the analysis.

Summary

No studies in this category measured hyperactivity or CGI as outcome measures. Only data on insomnia could be evaluated, and no differences were observed between treatment groups. These studies did not score very well in the quality assessment, and the results should be interpreted with caution.

ER-MPH medium dose (20–40 mg/day) plus non-drug intervention versus non-drug intervention

Only one study evaluated medium-dose (20–40 mg/day) extended-release MPH plus non-drug intervention compared with a non-drug intervention (*Table 29*; with additional information in Appendix 12). In this crossover trial, the non-drug intervention involved a behavioural programme incorporating parent training, teacher consultation and a point system.[82] One of the main outcomes examined was inattention/overactivity as measured using the IOWA-C. Behaviour was significantly improved in the combined treatment group compared with the non-drug intervention group when assessed by teachers, parents and counsellors (see Appendix 12).

Although Pelham and colleagues[82] did not examine CGI, they did measure global effectiveness (as assessed by parents and teachers). They observed that consistently higher percentages of children rated better in the combined treatment compared with the non-

TABLE 29 *ER-MPH medium dose (20–40 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Pelham, 2001[82]	C (3×)	OROS MPH (Concerta) (18, 36 or 54 mg/day, o.d.) vs parent training, teacher consultation and point systems (3 weeks) – 70	6–12	3	Core: no hyp; IOWA-C (inattention/overactivity) (teacher, parent, counsellor) QoL: no CGI; global effectiveness (parent/teacher) AE: questions regarding adverse events, sleep quality, appetite, and tics (parents) plus spontaneous reporting

C, crossover trial (number of crossovers); CGI, Clinical Global Impression.

TABLE 30 *DEX medium dose (10–20 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Conners, 1972[45]	P	DEX (20 mg/day, b.d.) – 28	6–12	8	Core: symptom checklist: hyperactivity; parent questionnaire: hyperactivity QoL: CGI AE: no specific scale reported
Gillberg, 1997[56]	P	DEX (17 mg/day, b.d.) – 32	6–11	15 months	Core: CPRS: impulsivity/ hyperactivity; CTRS: hyperactivity QoL: no CGI AE: incidence of 20 adverse events; weight

P, parallel, trial; CPRS, Conners' Parent Rating Scale; CGI, Clinical Global Impression.

TABLE 31 *Results for hyperactivity [DEX medium dose (10–20 mg/day) versus placebo]*

Study	Scale	DEX medium dose: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported)[a]
6–12 years				
Conners, 1972[45]	Symptom checklist (hyperactivity)	6.2 (SD not reported)	13.3 (SD not reported)	S – NR
	Parent questionnaire (hyperactivity)	10.6	13.4	NS

[a] Note that owing to the overall poor reporting of study methodology, *p*-Values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
NS, not significant; S – NR, significant (value not reported).

intervention group ($p < 0.001$ for parent and teacher scores) (see Appendix 12).

Adverse events

Participants suffered from a significantly greater loss of appetite in the MPH group compared with placebo (RR = 4.33; 95% CI 1.29 to 14.54). Differences in the incidence of headache, stomach ache or insomnia were not detected. Data on weight were not reported.

Summary

No studies in this category measured hyperactivity or CGI as outcome measures. Of the four adverse events, only loss of appetite was observed to be significantly greater in the MPH group than in the placebo group. This study did not score very well in the quality assessement, and the results should be interpreted with caution.

DEX versus placebo

DEX medium dose (10–20 mg/day) versus placebo

Two studies evaluated medium-dose (10–20 mg/day) DEX compared with placebo (*Table 30*; with additional information in Appendix 12). In both studies, DEX was administered twice per day and evaluated using a parallel design.

Hyperactivity

Both studies examined hyperactivity as one of the core outcome measures. However, Gillberg and colleagues[56] presented their results in graph form only, and their results could not be included in *Table 31*. Conners and colleagues[45] reported a significant difference between DEX and placebo when using a symptom checklist, but not when measured using the parent questionnaire.

TABLE 32 *DEX high dose (>20 mg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Arnold, 1976[36]	C (3×)	DEX (mean 21.75 mg/day, o.d.?) – 31	4.6–12	12	Core: Parents' Behaviour Checklist: hyperactivity; Conners' Teachers' Behaviour Checklist: hyperactivity QoL: global ratings (clinicians) AE: Parents' Behaviour Checklist: somatic complaints; Conners' Teachers' Behaviour Checklist: lack of health; weight
Conrad, 1971[47]	P	DEX (10–20 mg/day, o.d.?) – 17	4–6	4–6 months	Core: no hyp; behaviour ratings (teacher and parent) QoL: not reported AE: not reported
Administered two or more times daily					
Greenberg, 1972[58]	P	DEX (mean 25 mg/day, b.d.) – 17	6.5–11	8	Core: not reported QoL: not reported AE: incidence of side-effects

C, crossover trial (number of crossovers); P, parallel trial.

Quality of life
Conners and colleagues[45] evaluated Clinical Global Improvement as measured by a clinician. The authors reported that after 8 weeks, 33% were much improved in the DEX group compared with 9% in the placebo group.

Adverse events
No significant differences in the incidence of headache, loss of appetite, stomach ache or insomnia were detected between participants of the trial adequately reporting these outcomes.[56] Data on weight were not reported separately for those on DEX versus those on placebo.

Summary
One study presented reproducible results for hyperactivity.[45] In this study, the results were significant when assessed using the symptom checklist, but not when assessed using the parent questionnaire. This study also reported on Clinical Global Improvement, and reported that children in the DEX group were more often improved compared with the placebo group. No significant differences in the incidence of headache, loss of appetite, stomach ache or insomnia were reported in the one study that presented data on these adverse events.[56] The studies did not score very well in the quality assessment, and the results should be interpreted with caution.

DEX high dose (>20 mg/day) versus placebo
Three studies evaluated high dose (>20 mg/day) DEX compared with placebo (*Table 32*; with additional information in Appendix 12). Of these, two appeared to have examined DEX administered once daily and one examined DEX administered twice per day.

Only one of the studies evaluated hyperactivity as a core outcome, using a number of different scales.[36] In this study, children in the DEX group had consistently better scores than children in the placebo group; however, the authors did not report results for any statistical comparisons (see *Table 33*). Another study reported on behaviour ratings as assessed by teachers and parents[47] (see Appendix 12) and the final study reported only on adverse events (discussed separately below).[58]

Quality of life
Arnold and colleagues[36] reported on global ratings as assessed by clinicians. They reported that children in the DEX group rated better than those in the placebo group ($p < 0.01$).

Adverse events
Of the three trials comparing a high dose of DEX with placebo, one reported adequate data for the analysis of adverse events.[58] In this trial, participants assigned to DEX suffered from loss of

TABLE 33 *Results for hyperactivity [DEX high dose (>20 mg/day) versus placebo]*

Study	Scale	DEX high dose: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported)
4–12 years				
Arnold, 1976[36]	Parents' Behaviour Checklist (hyperactivity)	16.68 (6.59)	20.81 (6.83)	NR
	Conners' Teachers Behaviour Checklist (hyperactivity)	16.80 (5.54)	21.27 (5.63)	NR
	Davids' Hyperkinetic Rating Scale (hyperactivity)			
	(parents)	3.97 (1.40)	4.58 (1.26)	NR
	(teachers)	3.70 (1.49)	4.90 (1.30)	NR

Lower scores represent a better behavioural outcome.
NR, not reported.

TABLE 34 *DEX-TR versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (months)	Core outcomes
Administered once daily					
Arnold, 1989[38]	C (3×)	DEX-TR (10–15 mg/day, o.d.) – 18	6–12	3	Core: CTRS Hyperactivity Index QoL: global ratings (psychiatrist) AE: weight

C, crossover trial (number of crossovers); CTRS, Conners' Teacher Rating Scale.

appetite to a significantly greater extent than those assigned to placebo (RR = 3.82; 95% CI 1.08 to 13.58). Participants did not, however, suffer from headache, stomach ache or insomnia significantly more often when assigned to DEX. Data on weight were inadequately reported.

Summary

One study that evaluated hyperactivity reported that children in the DEX group had improved behaviour compared with the placebo group.[36] However, no statistical analyses were presented. The same study presented results for global ratings (as assessed by clinicians) and reported improvements with medication. Generally, this study rated well in the quality assessement, whereas the other studies did not score very well. One of these other studies reported usable data on adverse events.[58] Loss of appetite was significantly greater in the DEX group compared with placebo, but this was not observed for headache, stomach ache or insomnia.

DEX-TR versus placebo

One study evaluated 10–15 mg/day time-release DEX (DEX-TR) administered once daily (*Table 34*; with additional information in Appendix 12).

Hyperactivity

Arnold and colleagues[38] reported that DEX time-release capsules were significantly better than placebo using the Hyperactivity Index of the CTRS (*Table 35*).

Quality of life

Arnold and colleagues[38] also reported that global ratings, as assessed by a psychiatrist, were improved in the treatment group compared with the placebo group ($p < 0.05$) (see Appendix 12).

Adverse events

Data on weight were not adequately presented in this trial.

Summary

One study evaluated DEX-TR compared with placebo.[38] This study reported significant improvements in the treatment group compared with the placebo group for both hyperactivity and psychiatrist-assessed global ratings. Owing to the poor reporting of some methodological criteria, the results from this study should be interpreted with caution.

TABLE 35 *Results for hyperactivity (DEX-TR versus placebo)*

Study	Scale	DEX-TR: mean (SD)	Placebo: mean (SD)	*p*-Value (if reported)[a]
6–12 years				
Arnold, 1989[38]	CTRS (Hyperactivity Index)	1.39 (0.76)	2.10 (0.47)	<0.05

[a] Note that owing to poor reporting for some aspects of the study methodology, *p*-Values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
CTRS, Conners' Teacher Rating Scale.

TABLE 36 *DEX medium dose (10–20 mg/day) plus non-drug intervention versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (months)	Core outcomes
Administered once daily					
Conrad, 1971[47]	P	DEX (10–20 mg/day, o.d.?) plus prescriptive tutoring – 17	4–6	4–6	Core: no hyp; behaviour ratings (teacher, parent) QoL: not reported AE: not reported

P, parallel trial.

TABLE 37 *DEX high dose (>20 mg/day) versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (months)	Core outcomes
Administered once daily					
Conrad, 1971[47]	P	DEX (10–20 mg/day, o.d.?) vs prescriptive tutoring – 17	4–6	4–6	Core: no hyp; behaviour ratings (teacher, parent) QoL: not reported AE: not reported

P, parallel trial.

DEX medium dose (10–20 mg/day) plus non-drug intervention versus placebo

One study evaluated medium-dose (10–20 mg/day) DEX plus non-drug intervention compared with placebo (*Table 36*; with additional information in Appendix 12). In this study, DEX was administered once daily, and the intervention involved tutoring sessions twice per week. Conrad and colleagues[47] did not evaluate hyperactivity or CGI, but did report on behaviour ratings by teachers and parents. The authors reported improvements in the combined treatment group compared with placebo (see Appendix 12).

Summary

No studies in this category measured hyperactivity, CGI or adverse events as outcome measures.

DEX versus non-drug intervention

DEX high dose (>20 mg/day) versus non-drug intervention

One study evaluated high-dose (>20 mg/day) DEX compared with a non-drug intervention (*Table 37*; with additional information in Appendix 12). As presented above, this intervention involved tutoring sessions twice per week. Conrad and colleagues[47] did not evaluate hyperactivity or CGI, but reported on behaviour ratings by teachers and parents. The authors reported greater improvements in the treatment group than in the tutoring group, but the two groups were not directly compared (see Appendix 12).

TABLE 38 *DEX medium dose (10–20 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Conrad, 1971[47]	P	DEX (10–20 mg/day, o.d.?) vs prescriptive tutoring – 17	4–6	4–6	Core: no hyp; behaviour ratings (teacher, parent) QoL: not reported AE: not reported
Administered once weekly					
James, 2001[62]	C (4×)	DEX (5–30 mg/kg once per week for 2 weeks) vs formal academic instruction (a.m.) and therapeutic recreation (p.m.) (full time, 10 weeks) – 35	6.9–12.2	10	Core: CTRS: hyperactivity; Children's Psychiatric Rating Scale: hyperactivity (recreation therapist rated); CPRS: hyperactivity QoL: not reported AE: Stimulant Side Effect Rating Scale (nurse); Barkley Side Effect Rating Scale (parent); weight

C, Crossover trial (number of crossovers); CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; P, parallel trial.

TABLE 39 *Results for hyperactivity [DEX medium dose (10–20 mg/day) plus non-drug intervention versus non-drug intervention]*

Study	Scale	DEX medium dose + non-drug: mean (SD)	Non-drug: mean (SD)	*p*-Value (if reported)[a]
6–12 years				
James, 2001[62]	CTRS (hyperactivity)	50.5 (5.4)	63.1 (12.6)	S – NR
	Children's Psychiatric Rating Scale (hyperactivity)	2.5 (1.1)	3.8 (1.1)	<0.001
	CPRS (hyperactivity)	60.5 (14.7)	68.0 (14.5)	0.053

[a] Note that owing to poor reporting for some aspects of the study methodology, *p*-values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
S – NR, significant (value not reported); CTRS, Conners' Teacher Rating Scale; CPRS, Conners' Parent Rating Scale.

Summary
No studies in this category measured hyperactivity, CGI or adverse events as outcome measures.

DEX medium dose (10–20 mg/day) plus non-drug intervention versus non-drug intervention

Two studies evaluated medium-dose (10–20 mg/day) DEX plus non-drug intervention compared with a non-drug intervention (*Table 38*; with additional information in Appendix 12). The study by Conrad and colleagues[47] did not report on hyperactivity, CGI or adverse events; however, they did report on behavioural ratings (see Appendix 12).

Hyperactivity
James and colleagues[62] evaluated hyperactivity using three different scales. In this crossover study, immediate-release DEX was administered once weekly in addition to formal academic instruction and therapeutic recreation (e.g. sports, art therapy, structured social skills sessions). James and colleagues[62] observed significant results in favour of combined treatment when hyperactivity was measured using the CTRS and the Children's Psychiatric Rating Scale, but not when measured using the CPRS (*Table 39*). This study did not examine CGI as an outcome measure.

Adverse events
No data reported in James and colleagues' trial[62] could usefully contribute to the analysis of adverse events.

Summary
Only one study in this category examined hyperactivity as an outcome.[62] In this study, children who received DEX in combination with academic instruction and therapeutic recreation had better behaviour than those in the non-intervention group when assessed using the CTRS and the Children's Psychiatric Rating Scale, but not when assessed using the CPRS. No studies in this category evaluated CGI. Owing to the poor reporting of some methodological criteria, the results from this study should be interpreted with caution.

DEX high dose (>20 mg/day) plus non-drug intervention versus non-drug intervention

One study evaluated high-dose (>20 mg/day) DEX plus non-drug intervention compared with a non-drug intervention (*Table 40*; with additional information in Appendix 12). In this crossover study, drug treatment was combined with a multidisciplinary behaviour modification programme and low monoamine diet. Although the authors evaluated hyperactivity and CGI (with results favouring the combined treatment group), data were presented in graph form only and could not be reproduced.

Adverse events
A significantly higher incidence of reduced appetite and insomnia was detected during the active drug phase of this trial (RR = 93.00; 95% CI 5.90 to 1467.03 and RR = 3.00; 95% CI 1.85 to 4.87, respectively). Data on headache, stomach ache or weight were not reported.

Summary
No studies in this category reported reproducible data on hyperactivity or CGI. The one study in this category reported significantly greater incidence of loss of appetite and insomnia in the combined treatment group.

DEX-SR plus non-drug intervention versus non-drug intervention

Two studies examined sustained-release DEX (DEX-SR) plus non-drug intervention compared with a non-drug intervention (*Table 41*; with additional information in Appendix 12). In the study by Pelham and colleagues 1990,[78] hyperactivity was not assessed, although the authors did evaluate behaviour using the Abbreviated CTRS. They reported that behaviour was improved in the combined treatment group compared with the behaviour modification group ($p < 0.050$). This study also reported data on adverse events (see below).

In addition to evaluating immediate-release DEX, James and colleagues[62] examined DEX-SR administered once weekly in combination with formal academic instruction and therapeutic recreation. Hyperactivity was improved in the combined treatment group compared with the non-drug treatment group when assessed using the Children's Psychiatric Rating Scale and the CPRS. Statistical comparisons for the CTRS were not reported (*Table 42*). This study did not examine CGI as an outcome measure.

Adverse events
Of the two trials comparing DEX-SR and non-drug intervention with a non-drug intervention alone, one provided adequate data regarding the adverse events of interest.[78] Differences in the incidence of insomnia were not found between treatment phases. Incidence of headache, stomach ache or loss of appetite was not rated by patients or parents. Neither study reported data on weight.

Summary
Of the two studies included in this category, one evaluated hyperactivity as an outcome measure.[62] In this study, DEX-SR in combination with formal academic instruction and therapeutic recreation

TABLE 40 *DEX high dose (>20 mg/day) plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times a day					
Elia, 1991[51]	C (3×)	DEX (mean 10–45 mg/day, b.d.) vs multidisciplinary behaviour modification programme and diet (twice daily, 11 weeks) – 48	6–12	9	Core: CTRS: hyperactivity; CPQ: hyperactivity QoL: CGI (physician); C-GAS AE: STESS (physician, parents)

C, crossover trial (number of crossovers); C-GAS, Children's Global Assessment Scale; CGI, Clinical Global Impression; CPQ, Conners' Parent Questionnaire; CTRS, Conners' Teacher Rating Scale; STESS, Subject Treatment Emergent Symptom Scale.

TABLE 41 *DEX-SR plus non-drug intervention versus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Pelham, 1990[78]	C (5×)	DEX-SR (10 mg/day, o.d.) vs broad spectrum behaviour modification intervention (STP, 8 weeks) – 22	8.1–13.2	6.5	Core: no hyp; Abbreviated CTRS QoL: not reported AE: Side Effects Checklists (parents/teachers/counsellors)
Administered once weekly					
James, 2001[62]	C (4×)	DEX-SR (5–30 mg/kg in two doses, once per week) vs formal academic instruction (a.m.) and therapeutic recreation (p.m.) (full time, 10 weeks) – 35	6.9–12.2	10	Core: CTRS: hyperactivity; Children's Psychiatric Rating Scale: hyperactivity (recreation therapist rated); CPRS: hyperactivity QoL: not reported AE: Stimulant Side Effect Rating Scale (nurse); Barkley Side Effect Rating Scale (parent); weight

C, crossover trial (number of crossovers); CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale.

TABLE 42 *Results for hyperactivity (DEX-SR plus non-drug intervention versus non-drug intervention)*

Study	Scale	DEX medium dose + non-drug: mean (SD)	Non-drug: mean (SD)	*p*-Value (if reported)[a]
6–12 years				
James, 2001[62]	CTRS (Hyperactivity)	53.7 (9.1)	63.1 (12.6)	NR
	Children's Psychiatric Rating Scale (hyperactivity)	2.3 (1.0)	3.8 (1.1)	<0.001
	CPRS (hyperactivity)	60 (15.6)	68.0 (14.5)	<0.007

[a] Note that owing to poor reporting for some aspects of the study methodology, *p*-Values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; NR, not reported.

resulted in improved behaviour compared with non-drug intervention alone. Owing to the poor reporting of some methodological criteria, the results from this study should be interpreted with caution. The other study reported on adverse events of interest.[78] In this study, no significant differences in the incidence of insomnia were observed. Neither study assessed CGI.

ATX versus placebo

ATX low/medium dose (<1.5 mg/kg/day) versus placebo

Three parallel studies evaluated low/medium-dose (<1.5 mg/kg/day) ATX compared with placebo (*Table 43*; with additional information in Appendix 12).

Hyperactivity

All three studies examined hyperactivity/impulsivity using the ADHD Rating Scale (*Table 44*). One study also evaluated hyperactivity using the Conners' Parent Rating Scale – Revised (CPRS-R).[73] The results from these studies were statistically significant in favour of the drug treatment group, with one exception. Michelson and colleagues[73] observed no difference between ATX (0.5 mg/kg/day) and placebo when assessed using the ADHD Rating Scale. The studies were not pooled; however, given that all used the same scale and were parallel studies, mean differences were calculated and are presented in *Figure 15*.

TABLE 43 *ATX low/medium dose (< 1.5 mg/kg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Michelson, 2002[74]	P	ATX (1.0–1.5 mg/kg/day, o.d.) – 171	6–16	6	Core: ADHD-RS-IV: hyperactive/impulsive QoL: CGI AE: 16 types of adverse effects reported assessed by open-ended questioning; weight
Kelsey, 2004[63]	P	ATX (mean 1.3 mg/kg/day, o.d.) – 197	6–12	8	Core: ADHD-RS: hyperactive/impulsive QoL: CGI AE: open-ended questioning
Administered twice daily					
Michelson, 2001[73]	P	ATX (max. 0.5 mg/kg/day, b.d.) – 297 ATX (max. 1.2 mg/kg/day, b.d.) – 297	8–18	8	Core: CPRS-R: hyperactive; ADHD-RS-IV: hyperactive/impulsive QoL: CGI AE: open-ended questioning; weight

ADHD-RS-IV, Attention Deficit/Hyperactivity Disorder Rating Scale IV – Parent Version: investigator-administered and scored; CGI, Clinical Global Impression; CPRS-R, Conners' Parent Rating Scale – Revised; P, parallel trial.

TABLE 44 *Results for hyperactivity [ATX low/medium dose (< 1.5 mg/kg/day) versus placebo]*

Study	Scale	ATX low/medium dose: mean (SD)	Placebo: mean (SD)	Mean difference[a]
6–12 years				
Kelsey, 2004[63]	ADHD-RS (hyperactive/impulsive)	11.0 (7.7)	16.3 (7.5)	MD (95% CI) See *Figure 15*
6–16 years				
Michelson, 2002[74]	ADHD-RS-IV (hyperactive/impulsive)	Baseline/change from baseline 15.7 (8.0)/–5.7 (6.8)	Baseline/change from baseline 15.3 (7.1)/–2.1 (5.7)	See *Figure 15*
8–18 years				
Michelson, 2001[73]	ADHD-RS-IV (hyperactive/impulsive)	Baseline/change from baseline ATX 0.5: 17.8 (7.4)/–4.8 (7.9) ATX 1.2: 16.9 (7.1)/–6.6 (7.1)	Baseline/change from baseline 16.9 (6.6)/–3.2 (5.6)	See *Figure 15* See *Figure 15*
	CPRS-R (hyperactivity)	ATX 0.5: 12.0 (4.8)/–4.1 (4.4) ATX 1.2: 10.2 (5.1)/–4.1 (4.9)	10.3 (4.9)/–1.1 (3.9)	–3.00 (–4.73 to –1.27) –3.00 (–4.47 to –1.53)

[a] **[Confidential information removed]**.
Lower scores represent a better behavioural outcome.
ADHD-RS-IV, Attention Deficit/Hyperactivity Disorder Rating Scale IV – Parent Version: investigator-administered and scored; CPRS-R, Conners' Parent Rating Scale – Revised.

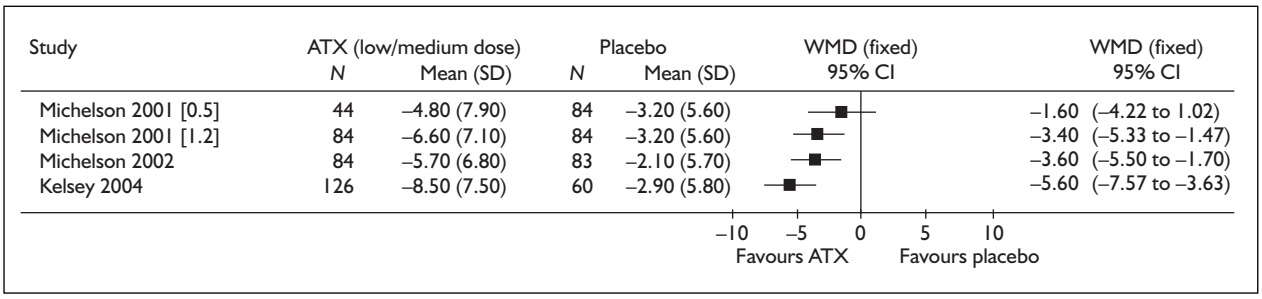

FIGURE 15 *Mean differences: ATX (low/medium dose) versus placebo*

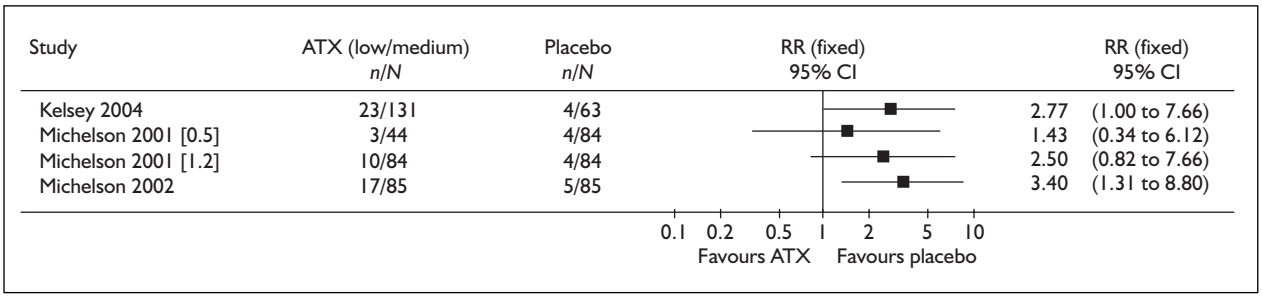

FIGURE 16 *Relative risks of loss of appetite: ATX (low/medium dose) versus placebo*

Quality of life

All three studies reported CGI severity as an outcome measure. Michelson and colleagues[74] and Kelsey and colleagues[63] both reported improvements in the ATX group compared with placebo ($p < 0.001$ and $p < 0.05$, respectively). Michelson and colleagues[73] observed a significant difference when 1.2 mg/kg/day was administered ($p = 0.002$), but not when 0.5 mg/kg/day was administered.

Adverse events

All studies in this category contributed to the analysis of adverse events. No significant differences were detected between treatment groups in the incidence of headache,[63,73,74] stomach ache[63,73,74] or insomnia.[73] However, participants in the ATX treatment groups displayed significant reductions in appetite in two of the three trials (*Figure 16*).

In the one trial that reported weight data,[73] a significantly different mean change was detected in the 0.5 and 1.2 mg/kg/day ATX treatment groups compared with placebo (RR = -–1.40; 95% CI –1.88 to –0.92 and RR = –2.10; 95% CI –2.56 to –1.64, respectively). The 0.5 mg/kg/day group increased in overall mean weight to a lesser degree than the placebo group; the 1.2 mg/kg/day group decreased in overall mean weight.

Summary

Three studies in this category examined hyperactivity and CGI,[63,73,74] with almost all results favouring ATX over placebo. However, the lowest dose of ATX examined (0.5 mg/kg/day) did not significantly improve behaviour when measured using the ADHD Rating Scale or CGI.[73] No differences were observed between treatment groups in the incidence of headache, stomach ache or insomnia, whereas there was some evidence for a reduction in appetite with ATX. Whereas two of the studies did not score very well in the quality assessement, the study by Michelson and colleagues[73] was deemed to be of good quality. Hence the results from this study are likely to be reliable.

ATX high dose (≥1.5 mg/kg/day) versus placebo

Six trials (published in five papers) evaluated high-dose (≥1.5 mg/kg/day) ATX compared with placebo (*Table 45*; with additional information in Appendix 12). Five trials used a parallel design and, with the exception of one study,[95] all evaluated hyperactivity and CGI. The study by Wernicke and colleagues[95] did evaluate ADHD Rating Scale Total Score and reported significant improvements in the ATX group compared with placebo (see Appendix 12).

TABLE 45 *ATX high dose (≥ 1.5 mg/kg/day) versus placebo*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Weiss, 2004[94]	P	ATX (max. 1.8 mg/kg/day, o.d.) – 153	8–12	7	Core: ADHD-RS-IV – Teacher: Inv: hyperactive/impulsive; CPRS-R: hyperactivity QoL: CGI (teacher/investigator) AE: open-ended discussion
Administered twice daily					
Michelson, 2001[73]	P	ATX (max. 1.8 mg/kg/day, b.d.) – 297	8–18	8	Core: CPRS-R: hyperactive; ADHD-RS-IV–Parent: Inv hyperactivity/impulsivity QoL: CGI AE: open-ended questioning; weight
Spencer, 2002[89]	P	ATX (max. 2.0 mg/kg/day, b.d.) – 147	7–13	9	Core: ADHD-RS: hyperactive/impulsive QoL: CGI AE: Unsolicited adverse events
Spencer, 2002[89]	P	ATX (max. 2.0 mg/kg/day, b.d.) – 144	7–13	9	Core: ADHD-RS: hyperactive/impulsive QoL: CGI AE: Unsolicited adverse events
Michelson, 2004[75]	P	ATX (mean 1.56 mg/kg/day, b.d.) – 416	6–15	9 months	Core: ADHD-RS: hyperactive/impulsive; CPRS/CTRS: hyperactivity QoL: CGI AE: Some adverse events reported
Wernicke, 2004[95]	P	ATX (max. 2.0 mg/kg/day, b.d.) – 194	7–12	9	Core: no hyp; ADHD-RS: total score QoL: not reported AE: Berkley Behaviour and Adverse Events Questionnaire – Modified; open-ended questions

ADHD-RS-IV, Attention Deficit/Hyperactivity Disorder Rating Scale IV–Parent (or Teacher) Version: investigator-administered and scored; CGI, Clinical Global Impression; CPRS, Conners' Parent Rating Scale; CPRS-R, Conners' Parent Rating Scale – Revised; CTRS, Conners' Teacher Rating Scale; P, parallel trial.

Hyperactivity

Five trials (published in four papers) evaluated hyperactivity/impulsivity using the ADHD Rating Scale (*Table 46*). Three of these studies also used a Conners' scale to measure hyperactivity.[73,75,94] All results were significantly in favour of ATX, except when the CTRS was used in the study by Michelson and colleagues.[75] The mean differences for ADHD Rating Scale are presented for each of the five studies in *Figure 17*.

Quality of life

Weiss and colleagues[94] presented results for CGI Severity and Clinical Global Improvement. For both measures, children in the ATX group had better behaviour than children in the placebo group ($p < 0.001$). Similar results were observed in the study by Michelson and colleagues[73] (CGI ADHD Severity: $p < 0.05$), Spencer and colleagues[89] (CGI ADHD Severity: $p = 0.003$) and Michelson and colleagues[75] (CGI Severity: $p = 0.003$).

TABLE 46 *Results for hyperactivity [ATX high dose (≥ 1.5 mg/kg/day) versus placebo]*

Study	Scale	ATX high dose: mean (SD)	Placebo: mean (SD)	Mean difference[a]
6–15 years				
Michelson, 2004[75]		Baseline/change from baseline	Baseline/change from baseline	MD (95% CI)
	ADHD-RS-IV (hyperactive/impulsive)	7.2 (5.5)/3.1 (7.0)	7.1 (5.5)/5.9 (7.4)	See *Figure 17*
	CPRS (hyperactivity)	4.5 (3.8)/1.5 (4.7)	4.6 (4.2)/3.1 (4.9)	–1.60 (–2.62 to –0.58)
	CTRS (hyperactivity)	7.7 (5.1)/0.4 (5.2)	8.1 (5.5)/1.4 (4.6)	–1.00 (–2.15 to 0.15)
7–13 years				
Spencer, 2002[89]	ADHD-RS (hyperactive/impulsive)	19.3 (6.1)/–8.0 (7.4)	19.2 (5.5)/–2.5 (5.9)	See *Figure 17*
Spencer, 2002[89]	ADHD-RS (hyperactive/impulsive)	16.8 (6.5)/–6.9 (6.6)	16.5 (6.1)/–2.9 (7.1)	See *Figure 17*
8–12 years				
Weiss, 2004[94]	ADHD-RS-IV–Teacher: Inv: (hyperactive/impulsive) CPRS-R (hyperactivity) subscale mean score (SD)	**[Confidential information removed]**		
8–18 years				
Michelson, 2001[73]	ADHD-RS-IV (hyperactive/impulsive)	17.6 (6.2)/–6.7 (7.5)	16.9 (6.6)/–3.2 (5.6)	see *Figure 17*
	CPRS-R (hyperactivity)	10.6 (4.6)/–4.3 (4.6)	10.3 (4.9)/–1.1 (3.9)	–3.20 (–4.59 to –1.81)

[a] Note that owing to the overall poor reporting of study methodology, values should be interpreted with caution (with the exception of Spencer and colleagues;[89] **[Confidential information removed]**.
Lower scores represent a better behavioural outcome.
ADHD-RS-IV: Attention Deficit/Hyperactivity Disorder Rating Scale IV–Parent Version: investigator-administered and scored; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; CPRS-R, Conners' Parent Rating Scale – Revised.

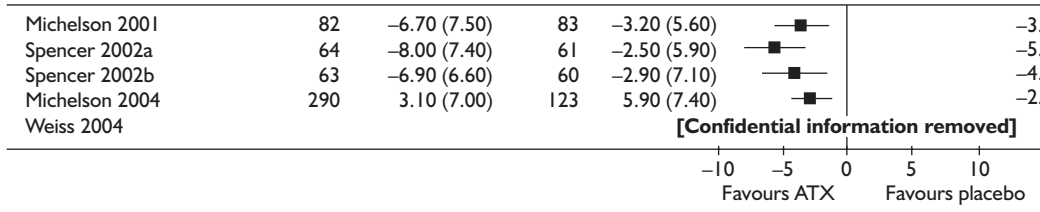

FIGURE 17 *Mean differences: ATX high dose versus placebo*

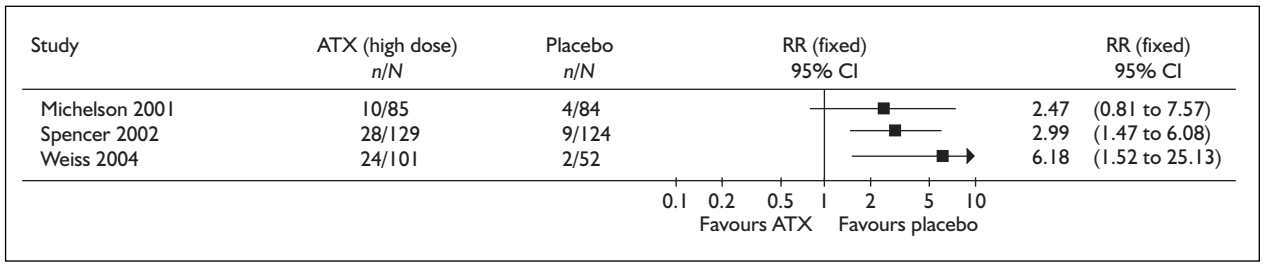

FIGURE 18 *Relative risks of loss of appetite: ATX (high dose) versus placebo*

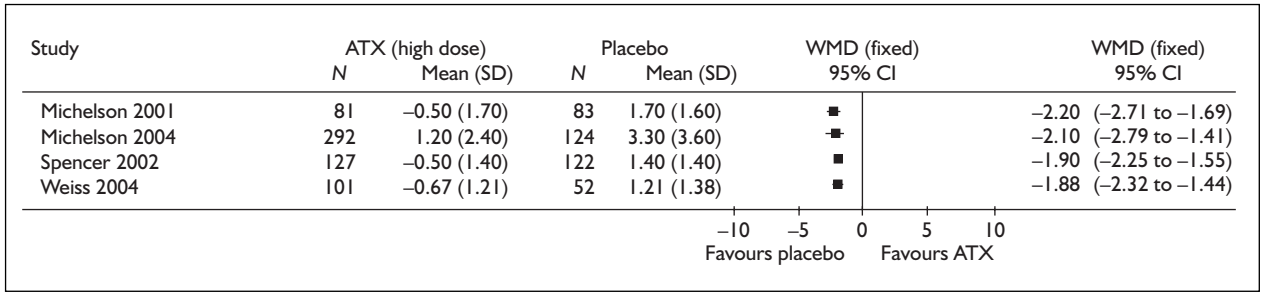

FIGURE 19 *Differences between mean weight change: ATX (high dose) versus placebo*

Adverse events

Of the six trials comparing a high dose of ATX with placebo, five presented data informative to the analysis of adverse events. Adverse events results were combined in the trials reported by Spencer and colleagues.[89] No significant differences in the incidence of headache,[73,89] stomach ache[73,89] or insomnia[73] were found. Participants in the ATX treatment groups displayed a significantly greater loss of appetite in two trials (*Figure 18*).

A detrimental effect of a high dose of ATX on mean change in weight was observed in all four trials (*Figure 19*).

Summary

High-dose ATX improved hyperactivity/impulsivity and QoL (as measured by CGI) compared with placebo. No significant differences in the incidence of headache, stomach ache or insomnia were observed between groups, although children in the ATX had greater loss of appetite in two of the trials. The studies by Michelson and colleagues[73] and Spencer and colleagues[89] rated well in the quality assessement, hence their results are likely to be reliable. The other studies did not score as well, and their results should be interpreted with caution.

ATX versus non-drug intervention

No studies evaluated ATX compared with non-drug intervention.

IR-MPH versus ER-MPH

IR-MPH low dose (≤ 15 mg/day) versus ER-MPH low dose (≤ 20 mg/day)

One study evaluated low-dose (≤ 15 mg/day) immediate-release MPH (IR-MPH) compared with low-dose (≤ 20 mg/day) extended-release MPH (ER-MPH) (*Table 47*; with additional information in Appendix 12). This study by Fitzpatrick and colleagues[55] examined hyperactivity using two different scales as assessed by both parents and teachers, and reported no significant differences between IR-MPH and ER-MPH (*Table 48*). This study did not evaluate CGI, but did present comment ratings by parents and teachers (see Appendix 12). Generally, the authors found no differences between the MPH conditions.

Adverse events

No significant differences in the incidence of headache, loss of appetite, stomach ache or insomnia were detected between treatments. Data on weight were not adequately reported.

Summary

The one study included in this category reported no differences between low-dose IR-MPH and low-dose ER-MPH for hyperactivity or any adverse events.[55] This study did not report on CGI. The quality of reporting for some aspects of study methodology was poor for this study, hence the results should be interpreted with caution.

TABLE 47 *IR-MPH low-dose (≤ 15 mg/day) versus ER-MPH low dose (≤ 20 mg/day)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered twice daily					
Fitzpatrick, 1992[55]	C (4×)	MPH (10–15 mg/day, b.d.) vs sustained-release MPH (Slow Release Ritalin, SR-20) (20 mg/day, o.d.) – 19	6.9–11.5	8	Core: Conners' Hyperactivity Index (parents/teacher); TOTS: hyperactivity (parents and teachers) QoL: no CGI; comments ratings (parent/teacher) AE: STESS (parents); weight

C, crossover trial (number of crossovers); CGI, Clinical Global Impression; STESS, Subject's Treatment Emergent Symptom Scale; TOTs, Loney's Time on Task Scale.

TABLE 48 *Results for hyperactivity [IR-MPH low dose (≤ 15 mg/day) versus ER-MPH low dose (≤ 20 mg/day)]*

Study	Scale	IR-MPH low dose: mean (SD)	ER-MPH low dose: mean (SD)	*p*-Value (if reported)[a]
6–11 years				
Fitzpatrick, 1992[55]		(? Mean, ? SD)	(? Mean, ? SD)	
	Conners' Hyperactivity Index (parents)	0.96 (0.50)	0.98 (0.72)	NS
	Conners' Hyperactivity Index (teacher)	0.73 (0.65)	0.77 (0.63)	NS
		Mean (SD)	Mean (SD)	
	TOTS (hyperactivity) (parents)	0.20 (0.31)	0.22 (0.50)	NS
	TOTS (hyperactivity) (teachers)	0.16 (0.44)	0.12 (0.51)	NS

[a] Note that owing to poor reporting for some aspects of the study methodology, *p*-Values should be interpreted with caution.
Lower scores represent a better behavioural outcome.
NS, not significant; TOTS, Loney's Time on Task Scale.

IR-MPH high dose (>30 mg/day) versus ER-MPH medium dose (20–40 mg/day)

Three studies evaluated high-dose (>30 mg/day) IR-MPH compared with medium-dose (20–40 mg/day) ER-MPH (*Table 49*; with additional information in Appendix 12). Only one of these studies reported data on hyperactivity (*Table 50*). In this study by Wolraich and colleagues,[97] no significant differences were reported between the two MPH treatment groups.

[Confidential information removed].

Quality of life

All three studies examined CGI. In the study by Wolraich and colleagues,[97] the percentages of those 'much or very much improved' were very similar between treatment groups (IR-MPH 47.2% vs ER-MPH 46.7%).

[Commercial information removed].

Adverse events

In the trial by Wolraich and colleagues,[97] participants assigned to the extended release form of MPH suffered from a significantly higher incidence of headache (*Figure 20*).

In the trial by Wolraich and colleagues,[97] no significant differences were observed with regard to loss of appetite or stomach ache. Data on insomnia or weight were not reported in this trial.
[Confidential information removed].

Summary

One study in this category assessed hyperactivity with no significant differences reported between high-dose IR-MPH and medium-dose ER-MPH.[97] All three studies evaluated CGI; the

TABLE 49 *IR-MPH high dose (>30 mg/day) versus ER-MPH medium dose (20–40 mg/day)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered twice daily					
Wolraich, 2001[97]	P	MPH (15, 30 or 45 mg/day, t.d.s.) vs OROS MPH (Concerta) (18, 36 or 54 mg/day, o.d.) – 312	6–12	4	Core: SNAP-IV: hyperactivity/ impulsivity (parent, teacher) QoL: CGI improvement (investigators) AE: solicited and spontaneous reports: focus on sleep quality, tics and appetite (parent)
Quinn, 2003[84]		**[Confidential information removed]**			
Steele, 2004[90]		**[Confidential information removed]**			
P, parallel trial.					

TABLE 50 *Results for hyperactivity [IR-MPH high dose (>30 mg/day) versus ER-MPH medium dose (20–40 mg/day)]*

Study	Scale	IR-MPH high dose: mean (SD)	ER-MPH medium dose: mean (SD)	Mean difference
6–12 years				
Wolraich, 2001[97]				MD (95% CI)
	SNAP-IV (hyperactivity/ impulsivity) (teacher rated)	0.93 (0.79)	0.96 (0.79)	–0.05 (–0.24 to 0.14)
	SNAP-IV (hyperactivity/ impulsivity) (parent rated)	1.10 (0.69)	1.11 (0.65)	0.17 (0.03 to 0.31)
Lower scores represent a better behavioural outcome.				

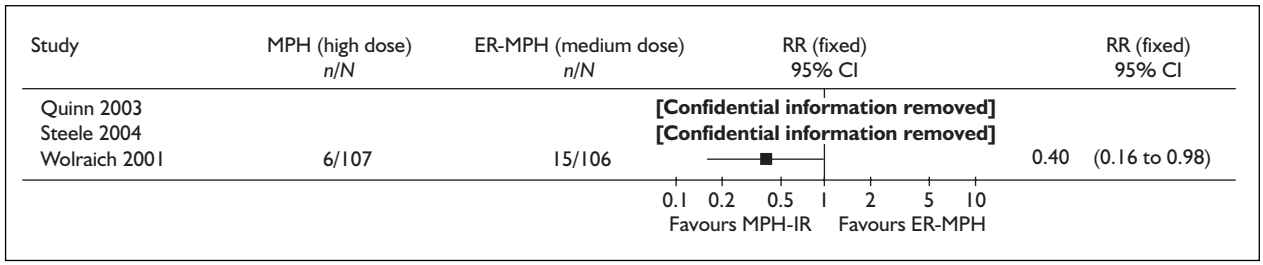

FIGURE 20 *Relative risks of headache: MPH high dose versus ER-MPH medium dose*

non-confidential study showed similar improvement between treatment groups. Regarding adverse events, the non-confidential trial found no differences between the treatment groups with regard to loss of appetite or stomach ache. However, this trial reported a higher incidence of headache with ER-MPH. The one study that examined hyperactivity rated poorly in the quality assessment.

[Confidential information removed].

IR-MPH medium dose (15–30 mg/day) plus non-drug intervention versus ER-MPH low dose (≤20 mg/day) plus non-drug intervention

Two studies evaluated medium-dose (15–30 mg/day) IR-MPH plus non-drug intervention compared with low-dose (≤20 mg/day) ER-MPH plus non-drug intervention (*Table 51*; with additional information in Appendix 12). These studies were both conducted by Pelham and colleagues and involved behaviour modification during an

TABLE 51 *IR-MPH medium dose (15–30 mg/day) plus non-drug intervention versus ER-MPH low dose (≤ 20 mg/day) plus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered twice daily					
Pelham, 1987[77]	C (3×)	MPH (20 mg/day, b.d.) vs sustained-release MPH (Slow Release Ritalin, SR-20) (20 mg/day, o.d.) plus behaviour modification (STP, 7 weeks) – 13	6.5–11	7	Core: no hyp; Abbreviated CTRS (teacher) QoL: not reported AE: Side Effects Checklists (parents, teachers, counsellors)
Pelham, 1990[78]	C (5×)	MPH (20 mg/day, b.d.) vs sustained-release MPH (Slow Release Ritalin, SR-20) (20 mg/day, o.d.) plus behaviour modification (STP, 8 weeks) – 22	8.1–13.2	8	Core: no hyp; Abbreviated CTRS (teachers/counsellors) QoL: not reported AE: Side Effects Checklists (parents, teachers, counsellors)

C, crossover trial (number of crossovers); STP, Summer Treatment Programme.

TABLE 52 *MPH high dose (>40 mg/day) plus non-drug intervention versus ER-MPH medium dose (20–40 mg/day) plus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered twice or more daily					
Pelham, 2001[82]	C (3×)	MPH (15, 30 or 45 mg/day, t.d.s.) vs OROS MPH (Concerta) (18, 36 or 54 mg/day, o.d.) plus parent training, teacher consultation and point systems (3 weeks) – 70	6–12	3	Core: no hyp; IOWA-C: inattention/overactivity (teacher and parent) QoL: no CGI; global effectiveness (parent and teacher) AE: questions regarding adverse events, sleep quality, appetite, and tics (parents); spontaneous reports of adverse events

C, crossover trial (number of crossovers); CGI, Clinical Global Impression.

STP.[77,78] Neither examined hyperactivity or CGI as core outcomes. Behaviour was assessed using the teacher-rated Abbreviated CTRS, and both studies reported no significant differences between the treatment groups (see Appendix 12).

Adverse events

Both trials reported on the incidence of insomnia; neither detected significant differences between treatments. Pelham and colleagues[77] reported the incidence of anorexia; however, no significant differences were found between treatments. No further data of interest were reported.

Summary

No studies in this category evaluated hyperactivity or CGI as outcomes. Two studies did report some adverse event data, and found no difference in insomnia or anorexia.

IR-MPH high dose (>40 mg/day) plus non-drug intervention versus ER-MPH medium dose (20–40 mg/day) plus non-drug intervention

One crossover study evaluated high-dose (>40 mg/day) IR-MPH plus non-drug intervention compared with medium-dose (20–40 mg/day) ER-MPH plus non-drug intervention (*Table 52*; with additional information in Appendix 12). The non-drug intervention involved a behavioural programme incorporating parent training, teacher consultation and a point system. This study by Pelham and colleagues[82] did not evaluate hyperactivity or CGI, but did assess a number of other core outcomes. For some outcomes, ER-MPH was superior to IR-MPH (see Appendix 12), but this was not the case when inattention/

overactivity was measured using the IOWA-C, except when assessed by parents. No significant differences between these two treatment arms were reported for global effectiveness (parent or teacher rated).

Adverse events

There were no significant differences between treatments in the incidence of headache, stomach ache, loss of appetite or insomnia. No data on weight were reported.

Summary

No studies in this category evaluated hyperactivity or CGI as outcomes. One study that reported adverse events data found no differences between the treatment groups.

MPH versus DEX

MPH medium dose (15–30 mg/day) versus DEX low dose (<10 mg/day)

One study evaluated medium-dose (15–30 mg/kg/day) IR-MPH compared with low-dose (<10 mg/day) DEX (*Table 53*; with additional information in Appendix 12). In this crossover study by Efron and colleagues,[50] hyperactivity was measured using four different Conners' scales. The authors reported significant differences in favour of MPH for the teacher-rated scales, but not for the parent-rated scales (*Table 54*). Efron and colleagues did not examine CGI, but did report on Parental Global Perceptions and Global Ratings of Response (by the child and parent). They reported no significant differences between the treatment groups for these outcomes.

TABLE 53 *MPH medium dose (15–30 mg/day) versus DEX low dose (<10 mg/day)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Efron, 1997[50]	C (2×)	MPH (0.60 mg/kg/day, b.d.) vs DEX (0.3 mg/kg/day, b.d.) – 125	5–14.9	4	Core: CPRS-R: impulsive–hyperactive factor; composite hyperactivity index; CTRS-R: hyperactivity factor; Hyperactivity Index QoL: no CGI; Parental Global Perceptions Questionnaire: overall perceptions; Child Global Perceptions Questionnaire AE: SERS (parents)

C, crossover trial (number of crossovers); CGI, Clinical Global Impression; CPRS-R, Conners' Parent Rating Scale – Revised; CTRS-R: Conners' Teacher Rating Scale – Revised; SERS, Side Effects Rating Scale.

TABLE 54 *Results for hyperactivity [MPH medium dose (15–30 mg/day) versus DEX low dose (<10 mg/day)]*

Study	Scale	MPH medium dose: mean (SD)	DEX low dose: mean (SD)	*p*-Value (if reported)[a]
5–14 years				
Efron, 1997[50]	CPRS-R (Composite Hyperactivity Index)	64.28 (13.46)	64.89 (13.74)	0.51
	CPRS-R (impulsive/hyperactive)	57.39 (10.53)	57.33 (11.22)	0.87
	CTRS-R (Hyperactivity Index)	56.14 (10.17)	58.76 (10.57)	<0.01
	CTRS-R (hyperactivity) Baseline: 71.26 (13.24)	56.20 (11.02)	58.88 (11.08)	<0.01

[a] Note that owing to poor reporting for some aspects of the study methodology, *p*-values should be interpreted with caution.

Lower scores represent a better behavioural outcome.

CPRS-R, Conners' Parent Rating Scale – Revised; CTRS-R, Conners' Teacher Rating Scale – Revised.

Adverse events
No significant differences were detected between DEX and MPH treatments in the incidence of headache, stomach ache, loss of appetite or insomnia. Data on weight were not reported.

Summary
One study evaluated medium-dose MPH compared with low-dose MPH.[50] This study reported significant effects in favour of MPH when hyperactivity was assessed by teachers, but not when assessed by parents. They reported no significant differences between treatments in the incidence of headache, stomach ache, loss of appetite or insomnia. Owing to the poor reporting of some methodological criteria, the results from this study should be interpreted with caution.

MPH medium dose (15–30 mg/day) versus DEX medium dose (10–20 mg/day)

One study evaluated medium-dose (15–30 mg/kg/day) immediate release IR-MPH compared with medium-dose (10–20 mg/day) DEX (*Table 55*; with additional information in Appendix 12). In this crossover study by Arnold and colleagues,[37] hyperactivity was assessed using four scales. The authors reported no differences between medium doses of MPH and DEX (*Table 56*). This study did not report on CGI. It generally scored well in the quality assessment.

Adverse events
Adverse event data were not reported adequately to be included in the analysis.

Summary
The one study that evaluated medium-dose MPH compared with medium-dose DEX reported no difference in hyperactivity scores between the treatment groups.[37] This study did not examine CGI or adequately report on adverse events data. It rated well in the quality assessment, hence the results for hyperactivity are likely to be reliable.

TABLE 55 *MPH medium dose (15–30 mg/day) versus DEX medium dose (10–20 mg/day)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Arnold, 1978[37]	C (3×)	MPH (1.25 mg/kg, 1 or 2×) vs DEX (0.63 mg/kg/day, 1 or 2×) – 29	5–12	3	Core: Conners' Teachers' Behaviour Problem Checklist: hyperactivity; Problem Behaviour Checklist (parents): hyperactivity; Davids' Hyperkinetic Rating Scale (parents and teachers) QoL: not reported AE: Problem Behaviour Checklist (parents): side-effects; weight loss
C, Crossover trial (number of crossovers).					

TABLE 56 *Results for hyperactivity [MPH medium dose (15–30 mg/day) versus DEX medium dose (10–20 mg/day)]*

Study	Scale	MPH medium dose: mean (SD)	DEX medium dose: mean (SD)	*p*-Value (if reported)
5–12 years				
Arnold, 1978[37]	Problem Behaviour Checklist (parents) (hyperactivity)	18.21 (5.61)	17.21 (5.45)	NR
	Conners' Teachers' Behaviour Problem Checklist (hyperactivity)	16.83 (5.50)	16.17 (4.64)	NS
	Davids' Hyperkinetic Rating Scale (parents) (hyperactivity)	4.31 (1.23)	4.28 (1.07)	NS
	Davids' Hyperkinetic Rating Scale (teachers) (hyperactivity)	3.83 (1.49)	3.90 (1.54)	NS
NR, not reported; NS, not significant.				

TABLE 57 *MPH high dose (>30 mg/day) plus non-drug intervention versus DEX high dose (>20 mg/day) plus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Elia, 1991[51]	C (3x)	MPH (25–90 mg/day, b.d.) vs DEX (mean 10–45 mg/day, b.d.) plus behaviour modification + diet (11 weeks) – 48	6–12	9	Core: CTRS: hyperactivity; CPQ: hyperactivity QoL: CGI (physician); C-GAS AE: STESS (physician, parents)
C, crossover trial (number of crossovers); CGI, Clinical Global Impression; C-GAS, Children's Global Assessment Scale; CPQ, Conners' Parent Questionnaire; CTRS, Conners' Teacher Rating Scale; STESS, Subject Treatment Emergent Symptom Scale.					

TABLE 58 *MPH medium dose (15–30 mg/day) plus non-drug intervention versus DEX-SR plus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered two or more times daily					
Pelham, 1990[78]	C (5×)	MPH (20 mg/day, b.d.) vs DEX-SR (10 mg/day, o.d.) plus behaviour modification (STP, 8 weeks) – 22	8.1–13.2	8	Core: no hyp; Abbreviated CTRS (teachers/counsellors) QoL: not reported AE: Side Effects Checklists (parents/teachers/counsellors)
C, crossover trial (number of crossovers); STP, Summer Treatment Programme.					

MPH high dose (>30 mg/day) plus non-drug intervention versus DEX high dose (>20 mg/day) plus non-drug intervention

One study evaluated high-dose (>30 mg/day) IR-MPH compared with high-dose (>20 mg/day) DEX (*Table 57*; with additional information in Appendix 12). Although this study by Elia and colleagues[51] examined hyperactivity and CGI as outcomes, the results were presented in graph form only and could not be reproduced in a table. The authors did report that both drugs were found to be equally efficacious.

Adverse events

No significant differences were detected in the incidence of decreased appetite or insomnia between treatment periods (RR = 1.12; 95% CI 0.98 to 1.28 and RR = 1.03; 95% CI 0.84 to 1.25). No further data were reported.

Summary

One study evaluated high-dose MPH plus non-drug intervention compared with high-dose DEX plus non-drug intervention,[51] but no data could be extracted for hyperactivity or CGI. The trial did not report any differences between groups for appetite or insomnia (the only adverse events that were examined). This study did not score very well in the quality assessment, and any results should be interpreted with caution.

MPH medium dose (15–30 mg/day) plus non-drug intervention versus DEX-SR plus non-drug intervention

One study evaluated medium-dose (15–30 mg/day) IR-MPH compared with DEX-SR plus non-drug intervention (*Table 58*; with additional information in Appendix 12). This study did not report any hyperactivity or QoL outcomes. They did measure behaviour using the Abbreviated CTRS (as assessed by teachers and counsellors). The scores between treatment groups were similar (see Appendix 12).

Adverse events

No significant differences were detected in the incidence of insomnia between DEX-SR and IR-MPH. Occurrences of headache, stomach ache and loss of appetite were not recorded by patients or parents. No weight data were reported.

Summary

One study was included in this category,[78] but it did not evaluate hyperactivity or CGI. This study

TABLE 59 *ER-MPH low dose (≤ 20 mg/day) plus non-drug intervention versus DEX-SR plus non-drug intervention*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Pelham, 1990[78]	C (5×)	Sustained-release MPH (Slow Release Ritalin, SR-20) (20 mg/day, o.d.) vs DEX-SR (10 mg/day, o.d.) plus behaviour modification (STP, 8 weeks) – 22	8.1–13.2	8	Core: no hyp; Abbreviated CTRS (teachers/counsellors) QoL: not reported AE: Side Effects Checklists (parents/teachers/counsellors)

C, crossover trial (number of crossovers); STP, Summer Treatment Programme.

TABLE 60 *MPH high dose (>30 mg/day) versus ATX high dose (≥ 1.5 mg/kg/day)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered twice daily					
Kratochvil, 2002[70]	P	MPH (31.3 mg/day 1–3×) vs ATX (max. 2.0 mg/kg/day, b.d.) – 228	7–15	10	Core: ADHD-RS-IV–Parent Version (investigator administered and scored): hyperactivity/impulsivity; CPRS-R: hyperactivity QoL: CGI AE: open-ended questions; weight

CPRS-R, Conners' Parent Rating Scale – Revised; CGI, Clinical Global Impression; P, parallel trial.

did report that there were no significant differences between treatments in the incidence of insomnia (other adverse events of interest were not examined). This study did not score very well in the quality assessment, and any results should be interpreted with caution.

ER-MPH low dose (≤ 20 mg/day) plus non-drug intervention versus DEX-SR plus non-drug intervention

One study evaluated low-dose (≤ 20 mg/day) ER-MPH compared with DEX-SR plus non-drug intervention (*Table 59*; with additional information in Appendix 12). As presented above, this study did not report any hyperactivity or QoL outcomes. The scores between treatment groups were similar when assessed using the Abbreviated CTRS (see Appendix 12).

Adverse events

No significant differences were detected in the incidence of insomnia between DEX-SR and ER-MPH. Occurrences of headache, stomach ache and loss of appetite were not recorded by patients or parents. No weight data were reported.

Summary

As above, one study was included in this category,[78] but it did not evaluate hyperactivity or CGI. This study reported that there were no significant differences between treatments in the incidence of insomnia (other adverse events of interest were not examined). This study did not score very well in the quality assessment, and any results should be interpreted with caution.

MPH versus ATX

MPH high dose (>30 mg/day) versus ATX high dose (≥ 1.5 mg/kg/day)

One study evaluated high-dose (>30 mg/day) IR-MPH compared with high-dose (≥ 1.5 mg/kg/day) ATX (*Table 60*; with additional information in Appendix 12).

In this parallel study by Kratochvil and colleagues,[70] hyperactivity was measured using two scales. No differences were reported between the treatment groups using either scale (*Table 61*). This study also reported on CGI – Severity. Again, no difference was reported in children in the MPH group compared with children in the DEX group ($p = 0.663$).

TABLE 61 *Results for hyperactivity [MPH high dose (>30 mg/day) versus ATX high dose (≥ 1.5 mg/kg/day)]*

Study	Scale	MPH high dose: mean (SD)	ATX high dose: mean (SD)	Mean difference
7–15 years				
Kratochvil, 2002[70]	ADHD-RS-IV (hyperactivity/impulsivity)	Baseline/change from baseline	Baseline/change from baseline	MD (95% CI)
	CPRS-R (hyperactivity)	16.95 (7.07)/–8.48 (7.08)	17.77 (6.31)/–9.50 (6.99)	1.02 (–1.40 to 3.44)
		10.05 (5.35)/–4.78 (4.49)	10.25 (4.39)/–5.56 (4.74)	0.78 (–0.82 to 2.38)

Lower scores represent a better behavioural outcome.
ADHD-RS-IV, ADHD Rating Scale–Parent Version (investigator administered and scored); CPRS-R, Conners' Parent Rating Scale – Revised.

Adverse events
No significant differences in the incidence of headache, loss of appetite, stomach ache or insomnia were detected between the ATX and MPH treatment groups. In addition, no differences in participants' mean change in weight were observed.

Summary
One study was included in this category.[70] No differences were reported between the two drugs for hyperactivity, CGI or adverse events (of interest). This study did not score very well in the quality assessment, and any results should be interpreted with caution.

ER-MPH medium dose (20–40 mg/day) versus ATX low/medium dose (<1.5 mg/kg/day)

One study evaluated medium-dose (20–40 mg/day) ER-MPH compared with low/medium-dose (<1.5 mg/kg/day) ATX (*Table 62*; with additional information in Appendix 12). This parallel study by Kemner and colleagues[64] reported a significant improvement in favour of MPH when measured using the ADHD Rating Scale for hyperactivity (*Table 63*). Similarly, the authors reported that CGI – Improvement responder rates were significantly better for the MPH group than for the ATX group (68.6 versus 52.8%, $p < 0.001$).

Adverse events
Incidence of headache and stomach ache did not differ significantly between the ATX and ER-MPH treatment groups. Participants assigned to ER-MPH suffered from a significantly higher incidence of reduced appetite and insomnia compared with those assigned to ATX (RR = 1.95; 95% CI 1.09 to 3.49 and RR = 2.88; 95% CI 1.57 to 5.28, respectively). No data on weight were reported in this study.

TABLE 62 *ER-MPH medium dose (20–40 mg/day) versus ATX low/medium dose (<1.5 mg/kg/day)*

Study	Design	Intervention – *N*	Age (years)	Duration (weeks)	Core outcomes
Administered once daily					
Kemner, 2004[64]	P	OROS MPH (Concerta) **[Confidential information removed]** vs ATX **[Confidential information removed]** – 1323	6–12	3	Core: ADHD-RS: hyperactivity (investigator rated) QoL: CGI Improvement AE: as reported by participants/parents to clinicians

ADHD-RS, ADHD Rating Scale; CGI, Clinical Global Impression; P, parallel trial.

TABLE 63 *Results for hyperactivity [ER-MPH medium dose (20–40 mg/day) versus ATX low/medium dose (<1.5 mg/kg/day)]*

Study	Scale	ER-MPH medium dose: mean (SD)	ATX low/medium dose: mean (SD)	*p*-Value (if reported)
6–12 years				
Kemner, 2004[64]	**[Commercial information removed]**			

Summary
The one study in this category reported a significant improvement in favour of MPH compared with ATX for both hyperactivity and CGI. However, this study also reported a higher incidence of reduced appetite and insomnia in the MPH group, but no differences in headache or stomach ache.

[Commercial information removed].

ATX versus DEX

No studies directly compared ATX and DEX.

The MTA trial

(This section of the report was copied from the original NICE review: Lord J, Paisley S. *The clinical effectiveness and cost-effectiveness of methylphenidate for hyperactivity in childhood*. London: National Institute for Clinical Excellence, Version 2; August 2000. Results of recently published papers were added.)

The Multimodal Treatment Study of Children with ADHD (MTA) 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.

Children between the ages of 7 and 9 years with a diagnosis of ADHD combined type (DSM-IV) were recruited through six centres. They had a range of co-morbid 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 pharmaco-therapist, 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 eight 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, which included 10–16 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 coordinate treatment, information was shared between the teacher, consultant and pharmaco-therapist. Average medication doses received also varied between the medication management and combined treatment groups.
4. **Community care.** Here children 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 and 3, 9 and 14 months. Further follow-up assessments are planned. Analyses were conducted on an ITT 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 children were intended to be representative of 'real-world' patients.[103] It is important to note that this trial did not include a placebo or 'no treatment' control group. Hence, the MTA trial cannot 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 USA and UK.[104] Most of the children in the community care group (97/146) received stimulant medication.

Results of the MTA trial

The MTA trial was designed to answer three questions:[76]

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 (one-tailed hypotheses)?*
   (a) Combined treatment and medication management do 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 three MTA treatments (medication management, behavioural treatment and combined treatment) show greater improvement over 14 months than those assigned to community care (one-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 subgroups with better or worse response to the various treatment strategies.[105] 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 co-morbid disruptive disorders. Behavioural treatment appeared to be more effective in children with anxiety disorders and children from deprived backgrounds.

Since the publication of the previous NICE report,[4] the authors of the MTA trial have published a number of related papers.[106–113] Most of these are cross-sectional analyses, overview studies or studies focusing on covariates, such as socio-economic status or ethnicity, which will not be discussed in this report.[106,107,110,111]

Other papers focused on subgroup analyses.[108,109,112] As the samples were not designed for this purpose, results should be interpreted with caution. Vitiello and colleagues examined the trajectory of MPH dosage over time, following a controlled titration.[108] The aim was to ascertain how accurately the titration was able to predict effective long-term treatment in children with ADHD. They concluded that for most children, initial titration found a dose of MPH in the general range of the effective maintenance dose, but did not prevent the need for subsequent maintenance adjustments.[108] Greenhill and colleagues[109] examined whether the trial identified the best MPH dose for each child with ADHD. They found that the MTA titration protocol validated the efficacy of weekend MPH dosing and established a total daily dose limit of 35 mg of MPH for children weighing <25 kg. It replicated previously reported MPH response rates (77%), distribution of best doses (10–50 mg/day) across children, effect sizes on impairment and deportation and dose-related adverse events.[109] Galanter and colleagues examined the response to MPH in children with ADHD and some manic symptoms.[112] Their findings suggested that these children respond robustly to MPH during the first month of treatment and that they are not more likely to have an adverse response to MPH.[112]

In 2004, the authors of the MTA trial published results of a follow-up 10 months beyond the 14 months of intensive intervention.[113] Of the 579 children who entered the study, 540 (93%) participated in this first follow-up. Results indicated that the MTA medication strategy

showed persisting significant superiority over behavioural treatment and community care for ADHD and oppositional–defiant symptoms at 24 months, although not as great as at 14 months. Significant additional benefits of combined treatment over medication management and of behavioural treatment over community care were not found. The groups differed significantly in mean dose (MPH equivalents: 30.4, 37.5, 25.7 and 24.0 mg/day, respectively).[113]

Summary of clinical effectiveness data

MPH versus placebo

Studies that evaluated low-dose MPH compared with placebo demonstrated variable results for hyperactivity.[43,54,55,60,61,96] No differences in CGI were reported between the groups[96] (no other studies measured this outcome). With medium-dose MPH, the majority of studies demonstrated that MPH was superior to placebo for hyperactivity;[42,43,46,54,60,61,68,98] (no results were significant in the study by Stein and colleagues[91]), and one study reported that MPH improved CGI compared with placebo[83] (no other studies measured this outcome). The two studies that evaluated hyperactivity with high-dose MPH demonstrated variable results,[43,77] although there was evidence that high-dose MPH improved CGI.[97] **[Confidential information from one study that evaluated the effectiveness of high-dose MPH on CGI removed].**

There was a paucity of studies that examined MPH (any dose) plus a non-drug intervention (e.g. cognitive therapy) compared with placebo. Only one study reported data for hyperactivity, and the results were not significant.[42] In addition, very few studies examined the effectiveness of ER-MPH compared with placebo. Of these studies, the majority reported that ER-MPH (low, medium or high) was superior to placebo for all outcomes of interest (hyperactivity[55;97] and CGI[59,93,97]). **[Confidential information from one study that reported on CGI removed].**

Again, very few studies compared MPH with a non-drug intervention (e.g. parent training, cognitive training and behavioural therapy). Three studies evaluated hyperactivity, two of which demonstrated that children receiving MPH were significantly improved compared with children receiving a non-drug intervention[42,53] and one which demonstrated variable results depending on the scale used.[65]

A larger number of studies examined MPH in combination with a non-drug intervention (e.g. parent training, one-to-one reading therapy, cognitive therapy and parent and teacher education) compared with a non-drug intervention. Of these, five presented reproducible results on hyperactivity and two reported results on CGS. Generally, combined treatment was superior to non-drug treatment for hyperactivity[42,53,71] and Clinical Global Impression.[51,65] In two studies, hyperactivity was improved when assessed by teachers, but not by parents[65,86] (in these cases the non-drug interventions were parent training or support and parent and teacher education).

No studies that compared ER-MPH plus non-drug intervention with a non-drug intervention evaluated hyperactivity or CGI.

Generally, the studies that evaluated MPH did not adequately report on study methodology, and the results should be interpreted with caution.

DEX versus placebo

Only two studies that compared DEX and placebo reported reproducible data on hyperactivity.[36,45] When assessing the efficacy of medium-dose DEX, the results for hyperactivity varied depending on the scale used.[45] For higher dose DEX, hyperactivity and CGI appeared to be improved with drug treatment[36] (statistical results for hyperactivity were not reported). Generally, this study rated well in the quality assessement. An additional study by Arnold and colleagues[38] evaluated DEX-TR compared with placebo. They observed significant improvements in hyperactivity with treatment. However, owing to the poor reporting of some methodological criteria, the results from this study should be interpreted with caution.

No studies comparing DEX plus non-drug treatment versus placebo or DEX versus non-drug intervention, measured hyperactivity or CGI as outcome measures. One study compared DEX in combination with a non-drug treatment (academic instruction and therapeutic recreation) with non-drug treatment alone with hyperactivity as an outcome.[62] Results were significant in favour of the combined treatment group when assessed using the CTRS and the Children's Psychiatric Rating Scale, but not when assessed using the CPRS. CGI was not examined. In addition to evaluating immediate release DEX, James and colleagues[62] also examined DEX-SR. In this study, combination treatment resulted in improved behaviour compared with non-drug treatment alone. However, this study did not score very well in the

quality assessment, and the results should be interpreted with caution.

ATX versus placebo

Generally, there was consistent evidence that ATX was superior to placebo for hyperactivity and CGI.[63,73–75,89] No studies compared ATX with non-drug treatment. Two of these studies were deemed to be of good quality (based on the reporting of the study methodology) and their results are likely to be reliable.[73,89] **[Confidential information from one study that examined hyperactivity and CGI removed].**

IR-MPH versus ER-MPH

Of the studies that evaluated IR-MPH compared with ER-MPH, no differences were reported for hyperactivity[55,97] or CGI.[97] However, these two studies scored poorly in the quality assessment, and the results should be interpreted with caution. **[Confidential information from two studies that reported on CGI removed].**

MPH versus DEX

The results of comparisons between MPH and DEX were variable. One study reported that MPH (medium dose) was superior to DEX (low dose) when assessed using Conners' teacher-rated scales, but not for Conners' parent-rated scales.[50] Another study observed no differences between MPH (medium dose) and DEX (medium dose) for hyperactivity.[37] CGI was not assessed in either study. The study that evaluated medium-dose MPH compared with medium-dose DEX rated well in the quality assessment, whereas the other did not score very well, and any results should be interpreted with caution.

MPH versus ATX

Very few studies compared MPH and ATX. One reported no difference between the two drugs for hyperactivity or CGI.[70] This study did not adequately report study methodology, and the results should be interpreted with caution. **[Confidential information from one study that evaluated ER-MPH with ATX on hyperactivity and CGI removed].**

ATX versus DEX

No studies compared ATX versus DEX.

Summary of adverse events data

MPH versus placebo

Primary studies

Amongst studies that compared low-dose MPH with placebo, no differences in adverse events were detected between the treatment groups.[55,60] However, amongst studies that compared medium- or high-dose MPH with placebo, there was evidence that treatment was associated with higher incidences of headaches, loss of appetite, stomach ache and insomnia compared with placebo.[35,39,44,46,57,60,66–68,83,91,95] **[Confidential information from one study that examined adverse events removed].**

None of the studies examining MPH (any dose) combined with a non-drug intervention compared with placebo presented adverse events data informative to our analysis.

Of the studies comparing ER-MPH (any dose) with placebo, treatment was associated with decreased appetite and increased insomnia amongst participants.[32,55,59,92,97] **[Confidential information from one study that examined adverse events removed].**

None of the studies comparing MPH (any dose) alone with a non-drug intervention reported adequate data on adverse events.

Amongst the trials comparing MPH in combination with a non-drug intervention with a non-drug intervention alone, the majority did not report differences in adverse events between treatment groups.[51,77,78,80–82,88]

Of the studies comparing ER-MPH plus non-drug intervention with a non-drug intervention alone, the medium-dose study reported that loss of appetite was significantly greater in the combined treatment group.[82]

Systematic reviews

Only one SR met the inclusion criteria for our analysis of adverse events;[114] this reported on studies assessing MPH treatment. The majority of the included studies that examined weight detected differences between treatment arms or baseline and active drug conditions. Fewer studies found effects on height, and some initial differences were no longer significant at long-term follow-up. Approximately half of the studies evaluating heart rate or blood pressure detected differences between treatment arms or baseline and active drug conditions. Loss of appetite, sleep disturbances, dizziness, headaches and stomach aches were the most commonly reported somatic complaints. The authors concluded that adverse events related to growth and cardiovascular outcomes were predominantly transient in nature,

easily rectified with dosage adjustments. They also highlighted the need for further research into somatic complaints, which may be associated with the disorder itself rather than the initiation of treatment. Appendix 13 presents the results of this review in more detail.

Tertiary sources

The BNF[29] details the following as possible physical side-effects resulting from the administration of MPH: tremor, rash, pruritus, urticaria, fever, arthralgia, alopecia, exfoliative dermatitis, erythema multiforme, thrombocytopenic purpura, thrombocytopenia, leucopoenia, dizziness, headache, gastrointestinal symptoms, anorexia, urinary disorders, dry mouth, sweating, convulsions, tachycardia, anginal pain, palpitations, increased blood pressure and visual disturbances. Rare cases of liver damage, muscle cramps and cerebral arteritis have been noted. In addition, cardiomyopathy has been reported with chronic use. Choreoathetoid movements, tics and Tourette syndrome have also been reported in predisposed individuals. Growth retardation in children has further been noted. Behavioural adverse effects listed include sleep disturbances, insomnia, depression, confusion, restlessness, irritability and excitability, nervousness, night terrors and euphoria. Some individuals have presented with drug dependence and tolerance or psychosis.

DEX versus placebo

Primary studies

Two studies comparing DEX with placebo adequately reported adverse events data of interest to our review. One study examining medium-dose DEX reported no difference in adverse events between treatment groups;[56] the other study examining high-dose DEX reported a greater incidence of loss of appetite, but detected no further differences.[58]

Adverse events data were not adequately reported in the one study comparing a time-release form of DEX with placebo.

No studies comparing combined DEX and behavioural treatment with placebo reported adequate adverse events data.

No adequate data were reported for studies comparing DEX alone with a non-drug intervention.

One study examining high-dose DEX combined with a non-drug intervention compared with a non-drug intervention alone reported adverse events data: significantly decreased appetite and increased insomnia were observed in the combined treatment group.[51]

One study comparing an extended-release form of DEX combined with a non-drug intervention with a non-drug intervention alone reported no differences in the incidence of insomnia between treatment phases.[78] No further adverse events data of interest were reported.

Systematic reviews

No SR examining the adverse event profile of DEX was identified.

Tertiary sources

The BNF[29] details the following as possible physical side-effects resulting from the administration of DEX: tremor, dizziness, headache, gastrointestinal symptoms, dry mouth, anorexia, sweating, convulsions, tachycardia, anginal pain, palpitations, increased blood pressure and visual disturbances. In addition, cardiomyopathy has been reported with chronic use. Choreoathetoid movements, tics and Tourette syndrome have also been reported in predisposed individuals. Growth retardation in children has further been noted. Behavioural adverse effects listed include insomnia, restlessness, irritability and excitability, nervousness, night terrors and euphoria. Some individuals have presented with drug dependence and tolerance or psychosis.

ATX versus placebo

Primary studies

Studies in this category presented evidence that ATX (all doses) results in significantly reduced appetite compared with placebo, but does not impact the incidence of headache, stomach ache or insomnia.[63,73–75,89,94] In the one trial that reported weight data, ATX appeared to have an adverse effect on children's weight gain.[73]

Systematic reviews

No SR examining the adverse event profile of atomoxetine hydrochloride was identified.

Tertiary sources

The BNF[29] cites the following as physical side-effects associated with the administration of ATX: anorexia, dry mouth, nausea, vomiting, abdominal pain, constipation, dyspepsia, flatulence, palpitations, tachycardia, increased blood pressure, postural hypotension, hot flushes, dizziness, headache, fatigue, lethargy, tremor, rigors, urinary retention, mydriasis, conjunctivitis,

dermatitis, pruritus, rash and sweating. Prostatitis in men and menstrual disturbances in women have also been observed. Some patients have suffered from cold extremities, although less commonly. Behavioural side-effects include sleep disturbances, depression, anxiety and sexual dysfunction.

IR-MPH versus ER-MPH

Primary studies

Of the studies that evaluated IR-MPH compared with ER-MPH, one study reported a significantly higher incidence of headache in the extended-release treatment group.[97]

MPH versus DEX

Primary studies

Amongst studies comparing IR-MPH with IR-DEX (of any respective dosage, with or without non-drug intervention), no significant differences were detected between treatment groups with regard to reported adverse events.[50,51]

No significant differences were detected in the incidence of insomnia in the one study comparing ER-DEX combined with a non-drug intervention with IR-MPH (medium dose) combined with a non-drug intervention. No further data were reported.[78]

Similarly, no significant differences were found in the incidence of insomnia between treatment phases in the one study comparing ER-MPH combined with a non-drug intervention with ER-DEX combined with a non-drug intervention. No further data were reported.[78]

MPH versus ATX

Primary studies

The study comparing MPH (high dose) with ATX (high dose) did not detect significant differences in adverse events between treatment groups.[70]

However, the study comparing an extended-release form of MPH (medium dose) with ATX (low/medium dose) found that participants assigned to ER-MPH suffered from reduced appetite and insomnia to a significantly greater extent. No differences were detected in the incidence of headache or stomach ache between treatment groups.[99]

ATX versus DEX

Primary studies

No studies compared ATX versus DEX.

Chapter 5

Review of economic evaluations of ADHD drug interventions in children and adolescents

Aim

The aim of this chapter is to review the published literature and company submissions to the NICE on the QoL and cost-effectiveness of

- oral MPH including Ritalin [Immediate Release (IR-MPH), Equasym (IR-MPH), Equasym® XL (Extended Release ER-MPH8 hour) and Concerta® XL (ER-MPH12 hour)]
- DES (Dexedrine)
- ATX (Strattera)

in children and adolescents (under 18 years of age) diagnosed with ADHD (including HKD). All studies in which MPH, DEX or ATX were used alone or in combination with other drugs or non-drug interventions [e.g. psychological/behavioural therapy (BT)] are included.

Literature review

The information scientist conducted a search on the published QoL and cost-effectiveness literature (see Appendix 2 for full details of the search strategies and databases used). The QoL searches identified 500 records (853 records before de-duplication, that is, before eliminating duplicates) that were assessed by the health economist for relevance. In addition, the 38 records (47 before de-duplication) identified from the database-specific searches for economic evaluations and the 6535 records (2450 before de-duplication) identified by the generic and adverse event searches were also sifted for relevant papers in relation to the cost-effectiveness of named drug therapies for ADHD. Five relevant cost-effectiveness and two relevant HRQoL papers were identified from the searches.

QoL studies were ordered if they contained health outcome data for use in economic evaluations of ADHD. The review of the economic evaluation literature included studies that compared two or more ADHD interventions in terms of their costs and outcomes and where at least one drug intervention was assessed. Economic evaluations included cost–consequence, cost–utility, cost-effectiveness, cost-minimisation and cost–benefit analyses. Economic evaluations reported as conference proceedings or abstracts were excluded since the data they contain may not be complete. Thirty-one QoL studies and five economic evaluation studies were ordered, of which two QoL studies and five economic evaluations were reviewed. A data extraction form used in previous Technology Assessment Reviews was used to abstract data on all economic evaluations reviewed (Appendix 7). Each economic evaluation was quality assessed independently by two health economists (Appendix 6) based on an economic evaluation checklist.[115]

Review of quality of life and cost-effectiveness literature

Quality of life

Searches (see Appendix 2) for studies on the QoL of children and adolescents with ADHD revealed a plethora of instruments, the majority measuring multiple, disaggregated dimensions of health designed to identify the extent to which health status is affected by the intervention in question. As such, many featured as outcome measures in the trials that are reviewed in the clinical effectiveness chapter (Chapter 4).

Two main types of instruments were used to evaluate ADHD interventions including those measuring (1) symptoms and functionality [e.g. the Peabody Individual Achievement Test (PIAT)][116] and those measuring (2) (HRQoL) in children with ADHD. The HRQoL instruments used included disease-specific instruments such as the (SNAP-IV) Rating Scale,[117] CTRS and CPRS.[118] A few instruments were generic measures that can be used to compare effectiveness across diseases, for example, the Index of Health Related Quality of Life (IHRQoL)[119] or the generic paediatric measures, for example the Child Health Questionnaire (CHQ).[120]

The choice of outcome measure is a critical design issue. ADHD is a complex neuro-developmental

constellation of problems rather than a single disorder, with core symptoms of inattention, hyperactivity and impulsivity and other more general symptoms such as poor school performance and poor social functioning.[121] Since these behavioural traits can be present in unaffected children, symptoms and functionality-based outcomes need to have discriminant validity, that is, they should be able to discriminate between children with and without ADHD. It has been suggested that there might be unique patterns of effects created by different treatments (e.g. drug interventions versus BT) and a single outcome measure might not be sufficiently sensitive.[118] Although measures that are used for reporting outcomes in a disaggregated way may be useful from a clinical perspective, the use of these instruments has limitations from a decision-making perspective. Many of the measures feature subscales, and the scoring of the instrument may not be designed to provide an overall summary score. Unless the relative importance of each subscale or of each different profile measure can be valued, it is not possible to use these measures to calculate the net impact on HRQoL.

When assessing the cost-effectiveness of an intervention, the use of such disparate measures may lead to conflicting results depending on the instrument or subscale used. One way to overcome this problem is to use a preference-based index of HRQoL. These provide a summary score, typically between 0 (death) and 1 (full health), with the relative importance of changes in different dimensions of health being weighted according to people's preferences. Given the perspective of NICE, the most relevant values are those of the general population of England and Wales. The focus of this review is children and adolescents so, in principle, their preferences may be most relevant. When preference values are obtained using the standard gamble (SG) or time-trade-off (TTO) techniques, they can be used to represent utilities. (The NICE technical guidance requires that health states should be measured in patients using a generic and validated classification system for which reliable UK population preference values, elicited using such a choice-based method, for example.[122]) Utility values for health states can be combined with the length of time spent in those health states to calculate quality-adjusted survival.

The quality-adjusted life-year (QALY) is commonly used to measure health outcomes in health economic evaluations, combining QoL with quality of life in a single measure. Two studies contained utility information for use in the construction of QALYs[123] (Gilmore and Milne[123] is based on the Wessex Institute DEC Report number 78[124]),[125] (authors include Eli Lilly employees, producers of Strattera/ATX).

Gilmore and Milne[123] generated QALYs based on data from the IHRQoL.[119] The population preference-based IHRQoL system was used, which incorporates three dimensions: disability, (physical) discomfort and (emotional) distress. Since the authors could not find accurate estimates of disability directly in the literature, they used their own judgement, in consideration of trial evidence. It was assumed that the QoL improvements were 0.086 per individual for a year. [The IHQoL health state was assumed to change from that of no pain, slight social disability (some role functions slightly impaired by social disability) and moderate emotional distress (anxious and depressed most of the time but happy and relaxed some of the time) to no pain, no physical or social disability and slight emotional distress (happy and relaxed more of the time, but anxious and depressed some of the time). Based on IHQoL data, this generates a score of 0.970 – 0.884 = 0.086]. Estimations were made for 1 year only, reflecting the better quality of shorter-term trial data.

Initially, to calculate QALYs it was assumed, based on the literature, that benefits observed at 4–6 months persisted for the year of follow-up provided that medication continued. In addition, it was assumed that 6% of individuals discontinued treatment over the year owing to side-effects and that the average response rate in those who remained within the trial was 70%. From this, it was estimated that 100 children gained 94.06 QALYs per year using MPH compared with 88.4 QALYs per year for the placebo arm, an incremental difference of 5.66 QALYs or 0.0566 QALYs per child.

There are a number of caveats surrounding the usefulness of these findings. The authors acknowledge that the main limitation of their work lies in the generation of the QALY using the IHRQoL. Values for health states for children with ADHD were obtained using expert judgement with consideration of published trials. The process of synthesising this information from the literature was not explained. The authors state that the IHRQoL is not a sensitive tool for measuring the types of disabilities encountered in ADHD. They mention that typically children with ADHD have moderate to severe social disability, whereas the

only level of social disability that IHRQoL includes is slight social disability. This is an oft-cited criticism of generic indexes of HRQoL: that their content validity may be weak when applied in specific disease areas. In practice, the IHRQoL is rarely used today and values of health states were gained from a small sample of individuals whose preferences are unlikely to be representative of the population of England and Wales as a whole. The authors undertook multi-way sensitivity analyses in order to explore the effect that modelling plausible variations in quality of life improvements pre- and post-treatment had on cost–utility estimates. Overall, the effect of modelling different disability/distress levels had little impact on the estimates. The authors did not report on any uncertainty associated with the QALY estimates.

An alternative approach to employing a generic preference-based health index of HRQoL is to describe health states specific to the disease under consideration, and value them directly using techniques such as SG or TTO. The validity of these measures depends on the content and style of the vignette used to describe each health state. Matza and colleagues[125] published an abstract including utility information based on the SG technique. Utility information was elicited from 43 parents of children with ADHD. Eleven hypothetical health states were developed based on the opinion of doctors and informed by published literature and unpublished clinical trial data. Health states that were valued included untreated ADHD, stimulant treatment and non-stimulant treatment (e.g. ATX). The actual vignettes used to describe each health state were not available to us as the study is currently published only as an abstract. The parents rated each health state including the current health state of their child (mean parent SG rating = 0.74), and the SG utility scores varied from severe untreated ADHD (0.48) to effective, tolerable ATX non-stimulant treatment (0.88). However, the full range of utilities for all 11 health states was not reported in the abstract and neither were any data on the variation around each estimate. The authors stated that comparisons between health states found expected differences between untreated mild, moderate and severe ADHD states. In the case where stimulant and non-stimulant medication were both effective and tolerable, parents preferred the latter (ATX) ($p < 0.03$).

A potential advantage of this approach, therefore, is that small differences in health states can be estimated in terms of utility values. Also, with reference to this review, the values are based on direct patient valuations, rather than expert judgement. We note that NICE prefers a generic and validated classification system for the estimation of health state utilities. However, the estimated utilities available for ADHD using generic instruments are crude, and based on expert opinion. Hence values obtained directly from patients, using SG methodology, may be more relevant for this review.

Cost-effectiveness

Five relevant economic evaluations were found in the published literature,[4,123,126,128,129] including Lord and Paisley,[4] which was part of the original NICE appraisal. (Reference 126 is reported in the economic evaluation section of Miller and colleagues[30] and is also reported in brief in Shukla and Otten[127].) The last two studies[128,129] are not formal economic evaluations since costs were not compared with outcomes for the interventions being assessed. However, they do include the benefit of response to treatment in terms of reduced costs and therefore provide useful data.

Gilmore and Milne[123] assessed the cost-utility of IR-MPH compared with placebo for children diagnosed using DSM Criteria for Pervasive ADHD/ADDH[2] or Barkley's research criteria[130] who are otherwise normal. Gilmore and Milne[123] argue that they chose to use placebo-controlled trials as placebo effects are important.

The NHS healthcare perspective was adopted and utility information was determined as described in the QoL section above. In terms of resource use, the dosage of MPH and the average number of outpatient clinic attendances over the year were estimated based on the opinion of five child and adolescent psychiatrists (personal communication: it is likely that paediatricians' case loads have different population characteristics and that this will have significant implications for the number of attendances. It should be acknowledged that the growing development of nurse-led ADHD services will also have economic implications). It was assumed that all follow-up was hospital-based, that those who terminated treatment or those who did not respond were treated for 6 weeks, on average, and that those who were included in the analysis for 1 year received five outpatient appointments. Additional information on drug dosages was obtained from the literature, and data on children's weights were taken from percentile charts. The cost of the drugs was obtained from MIMS (August 1997)[131] and the cost of child and

adolescent psychiatry and family therapy outpatient clinics was obtained from fund-holding tariffs of four Trusts in the South West region. Prices relate to the year 1997.

The incremental cost per QALY gained over placebo with MPH per child was £9177 (range £5965–14,233) assuming a 70% response rate. A few multi-way sensitivity analyses, that is, varying more than one parameter at a time, were undertaken to test the robustness of findings to plausible variations in QoL improvements, the response rate and costs. Under the most optimistic scenario, the cost–utility estimate was £5965 and the most pessimistic scenario was £29,049.

In addition to the caveats mentioned in the review of clinical effectiveness in Chapter 4 relating to the outcomes measurement, there are a few concerns about the economic evaluation data. Little information was provided about the process of obtaining resource use information from the experts. NICE guidance states that the reference case comparator should include alternative therapies routinely used in the NHS rather than a placebo alternative. However, it is recognised that such head-to-head data may not be available.

Lord and Paisley[4] conducted an economic evaluation based on data from the MTA trial. They compared combined treatment, based on IR-MPH and BT, versus BT alone. The analysis was conducted from the NHS perspective over 14 months, the length of the MTA trial, and only the incremental costs of medication were considered since the cost of BT was assumed to be common to both interventions. A total of 94% of children started with a 28-day dose titration, taking an average of 10 mg of MPH per day, 70% took an average of 30 mg per day over the 13-month maintenance period, 12% took an average dose of 15 mg per day of DEX over the 13-month maintenance period and 2% received an average dose of 50 mg per day of imipramine. Half-hour consultations with a pharmacotherapist were also included. It was assumed that two visits were made during the titration period and then monthly visits throughout the maintenance period. Additionally, it was assumed that 6% of children did not start titration and that 7% of children who did not make these visits remained persistently unmedicated during the maintenance period.

There were 19 different outcome measures used in the MTA trial and Lord and Paisley[4] chose the teacher version of the SNAP-IV index of hyperactivity/impulsivity since they argued that no HRQoL measure was available and that SNAP-IV was the most similar to the CTRS used in the CCOHTA economic evaluation.

The best estimate of the incremental cost-effectiveness ratio (ICER) for combined therapy versus BT was £1600 per one SD in the SNAP-IV measure (UK 1999 £) as seen in *Table 64*. A few one-way sensitivity analyses were conducted including varying the incremental cost of combination therapy (average of £750 per patient over 14 months) over BT from £500 to £1000. Sensitivity analysis conducted on the ICER suggested that the ratio could be in the range £700–4500.

The study of Lord and Paisley[4] was primarily based on the MTA that was conducted in the USA, where the diagnosis and treatment of ADHD differs in a few respects from the UK, namely that the diagnosis criteria are less stringent. The behavioural treatment in the MTA trial was more intensive than typical treatment in the UK. Little information was reported about the two-way sensitivity analyses conducted and a number of assumptions included in the analysis do not appear to have been tested in the sensitivity analysis. As the authors mention, the MTA trial

TABLE 64 *Cost-effectiveness estimates based on the MTA trial*

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

CL, confidence limit.

did not include a 'global' HRQoL measure for use as the primary outcome measure in an economic evaluation.

The CCOHTA analysis by Zupancic and colleagues[126] undertook a cost-effectiveness analysis using a decision analytic model to compare six interventions including the pharmacological intervention magnesium pemoline (PEM). The base case analysis was conducted excluding PEM and this is of most relevance in the UK where PEM is no longer prescribed owing to an increased risk of liver failure. Therefore, five interventions were compared including two pharmacological strategies: IR-MPH and DEX, one psychological/BT and one combination of psychological/BT and IR-MPH for ADHD in children and adolescents. The interventions were compared with a no treatment alternative. The analysis was conducted from the Canadian, third-party payer perspective and, like the Gilmore and Milne study[123] a 1-year time horizon was adopted.

The effectiveness measure used in the economic evaluation was the Abbreviated CTRS and estimates were derived from the meta-analysis of published clinical trials. The model determined cost in relation to a one- and a six-point reduction in mean CTRS. A six-point reduction in CTRS was considered as a valid and reliable indicator of a clinical response to treatments for ADHD,[54] corresponding to approximately one SD in the distribution of the CTRS in the studies analysed. The CTRS is widely used in trials and contains core and associated features of children with ADHD that the authors believed to be important. The CTRS contains 10 items that have been found to be sensitive indicators of medication effects. Five items relate to core ADHD symptoms of inattention/distractibility, hyperactivity and impulsivity and five to commonly associated characteristics including social and academic adjustment problems that these children experience (disruptive behaviour, inconsistency, low frustration tolerance, emotional lability). Two key assumptions are implicit in using the CTRS as a continuous rating scale, that is, that the cost and desirability of achieving a small gain in CTRS score for many children are assumed to be the same as those of achieving a large gain in CTRS score for few children and that efficacy is constant across baseline levels of ADHD severity. However, the efficacy of stimulants may depend on the quality and severity of symptoms. An attrition rate of 35% was modelled over 6 months based on a previous study (Miller and colleagues, unpublished work) and at 1 year this was estimated to be 15%.

The costs of care included all interventions (including drugs and/or BT contacts), doctor visits and hospitalisations. Resource use was based on evidence in the literature and three expert panels. Unit cost data were obtained from the literature and were expressed in 1997 Canadian dollars. Typically in Canada, the costs for psychological therapies accrue to families except where the service is obtained from the public sector; however, for the sake of consistency, it was assumed these costs were borne by the Ministry. Children on IR-MPH were assumed to have four doctor visits and two specialist visits per year and two laboratory tests at baseline and at 1 year. Children on DEX were assumed to have three doctor visits and two specialist visits. BT included 16 hours of counselling, 8 hours of parent training and 2 hours of teacher training. Combined therapy combined the resource use of BT and IR-MPH above. Children on no treatment were assumed to receive an additional four doctor visits compared with their unaffected peers. It was assumed that the children remained on drug treatment for 1 year and that any adverse drug reactions, beneficial effects and costs ceased with discontinuation of the therapy.

Analysis of expected costs and outcomes of different options indicated that IR-MPH was the

TABLE 65 *Expected costs and effects of alternative strategies, excluding PEM*

Strategy	Cost (Can$)	Incremental cost (Can$)	Effectiveness (CTRS points)	Incremental effectiveness (CTRS points)	Incremental cost-effectiveness
Do nothing	128		0		
IR-MPH	559	431	6.7	6.7	64
DEX	566	7	4.7	–2.0	D
BT	1946	1380	0.3	–4.4	D
BT/IR-MPH combination	2505	559	3.8	3.5	D

D, dominated.

TABLE 66 *Sensitivity analyses (excluding PEM)*

Variable tested	Cost-effectiveness with reference to non-treatment comparator (Can $)			
	IR-MPH	DEX	BT	Combination
Base case	83	D	D	D
Generic IR-MPH	75	D	D	D
School days only	119	D	D	630
120% clinician fee	91	ED	D	D
80% clinician fee	76	D	D	D
Fewer counselling hours but same effect	83	D	D	D
Confidence limits	95	D	D	D
IR-MPH low	74	D	D	D
IR-MPH high	83	D	D	D
DEX low	83	D	D	D
DEX high	83	D	D	D
No treatment low	83	D	D	D
No treatment high	83	D	D	D
Combination low	83	D	D	D
Combination high	83	D	D	311
Worst-case scenario (favouring BT)	103	D	D	196
Weight 16 kg	66	ED	D	D
Weight 40 kg	101	D	D	D

D, dominated; ED, extended dominated, in weighted average with no-treatment comparator.

most cost-effective option for the management of ADHD at Can$64 per CTRS point or Can$384 for a six-point, one-SD gain, as shown in *Table 65*. (For the PEM inclusive programme, high-dose PEM was the next most cost-effective choice; however, its effectiveness data were obtained from one small study in 28 patients and no consideration of hepatotoxicity was made.) DEX did not show a six-point reduction in CTRS but this estimate of lower efficacy was not statistically significant. BT and combination therapies were not shown to be effective in producing clinically significant outcomes.

A number of one-way and extreme-case sensitivity analyses were undertaken for both costs and effects as shown in *Table 66*. A number of variables were tested in the sensitivity analyses and MPH remained the dominant strategy under most assumptions. The results were not sensitive to the upper CI of effectiveness data for DEX, BT and combination therapy. Under the worst-case scenario that favoured BT, the combination therapy was no longer dominated; however, it was still relatively less cost-effective (compared with no treatment) than IR-MPH.

It is worth noting that the cost-effectiveness estimates tested in the sensitivity analyses were based on average cost-effectiveness (with the effect being IR-MPH effect minus the no treatment effect) per effect rather than incremental cost-effectiveness. There are a number of other caveats that might be considered. Perhaps most importantly one might question the key model assumption that improvement in behavioural rating scales is a good surrogate for clinically significant improvements. It is not clear, from the presentation of the results, whether the distribution of change in CTRS is normal and, unless this is so, estimating the number of patients experiencing a six-point reduction using the reported overall mean CTRS will not be accurate. It has been shown that a change in the mean CTRS score can give a different outcome compared with calculating change in numbers of respondents, if the distribution is non-normal (Foster N, personal communication, 2004). Therefore, it may be appropriate to estimate response on an individual, patient-level basis.

The authors note that there is no proven decrease in drug effectiveness over time and that any change in length of drug therapy should result in proportionate changes to both costs and effects over time and therefore that the results may be generalised to any time horizon. However, the same may not be true of non-medical therapy since, as Zupancic and colleagues[126] hypothesise, BT effectiveness might change over time, arguing that skills learnt in early counselling sessions might be forgotten and therefore effectiveness

might decrease but costs would be expected to remain constant.

Other study limitations include the significant heterogeneity of efficacy studies (including decreased power and relatively poor quality of effectiveness studies on the psychological and combination interventions), the sensitivity of results to patient drug compliance and the 1-year time horizon. The latter assumption may bias the results against psychological and combination therapies since the intervention is received for 16 hours yearly rather than daily as for the drug interventions. BT effectiveness was based on a synthesis of two studies. The definition of BT is broad and may differ considerably across studies.

Marchetti and colleagues[128] used a decision analytic model to compute total expected direct costs for the treatment and management of school-aged children with ADHD, comparing six pharmacotherapies: ER-MPH8, IR-MPH, Metadate CD (branded ER-MPH8), Concerta (branded ER-MPH12), Ritalin (branded IR-MPH) and Adderall (a combination of DEX and amphetamine salts). It is worth noting that Adderall is not licensed for use in the UK. All treatments required midday dosing apart from Metadate CD and Concerta. The evaluation was conducted in the USA from the payer perspective, although school-related costs were included.

A clinical algorithm for ADHD management was developed, based on expert opinion, for use as the analytical framework for an economic model to compute total expected costs. Office visits, laboratory tests and use of therapeutic interventions were estimated by the clinicians, and unit costs from the literature were applied. Dosages for the treatments were calculated based on clinical trial data or manufacturers' instructions. To cost the use of midday medication taken at school, a telephone survey of school nurses or members of staff at eight public elementary schools in four US States was undertaken.

Probabilities of clinical success, failure and related information were calculated based on a meta-analysis of studies in the published literature. An effect size was calculated for each outcome in each study based on subtracting the final group mean outcome for the placebo group from that of the intervention group and dividing by the pooled standard deviation of the data. The mean of all effect sizes from all studies was calculated and then recalculated omitting each study in turn to give a set of individual effect sizes using Tukey's jack-knife method. The individual effect sizes were then weighted by the number of studies and subtracted from the overall mean to provide an effect size representing the true overall effect of the intervention irrespective of the outcome measure used. Finally, the effect sizes were combined in a random-effects model to estimate the underlying response rate.

Response rates for Metadate CD, IR-MPH and Adderall were computed based on 10 articles deemed acceptable to reviewers for data extraction and analysis. There were no statistically significant differences among these response rates. Response rates of the other interventions were not available to meta-analyse. The response rates for Ritalin and ER-MPH8 were assumed to be the same as IR-MPH and, to estimate the response rate for Concerta XL (ER-MPH12), the mean responses for Metadate CD, Adderall and IR-MPH were used.

The evaluation period for the model was 4 weeks, as the clinical experts estimated that this was the average time taken to evaluate response to medication. The model assumed that if the patients responded to treatment they would continue to respond over 1 year. If patients did not respond within 4 weeks or if they experienced adverse events related to the medication, it was assumed that the dose would be adjusted in clinical practice and the patient would be re-evaluated after a further 4 weeks. If at this time patients did not respond, they would be re-evaluated and the medication would be switched. If the patient did not respond after four evaluations (16 weeks), the model assumed that the patient would require non-drug interventions in addition to primary ADHD care. Metadate CD had the lowest total annual per patient expected cost ($1487), followed by Concerta XL ($1631), ER-MPH8 ($1792), IR-MPH ($1845), Ritalin ($2080) and Adderall ($2232).

Rank order (one-way) sensitivity analyses were conducted to test the robustness of the results to changes in the drug acquisition cost (per tablet) and the cost of in-school dosing. Threshold analyses for drug acquisition costs and response rates were also undertaken. The rank ordering of results remained fairly robust to these tests.

Compliance was not considered in the analysis. However, the authors state that once-daily dosing tends to have a compliance benefit over twice-daily and three times daily dosing. Lack of compliance

associated with multiple daily dosing is expected to result in higher total costs. The impact of co-morbid conditions on the costs of care was not assessed, nor were patient preferences or QoL variables. The model relies on assumptions about the relative efficacy of the drugs evaluated and does not have a strong evidence base. Metadate CD was assumed to have a higher response rate than its generic counterpart, ER-MPH8, and the authors failed to justify this.

Vanoverbeke and colleagues[129] also used a decision-analytic framework to model costs for management of ADHD in 6–16-year-old children in the UK. Medications compared starting treatment with IR-MPH (once, twice or three times daily), Concerta XL or BT over a 1-year time horizon.

An incidence-based decision tree was constructed and the probabilities of success or failure were based on average probabilities derived from the literature. The probabilities for second-line treatment were obtained from an expert panel of eight UK psychiatrists and paediatricians, as were data on treatment choices in response to adverse events, co-morbidities and/or insufficient response to treatment. Six out of the eight experts involved also estimated resource use data for a typical ADHD patient requiring treatment. To obtain the data from an expert panel a two-stage approach was followed, including a questionnaire completed independently. Group average responses and range of responses for each item were presented and the experts were asked to provide new estimates and a 'certainty score' to indicate the expected variability associated with a given value (of between one and four).

Costs were based on published estimates and hospital prices and relate to 2001. Costs of medications, laboratory tests, clinical personnel and school staff personnel involved in BT were included. Clinical outcomes for BT and IR-MPH were obtained from the MTA trial and for Concerta XL were obtained from Pelham and colleagues.[82]

The cost of starting treatment with IR-MPH was marginally lower than with Concerta XL (£1332 and £1362, respectively) and BT was the most costly initial treatment (£2147). The probability of treatment success was highest for Concerta XL (77.8%),[82] then IR-MPH (55.6%),[133] followed by BT (33.8%).[133]

Data from different trials were used in the model and this breaks the randomisation achieved in the individual trials. As the authors state, Pelham and colleagues' study[82] on which the Concerta XL clinical outcomes are based was a short-term, small-scale study. A probabilistic sensitivity analysis was undertaken which showed that results were sensitive to treatment success and the proportion of patients with co-morbidities. Although the sensitivity analysis did not alter the results, the response rates used in the model may be questioned.

In summary, across the five studies reviewed above, all were based on a 1-year time horizon, with the exception of the Lord and Paisley study[4] that covered a period of 14 months. However, ADHD and treatment are known to continue for much longer. Therefore, no consideration of long-term adverse events or outcomes is incorporated within the analyses. None of the full economic evaluations compared all treatment strategies relevant to this review. Zupancic and colleagues[126] did compare a number of treatments, but no assessment of ATX drug therapy, which is necessary for this review, was provided. A common feature across all studies is the lack of data, with expert/author opinion being used to fill in gaps.

In addition to the existing economic evaluations, three submissions were received from Janssen-Cilag, Celltech and Eli Lilly.

Review of the Janssen-Cilag submission

Overview

The aim of the Janssen-Cilag submission was to compare Concerta XL (ER-MPH12) with IR-MPH, ATX, Equasym XL (ER-MPH8) and behavioural therapy (BT) using new evidence made available since the previous NICE guidance was issued.[134] The previous guidance recommended the use of IR-MPH as part of a comprehensive treatment programme, including advice and support to parents and/or teachers and potentially BT, for children diagnosed with severe ADHD. 'Severe ADHD' was defined as broadly similar to HKD, although it also includes some patients with severe problems with inattention and/or hyperactivity who do not meet the diagnostic criteria for HKD. Treatment initiation was restricted to child and adolescent psychiatrists or paediatricians, but prescriptions could then be maintained by GPs.

A cost–utility analysis (classified CIC) was conducted based on the results of two recent randomised, open-label studies comparing Concerta XL with IR-MPH[90] and ATX[99] and the MTA trial.[133] The model took the form of a

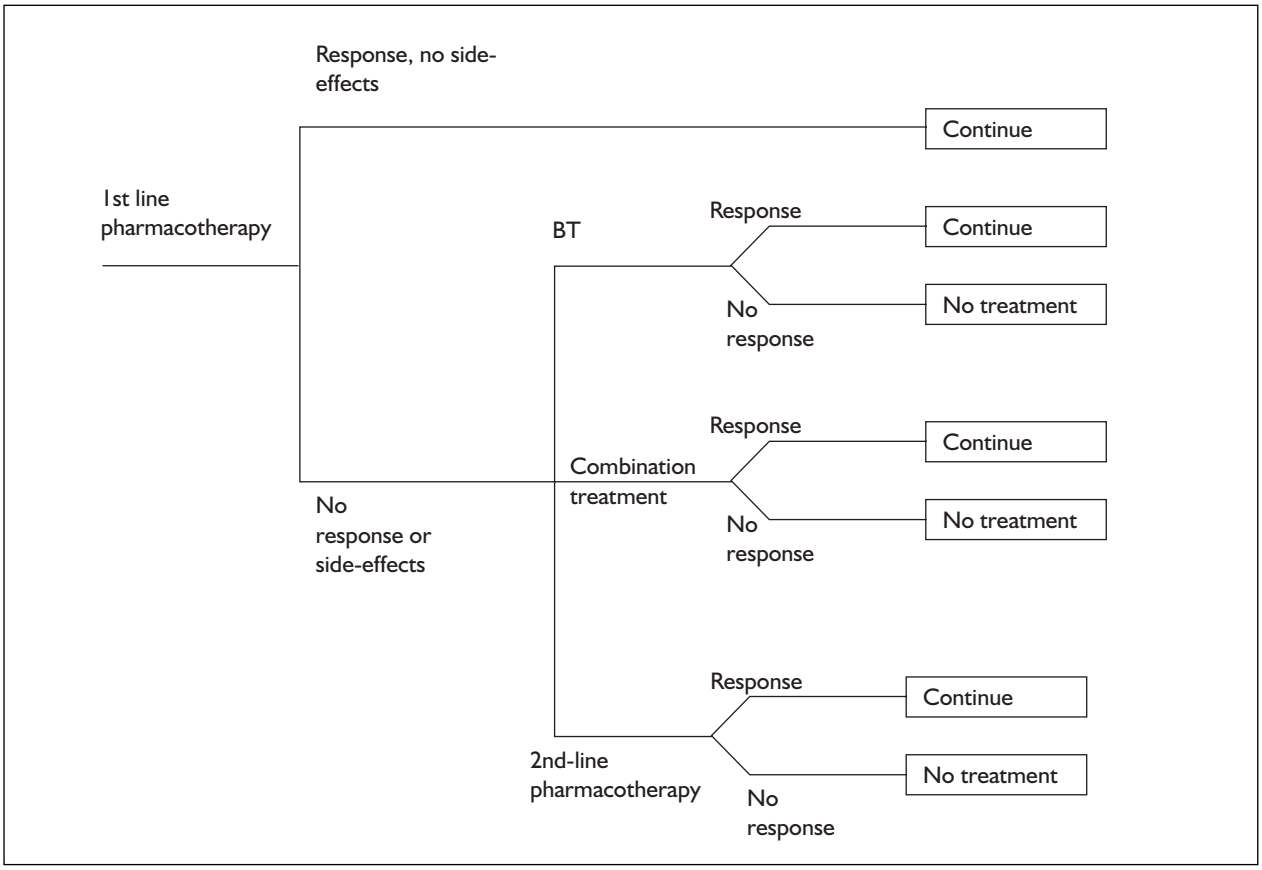

FIGURE 21 *Flow-chart of the cost–utility model submitted by Janssen-Cilag*

decision tree with a time horizon of 1 year, and was conducted from the perspective of the UK NHS. A 'no treatment' arm was not included on the basis of the previous NICE guidance.[134]

Model structure

In the model, patients begin therapy on BT, IR-MPH, Concerta XL, ATX or Equasym XL. If they responded to this first-line therapy and experienced no side-effects, then they were assumed to continue on the same treatment for the rest of the year. If patients failed to respond to first-line treatment, or experienced intolerable side-effects within 1 month, they could then switch to second-line treatment with BT (where BT was not the first-line therapy), combination treatment (BT plus the first-line pharmacotherapy) or other drug treatment. The BT components were not defined explicitly in the model, but as the effectiveness data are sourced from the MTA trial[133] we may assume that they correspond to that trial protocol. The other drug treatment was assumed to be DEX for patients receiving first-line pharmacotherapy and IR-MPH for patients receiving first-line BT. Patients responding to second-line treatment remained on that therapy for the remainder of the year, and patients not responding within 1 month of beginning second-line therapy were assumed to discontinue all treatment. *Figure 21* presents a flow-chart of the model. Owing to the 1-year time horizon, discounting was not necessary.

Summary of effectiveness data

The measure of clinical effectiveness used in the model was response rate to treatment. For the comparison of Concerta XL with IR-MPH, the effectiveness evidence was taken from the CON-CAN-1 study.[90] The definition of a response was taken from Swanson and colleagues[133] as a mean score of ≤1 on the parent-rated SNAP-IV scale. The same definition of response was used to extract effectiveness data for BT from the BT-only arm of the MTA trial. For the comparison of Concerta XL with ATX, the effectiveness evidence was taken from the FOCUS study.[99]

[Confidential information removed].

The model also allowed patients to discontinue therapy owing to inefficacy or adverse events within 1 month. The data on discontinuation rates

TABLE 67 *Response rates and discontinuation rates used in the cost–utility model submitted by Janssen-Cilag*

Treatment	Response rate	Discontinuation rate
BT IR-MPH Concerta XL ATX Equasym XL Combination treatment DEX	**[Confidential information removed]**	

TABLE 68 *Proportions of patients switching to alternative second-line therapies in cost–utility model submitted by Janssen-Cilag*

	Switch from	
Switch to	**1st line BT (%)**	**1st line pharmacotherapy (%)**
IR-MPH	57.92	NA
Combination treatment	42.08	37.42
BT	NA	17.35
DEX	NA	45.24

NA, not applicable.

TABLE 69 *Annual treatment, follow-up and monitoring costs used in cost–utility model submitted by Janssen-Cilag*

Item	Behavioural therapy (£)	Drug treatment (£)	Combination treatment (£)
Programme cost	1033	Varies	1033 + drug cost
Consultations:			
Responders	333	737	737
Non-responders	808	1012	1012
Co-morbidities	652	349	349
Tests:			
Responders	5.3	0.5	0.5
Non-responders	43	79.6	80
Co-morbidities	6.0	4.9	4.9

were based on CON-CAN-1[90] for Concerta XL and IR-MPH.

[Confidential information removed].

The response rates and discontinuation rates used in the submission are shown in *Table 67*.

The proportions of patients switching to BT, combination treatment or DEX as second-line therapy were based on a previously published study that used expert opinion.[129] These proportions are shown in *Table 68*.

Summary of resource utilisation and cost data

The resource use associated with managing ADHD patients on BT, pharmacotherapy and combination treatment was based on an update of a previously published study that used expert opinion.[129] Resource use quantities were estimated separately for responders and non-responders and for the presence of co-morbidities. The panel estimated the annual costs of each programme, including the cost of the BT, the cost of follow-up consultations and the cost of monitoring tests, and these were divided into monthly figures for the purpose of the model. In order to do this, annual costs were divided by 12, with the exception of the treatment cost of BT. This was assumed to take place over a period of 8.63 weeks, and so the cost of this was divided by 8.63 and multiplied by 4 weeks (assuming 4 weeks = 1 month), and was only applied in the first 2 months in the model. *Table 69* shows the relevant annual costs for each strategy.

TABLE 70 *Data for weighted average daily dose in the cost–utility model submitted by Janssen-Cilag*

Dosing IR-MPH or DEX	Nearest equivalent dose Concerta XL	Patients continue on dose (%)
[Confidential information removed]		

TABLE 71 *Annual costs of pharmacotherapy used in the cost–utility model submitted by Janssen-Cilag*

Drug	Annual cost (£)
DEX	112
IR-MPH	110
Concerta XL	381
Equasym XL	317
ATX	914

The follow-up consultations and monitoring tests include those resulting from adverse events. The costs were inflated to 2003 values using the inflation rate for hospital and community health services in the UK.[135] For the purpose of the model, it was assumed that 50% of patients had co-morbidities. The cost of a patient discontinuing all therapy was assumed to be equal to that of a non-responder to behavioural therapy.

The unit costs of the pharmacotherapy were based on published sources for those treatments available in the UK.[29] The cost per milligram of each of the drugs is £0.019 for DEX and IR-MPH, £0.050 for 18-mg tablets of Concerta XL and £0.034 for 36-mg tablets of Concerta XL.

[Confidential information removed].

The dosing schedules considered are shown in *Table 70*.

[Confidential information removed].

The price of Equasym XL was not available for the UK, so it was assumed to be £1 per day, which was entered into the model as 0.8 times the weighted average cost of Concerta XL. The annual costs of each drug are shown in *Table 71*.

Summary of utility data

The utility data were based on a previously published poster[136] that obtained UK-based EQ-5D scores elicited from parents acting as proxies for their children with ADHD. The utility values were 0.837 for responders, and 0.773 for non-responders, regardless of treatment type.

[Confidential information removed].

Summary of cost-effectiveness

The results from the deterministic model are shown in *Table 72*. First-line Equasym XL, BT and ATX were all found to be dominated by Concerta XL. A treatment dominates an alternative when it is less costly and more effective. The cost per QALY gained with Concerta XL compared with IR-MPH is well within the commonly used values of willingness to pay for a QALY.

[Confidential information removed].

The data used for the probabilistic analysis are shown in *Tables 73* and *74*.

The CIs around the non-drug resource use are relatively wide. It is not clear, either from the submission or the previous publication, whether these estimates represent first- or second-order uncertainty. One would expect first-order uncertainty to be greater than second-order uncertainty, which may explain the width of the CIs, but this would mean that the uncertainty in the model results is slightly overestimated.

TABLE 72 *Cost-effectiveness results from the model submitted by Janssen-Cilag*

First-line treatment	Cost per patient £)	QALYs per patient	ICER
IR-MPH	**[Confidential information removed]**		–
Concerta XL			4992
Equasym XL			D
ATX			D
BT			D

TABLE 73 *Effectiveness data for probabilistic analysis in the cost–utility model submitted by Janssen-Cilag*

Parameter	Mean	SE
Response rate (%)		
BT		
IR-MPH		
Concerta XL		
ATX		
Equasym XL		
Combination treatment		
DEX		**[Confidential information removed]**
Discontinuation rate (%)		
BT		
IR-MPH		
Concerta XL		
ATX		
Equasym XL		
DEX		
Switching probabilities (%)		
From 1st-line BT		
To IR-MPH	57.92	
To combination treatment	42.08	
From 1st-line pharmacotherapy		
To BT	17.35	
To combination treatment	37.42	
To DEX	45.24	

SE, standard error.

TABLE 74 *Annual cost data for probabilistic analysis in the cost-utility model submitted by Janssen–Cilag*

Parameter	Mean (£)	Minimum (£)	Maximum (£)	Median (£)
BT				
Programme cost	1033			
Consultations – responders	333			
Consultations – non-responders	808			
Consultations – co-morbidities	652			
Tests – responders	5			
Tests – non-responders	43			
Tests – co-morbidities	6			
Pharmacotherapy				
Consultations – responders	737			
Consultations – non-responders	1012	**[Confidential information removed]**		
Consultations – co-morbidities	349			
Tests – responders	0			
Tests – non-responders	80			
Tests – comorbidities	5			
Drug costs				
IR-MPH	110			
Concerta XL	381			
DEX	112			
ATX	941			
Equasym XL	317			

The probabilistic results were used to construct cost-effectiveness acceptability curves (CEACs) comparing all five treatment strategies, according to the method described by Fenwick and colleagues.[137]

[Confidential information removed].

Comments on methodology

Time horizon

Although ADHD is a chronic condition, the submission assesses the cost-effectiveness of the alternative treatment strategies over the course of 1 year. **[Confidential information removed]**. It is important to note that although the treatment decision may be reviewed annually, the decision problem at the point of review is different to the initial treatment decision. At the point of review, the GP will know which treatments the patient has failed to respond to, which caused adverse events and which produced a favourable response.

[Confidential information removed].

The consequence of the short time horizon is that long-term implications of treatment for ADHD are not considered. As a consequence, it is difficult to know how cost-effective Concerta XL would appear over a time horizon longer than 1 year.

Use of trial data

The cost–utility model in the submission made very selective use of the body of evidence concerning the efficacy of the alternative treatment strategies. The effectiveness evidence was based on only three trials,[90,99,133] out of 65 potentially relevant studies identified in the clinical effectiveness review in Chapter 4. The justification for ignoring the majority of the RCT data was that double-blind, double-dummy trials cannot assess the effectiveness of a once-daily extended release formulation of IR-MPH in comparison with twice- or three times daily administration of IR-MPH as both arms receive the same number of pills. Janssen-Cilag argue that compliance to a product given once in the morning may be higher than one needing to be taken during the school day, and hence they make use of two open-label pragmatic randomised trials.[90,99]

[Confidential information removed].

The response rates to BT, **[Confidential information removed]** were taken directly from the MTA trial.[133] This extraction of data from single arms of a trial breaks the randomisation, and implicitly assumes that the baseline characteristics of the patients in the CON-CAN-1, FOCUS and MTA trials are identical. This is unlikely to be the case and this methodology is inappropriate. A more appropriate approach would have been to take the relative treatment effects from each study and apply them to a common baseline. Finally, the definition of response for ATX **[Confidential information removed]** differs from that used for the other comparators considered in the model (£1 mean parent-rated SNAP-IV score). This is most likely due to a lack of outcome data employing the SNAP-IV scale for ATX. The submission does not provide evidence as to the comparability of these two definitions of response.

The discontinuation rates were also based only on CON-CAN-1 **[Confidential information removed]**. This limited use of data will fail to incorporate differences in side-effect profiles between these drugs. The costs associated with adverse events were also not differentiated by drug. In this respect, it is important to consider that the minimum dose of Concerta XL is 18 mg per day, as it is not possible to divide the extended-release capsules. This compares with a minimum dose of 5 mg with the other drugs, and so patients requiring <18 mg per day, or >18 mg and <36 mg per day, would receive a higher dose of IR-MPH on Concerta XL compared with, for example, IR-MPH (see *Table 70*). The submission by Celltech states that Equasym XL will be available in 10, 20 and 30 mg. It is also important to consider that Concerta XL, owing to its 12-hour action, is suitable for replacing three times daily dosing of IR-MPH, and so may not be suitable for patients requiring once- or twice-daily IR-MPH. Likewise, Equasym XL, with its 8-hour action, would not be suitable for a patient requiring IR-MPH once daily, but could be combined with an evening dose of IR-MPH for children requiring doses three times daily. A further concern is that the definition of discontinuation is given as 'discontinuation due to inefficacy or adverse events', which may overlap with non-response. Those patients who withdraw from treatment owing to inefficacy would be included in the calculation of response rate in an ITT analysis, and thus be represented in both the discontinuation rate and the rate of non-response. In the model, these patients would be counted twice, and therefore the model may overestimate the number of patients discontinuing treatment owing to inefficacy or adverse events. The model results were shown to be sensitive to the choice of discontinuation rate.

TABLE 75 *Results of amendments to the cost–utility model submitted by Janssen-Cilag*

Amendment	Comparison	Incremental cost per QALY (£)
None – base case	Concerta XL vs IR-MPH	4,992
Second-line combination therapy with DEX (1)	Concerta XL vs IR-MPH	4,903
Including drug costs during titration (2)	Concerta XL vs IR-MPH	7,954
Taking BT component out of cost of discontinuing treatment (3)	Concerta XL vs IR-MPH	19,303
Including co-morbidity costs as additional to responder/non-responder costs (4)	Concerta XL vs IR-MPH	61
All of the above (1-4)	**Concerta XL vs IR-MPH**	**9,253**

Model structure

The model assumes the same response to combination treatment (i.e. drug treatment plus BT), regardless of the accompanying drug therapy. The model allows the combination treatment to include the drug to which the patient has previously failed to respond, or experienced adverse events with as first-line therapy. A more realistic assumption would have been to have combination treatment with DEX, according to the assumption used for third-line pharmacotherapy in the model. This amendment forms option 1 for the re-analyses shown in *Table 75*.

Errors in model

As mentioned earlier in the review, the annual cost of each drug excludes the cost during the average titration period **[Confidential information removed]**. This appears to have been omitted in error. Correcting for this error forms option 2 for the re-analyses shown in *Table 75*. An alternative method would be to calculate more precisely a weighted average cost using the actual number of days spent on each dosage, rather than the average over all doses. The monthly cost of a patient discontinuing all treatments is assumed to be equal to that for a non-responder to BT, but in the model the cost also includes the total cost of a BT treatment programme divided by 12. The reasons for this are unclear; such a patient would not receive the BT programme, only the follow-up consultations and tests. This extra monthly cost is fairly high (£86), and the effect of its removal can be seen in option 3 in *Table 75*. Another error appears to be present in the way that the cost of co-morbidity is included in the model. As *Table 69* shows, the annual medical cost associated with co-morbidities for patients receiving medical treatment is lower than that for responders and non-responders. Hence the 50% of non-responders who are assumed to have co-morbid conditions cost less than those without co-morbidities. It appears that the quoted cost of co-morbidities actually refers to the **additional** cost of co-morbidities, on top of medical costs for responders and non-responders. This forms option 4 in *Table 75*.

The assumption that the utility for the first month of any treatment is equal to **[Confidential information removed]** seems rather arbitrary. An alternative approach would have been to observe the number of patients responding at 1 month for each treatment, and assume that on average these patients responded half way through the first month.

When re-run, the results of the probabilistic analysis proved to be fairly variable. This can be overcome by increasing the number of simulations from 1000 to, for example, 10,000.

In the probabilistic sensitivity analysis, the proportions switching to each second-line therapy were modelled independently. This allowed the sum of those proportions to fall below or exceed one in nearly all simulations. Clearly, it is not appropriate in a decision-modelling context to have proportions or probabilities not summing to one when all possible paths have been identified. Therefore, for the two transitions possible following first-line BT, this error is corrected by making one of those probabilities (for example, the probability of switching to DEX) equal to one minus the other. For the three transitions possible following first-line pharmacotherapy, this error is corrected by dichotomising the three-way transition and adjusting the estimated probabilities appropriately using Bayes' revision theorem. These adjustments ensure that the number of patients in the model remains constant and does not increase or decrease.

The review also uncovered a mis-reference in calculating the costs of behavioural therapy. Correcting this error did not change the results as behavioural therapy was consistently dominated. We re-analysed the model by Janssen-Cilag, correcting for each of the detailed errors in turn. The results of these re-analyses are shown in *Table 75*.

Review of the Celltech submission

Overview

The aim of the Celltech submission was to compare Equasym XL (ER-MPH8) with no treatment in patients unable to comply with twice-daily IR-MPH, using new evidence made available since the previous NICE guidance was issued.[134] The submission therefore concentrates on data concerning the effectiveness of Equasym XL, which was not included in the previous review. A secondary analysis also compared Equasym XL with no treatment and twice-daily IR-MPH.

A partially probabilistic cost–utility analysis was conducted based primarily on reviews of treatment for ADHD. The model took the form of a decision tree with a time horizon of 1 year, and was conducted from the perspective of the UK NHS. Concerta XL (ER-MPH12) and ATX were not included as comparators.

Model structure

Patients enter the model on MPH, in the form of Equasym XL, in the base case. IR-MPH is added as a second comparator in the secondary analysis. After a 42-day titration period, patients may comply or not with treatment. Non-compliers are assumed to continue on treatment, but experience no health benefits. Among those complying with treatment, the proportion that experience a response and no intolerable side-effects are assumed to remain on treatment for the rest of the year; the proportion who do not respond, or who experience intolerable side-effects, progress to second-line treatment with DEX. Second-line therapy follows the same pattern as first-line therapy, with a 42-day titration period, compliers/non-compliers and discontinuations due to inefficacy or adverse events. Those patients who discontinue DEX may progress to BT or no treatment. In the base case it is assumed that 50% of these patients will progress to BT and experience health benefits, whereas the remaining 50% will progress to no treatment and receive no health benefits. The BT was described as intensive psychosocial treatment involving eight visits to members of child/adolescent psychiatry or psychology teams.

Patients progressing through the model were compared with 'no treatment' in the base case, which was assumed to incur no health costs or health benefits. Owing to the 1-year time horizon, discounting was not necessary.

Summary of effectiveness data

The model assumed that compliance with morning doses of each drug would be 85% (95% CI 50 to 100%) and compliance with lunchtime doses of twice-daily drugs would be 55% (95% CI 40 to 85%). The uncertainty around these estimates was characterised using a normal distribution. These values were chosen to correspond to reported figures of overall compliance to IR-MPH of 65–75%.[41,138] Hence compliance to Equasym is calculated to be 85% and compliance to IR-MPH or DEX is, on average, 70%.

The measure of effectiveness used in the model was response rate to treatment. The model assumes that response rates to IR-MPH, Equasym XL and DEX will be equal, based on previously published evidence that they are similar.[59,139] The response rate is set at 70% (Scottish Intercollegiate Guidelines Network, 2001).[4,123] A definition of response is not provided. The model also assumed that around 6% of patients beginning any of the drug therapies would discontinue owing to adverse events,[123] which gives a continuation rate of 66% (70% of 94%). The uncertainty around this estimate was characterised using a normal distribution where the upper and lower bounds of the 95% CI were assumed to be 60 and 82%, respectively.

Summary of resource utilisation and cost data

The unit costs of medication were based on published pricing lists for the UK (BNF 47). Equasym XL is not currently priced in the UK, and so the submission includes costs specified by the manufacturer. The prices used are shown in *Table 76*.

During the titration period, it was assumed that one-third of patients would be on the equivalent of 5, 10 and 15 mg of IR-MPH twice daily, respectively. The average dose after titration was assumed to be 30 mg per day, based on previously published data[123] and data from the IMS Health Disease Analyser Mediplus dataset (reference not provided in submission). Patients progressing to DEX were assumed to receive 5 mg once daily at the start of the titration period, and assumed to reach an average of 10 mg per day subsequently,

TABLE 76 *Unit costs of IR-MPH, Equasym XL and DEX used in the cost–utility model submitted by Celltech*

Drug	Pack	Price (£)
DEX	5 mg × 28	2.61
IR-MPH	5 mg × 30	2.78
	10 mg × 30	5.57
	20 mg × 30	9.98
Equasym XL	10 mg × 30	25.00
	20 mg × 30	30.00
	30 mg × 30	35.00

according to a published UK protocol.[140] It was assumed that 50% of the titration period would be at an average dose of 5 mg and 50% at an average of 10 mg once daily. Non-compliers were assumed to incur the same drug costs as those complying with therapy.

The resource use associated with ADHD was based on Wessex DEC evaluation,[123] which used expert opinion to determine treatment patterns. All patients receiving drugs were assumed to receive six outpatient visits with a child psychiatrist or paediatrician at a cost of £111 per visit, and six GP visits per year at a cost of £20.[141] Patients discontinuing treatment were assumed to receive two outpatient visits per year. Patients receiving BT were assumed to receive eight 100-minute consultations, 50% with members of a child/adolescent psychiatry team and 50% with members of a clinical psychology team. The cost of these was obtained from published UK sources,[141] and was £64 per person-hour for the psychiatry team and £39 per hour for the psychology team. Non-compliers were again assumed to receive the same cost as compliers.

The model did not include any costs associated with side-effects of treatment.

Summary of utility data

The base case analysis used utility values from a previously published evaluation of treatments for ADHD.[4] These were calculated using EQ-5D, by assuming that an untreated ADHD patient corresponded to the EQ-5D health state 11211, which gives a utility of 0.883. A successfully treated patient was assumed to return to full health, health state 11111, giving a utility of 1.000.

Summary of cost-effectiveness

The base case analysis compared Equasym XL with no treatment in patients unable to comply with twice-daily IR-MPH. The estimated total costs and QALYs for no treatment were £0 and 0.883 (no probabilistic parameters were involved in this calculation). The total costs and QALYs for Equasym XL were estimated to be £1073 (95% CI £1035 to 1116) and 0.9562 (95% CI 0.9425 to 0.9667). The ICER for Equasym XL compared with no treatment was therefore estimated to be £14,657 per QALY (95% CI £12,564 to 18,538). The 95% CI for the ICER was calculated by taking the 5th and 95th percentile of the 10,000 probabilistic simulations. In this instance this method is valid because all of the simulated incremental costs and benefits of Equasym XL lay in the northeast quadrant of the cost-effectiveness plane (i.e. Equasym XL was more effective and more expensive than no treatment in all simulations), and so the problem of negative ICERs did not arise. The probabilistic simulations were used to plot a CEAC, which showed that at a willingness-to-pay threshold of £30,000 per QALY, Equasym XL was the most cost-effective strategy in 100% of simulations.

A number of one-way sensitivity analyses were also conducted in which the ICER for Equasym XL compared with no treatment was shown to remain under £30,000 per QALY for a range of values input for compliance to the morning dose of medication, the utility estimates, response rate, length of titration, cost of paediatric outpatient appointments and drug costs for non-compliant patients. The results of these are shown in *Table* 77.

A second scenario considered three times daily dosing, where the dose of Equasym XL must be supplemented with an evening dose of IR-MPH. This increased the costs of Equasym XL to £1.45 per day. Compliance to this evening dose of IR-MPH was assumed to be 85%. The reported result from this analysis is an ICER of £15,536 for Equasym XL relative to no treatment.

The secondary analysis compared Equasym XL with IR-MPH and no treatment. The estimated costs and QALYs for the no treatment and

TABLE 77 *Results of sensitivity analyses conducted in the cost–utility model submitted by Celltech*

Parameter value	ICER for Equasym vs no treatment (£)
Compliance to morning dose (£)	
50	26,748
100	12,066
Utility (treated, non-treated)	
1.000, 0.692	5,568
0.970, 0.884	15,238
Daily cost Equasym XL (baseline £1.17) (£)	
0.58	12,827
1.76	16,487
Response rate (%)	
60	14,836
82	14,237
Length of titration period (days)	
21	13,634
70	16,256
Cost of outpatient appointment (£)	
89	12,991
138	16,702
Reduction in drug cost for non-compliant (%)	
50	14,383
100	14,108

Equasym XL arms remained the same as in the base case analysis. The estimated total costs and QALYs for IR-MPH were £930 and 0.9433. When more than two programmes are being compared, the ICERs are calculated using the following process:

1. The strategies are ranked in terms of cost (from the least expensive to the most costly).
2. If a strategy is more expensive and less effective than the previous strategy, then this strategy is said to be dominated and is excluded from the calculation of the ICERs.
3. The ICERs are calculated for each successive alternative, from the cheapest to the most costly. If the ICER for a given strategy is higher than that of the next more effective strategy, then this strategy is ruled out on the basis of extended dominance.

Finally, the ICERs are recalculated excluding any strategies that are ruled out using the notions of dominance and extended dominance. The ICER for IR-MPH compared with no treatment was £15,432 per QALY and the ICER for Equasym XL compared with IR-MPH was £11,043 per QALY. Hence in the secondary analysis, IR-MPH was extended dominated by Equasym XL. The results of the secondary analysis were very sensitive to the choice of compliance rates, and the results of a two-way sensitivity analysis of these are shown in *Table 78*.

Although the submission does not clarify whether the negative ICERs are the result of a positive difference in cost and a negative difference in effect, or of a negative difference in cost and a positive difference in effect, one can assume that they were a result of the former as they fall into those analyses where the compliance to the lunchtime dose is higher than compliance to the morning dose.

Introducing costs for the in-school administration of a lunchtime dose into this secondary analysis improved (reduced) the ICER for Equasym XL compared with IR-MPH.

Comments on methodology

Choice of comparators

The model did not include the full range of comparators. This was justified in the model by specifying the potential population to be those patients who were intended to receive IR-MPH twice daily, and so longer-acting alternatives such as Concerta XL and ATX would not be relevant. A secondary analysis that considered patients requiring IR-MPH three times daily also did not then introduce those further relevant comparators such as Concerta XL and ATX.

TABLE 78 *Two-way sensitivity analysis of morning and lunchtime compliance rates in secondary analysis of the cost–utility model submitted by Celltech*

	ICER for Equasym XL compared to IR-MPH (£)									
	Lunchtime compliance (%)									
Morning compliance (%)	50	55	60	65	70	75	80	85	90	95
50		–90,012	–45,925	–31,229	–23,882	–19,473	–16,534	–14,435	–12,860	–11,635
55	84,780		–88,457	–45,148	–30,711	–23,493	–19,162	–16,275	–14,212	–12,666
60	40,694	83,226		–86,902	–44,370	–30,193	–23,104	–18,851	–16,016	–13,990
65	25,998	39,916	81,671		–85,348	–43,593	–29,675	–22,716	–18,540	–15,757
70	18,650	25,480	39,139	80,116		–83,793	–42,816	–29,156	–22,327	–18,229
75	14,242	18,262	24,962	38,362	78,561		–82,238	–42,038	–28,638	–21,938
80	11,302	13,931	17,873	24,443	37,584	77,007		–80,683	–41,261	–28,120
85	9,203	**11,043**	13,620	17,484	23,925	36,807	75,452		–79,128	–40,483
90	7,629	8,981	10,784	13,309	17,096	23,407	36,029	73,897		–77,574
95	6,404	7,434	8,759	10,525	12,998	16,707	22,889	35,252	72,342	

TABLE 79 *Subgroups considered in the cost–utility model submitted by Eli Lilly*

Subgroup	Description
1	Stimulant-naïve patients with no contraindications to any treatment option
2	Stimulant-naïve patients with contraindications to stimulants (MPH and DEX)
3	Stimulant-exposed patients who have previously failed on MPH therapy owing to adverse events or inefficacy
4	Stimulant-exposed patients with contraindications to stimulants (MPH and DEX)
5	Stimulant-exposed patients who have no contraindications to any treatment option, and who have not failed on previous therapy for either adverse events or inefficacy

Time horizon

The model employed a time horizon of 1 year, which excludes consideration of the longer term outcomes associated with ADHD and its treatment.

Compliance

The main difference between treatments is the assumed levels of compliance to morning and afternoon doses of medication. Unfortunately, this information was based on expert opinion using an estimate of overall compliance and a two-way sensitivity analysis showed that the results were very sensitive to the assumption made. The submission also fails to justify why compliant non-responders would be identified and moved to an alternative treatment, but non-compliers, who by definition fail to respond, would not be identified as non-responders.

Review of the Eli Lilly submission

The electronic model to accompany the Eli Lilly submission was not examined owing to its late submission. Therefore, this review reports the model structure, inputs and results as reported by Eli Lilly, but these values could not be validated by examination of the model.

Overview

The submission states that a Markov model was used to examine the cost-effectiveness of adding ATX to an existing strategy of medical management for ADHD. The underlying general strategy was that a new patient would be given an MPH formulation first-line, followed by DEX as a second-line alternative in the event of treatment discontinuation, followed by no treatment. ATX was added as an additional treatment option prior to MPH. The model considered five subgroups with varying ineligibility for one or more of the treatment options. *Table 79* details the subgroups considered in the model.

For groups 1 and 5, the treatment strategies compared are IR-MPH or ER-MPH, followed by DEX, followed by no treatment, with or without ATX prior to MPH. For groups 2 and 4, the

TABLE 80 *Response[a] rates (%) estimated in the meta-regression submitted by Eli Lilly*

Treatment	Stimulant-naïve patients (%)	Stimulant-exposed patients (%)	Overall (%)
ATX	70.51	62.17	65.08
Methylphenidate	77.27	70.03	73.35
Placebo	41.46	32.75	35.85

[a] Response is defined as ≥ 25% reduction in parent-rated ADHD-RS.

treatment strategies are no treatment, with or without ATX as first-line therapy. For group 3, the treatment strategies are DEX, followed by no treatment, with or without ATX prior to DEX.

Model structure

Patients beginning the model on active treatment could experience a response to that treatment. Patients responding to treatment could relapse in subsequent cycles to become non-responders. Patients on active treatment could also experience adverse events, which may resolve in subsequent cycles, or discontinue with treatment. Patients could discontinue treatment owing to lack of response, in reaction to an adverse event or for other reasons. Discontinuation of treatment is followed by the next treatment in the prespecified strategy, until the patient reaches no treatment at the end of the strategy.

The model was estimated using patient-level simulation, and 20,000 simulations were executed for each run of the model. The submission states that the model was used to determine which of the five subgroups each simulated patient would fall into, although further details of this process are not given. Further details of the execution of the patient-level simulation are not provided. The time horizon was 1 year, and so discounting was not relevant.

Summary of effectiveness data

The response rates were calculated from a meta-regression using patient-level data from five clinical trials[70,89,142] (two of which are currently unpublished) comparing ATX with MPH, and in some cases also to placebo. One of the trials included ER-MPH (unpublished) and the remaining four included IR-MPH. Four were randomised double-blind studies and the fifth was a randomised open-label study.[70] The model assumes equivalence of IR-MPH and ER-MPH, and does not differentiate between study types. Response was defined as ≥ 25% reduction in parent-rated ADHD-RS score, and was estimated using a fixed-effects logistic regression with treatment, stimulant exposure, age, sex and duration of treatment as covariates. Duration of treatment refers to the duration of the acute phase of each trial. An additional study-level covariate was included to allow differences in baseline between studies. The results of the logistic regression are shown in *Table 80*.

Data on relapse was obtained from two trials,[56,75] both specifically designed to look at relapse to ATX and amphetamine sulphate, respectively. The relapse rates over 9 months were approximately 20% for ATX and 30% for amphetamine sulphate, compared with placebo rates of 40 and 70%, respectively. The submission states that owing to differences in the definition of response and relapse used in the two trials, and the absence of data regarding MPH, they deem the evidence insufficient for differentiating between the alternative treatments. Hence the probability of relapse is the same for all active treatments.

The probability of response to treatment in patients who have failed MPH was taken from a crossover trial of IR-MPH and DEX[143] where 67.74% of a subgroup of patients who failed to respond to first-line therapy with MPH subsequently responded to DEX. The definition of response in the study was a ≥10-point reduction in the hyperactivity subscale of the revised CPRS. The model assumes that the response to ATX in patients who have failed MPH will be equal to that with DEX. The submission does not report the response rate to DEX in patients who have not failed on MPH. The relative risk of response for placebo compared with ATX calculated in the meta-regression was applied to the rate of response in MPH-failed patients receiving DEX to calculate the response rate for no treatment. In patients contraindicated for stimulants, the response rate for ATX was taken from a clinical trial whose inclusion criteria included the presence of tics disorder or Tourette syndrome (unpublished – no further information provided in submission). The response rate to ATX is reported to be 66.67% in this co-diagnosed population. *Table 81* shows the response and relapse rates used for each subgroup examined in the model.

TABLE 81 *Monthly response and relapse transition probabilities by subgroup used in the cost–utility model submitted by Eli Lilly*

Parameter	ATX	MPH (instant or extended release)	DEX	No treatment
Subgroup 1				
Response	0.7051	0.7727	NA	NA
Relapse	0.0206	0.0206	NA	NA
Subgroup 2				
Response	0.6667	NA	NA	0.4231
Relapse	0.0206	NA	NA	0.0387
Subgroup 3				
Response	0.6774	NA	0.6774	0.3983
Relapse	0.0257	NA	0.0257	0.0447
Subgroup 4				
Response	0.5273	NA	NA	0.3478
Relapse	0.0257	NA	NA	0.0447
Subgroup 5				
Response	0.6217	0.7003	NA	NA
Relapse	0.0257	0.0257	NA	NA

NA, not applicable.

It is not clear why the response and relapse rates for DEX and no treatment are not applicable for subgroups 1 and 5, as these patients are eligible for these treatments, which both also feature in the treatment strategy assigned to that subgroup. It is also not made clear why the probability of relapse differs for sub-groups 1 and 2, as compared with 3, 4 and 5. These and other unexplained variations in the reported figures cannot be verified without examining the electronic model. It was not possible to ascertain whether the response rates extracted and estimated were monthly response rates, or whether an overall response rate from the trials was applied as a monthly transition probability in the model, which would overestimate response in the model given that the average trial length was > 1 month.

The probabilities of adverse events, discontinuation due to adverse events, discontinuations in non-responders due to inefficacy, discontinuations due to other reasons and the persistence of insomnia to the next cycle are all assumed equal between active treatment options. The probability of experiencing any adverse event and the probability of discontinuation are taken from a *post hoc* analysis of data pooled from six trials comparing ATX with placebo.[63,73,74,89,142,144] One of the trials[142] was a subset analysis of another[89] and so to pool these two trials was not appropriate. The pooled data showed an adverse event rate of 49.2% on ATX and 36.3% on placebo, and so the submission employs the difference of 12.9% as the monthly transition probability. Again, it is unclear whether this rate was the monthly rate in the trials or, as is more likely, the overall rate from the trials. The average length of the six trials was just over 9 weeks, and so applying an overall rate as a monthly transition probability would overestimate the number of adverse events in the model. The probability of discontinuation due to other reasons (i.e. not inefficacy or adverse events) was estimated to be 9.46% and may suffer from the same problems as just detailed.

The probability of discontinuation due to inefficacy does appear to have been calculated correctly as a monthly probability of 9.89%; although the assumptions used in this calculation are not specified, we may infer that it was calculated by assuming a constant transition rate and hence an exponential distribution. The same may be true of the monthly probability of discontinuation due to adverse events, estimated to be 12.09%.

An indirect meta-analysis of safety data (not referenced) estimated an RR of insomnia of 0.428 for ATX compared with IR-MPH. This was applied to an estimate of the risk of insomnia on ATX of 4.7% from the six pooled placebo-controlled trials.[63,73,74,89,142,144] The subsequent rate of insomnia on IR-MPH of 11.0% was then net of the rate of insomnia on placebo from the same studies (5.1%) as the model assumed that insomnia was only experienced on medication. This net rate was

TABLE 82 *Drug costs used in the cost–utility model submitted by Eli Lilly*

Value	ATX	IR-MPH	ER-MPH	DEX
Average daily dose	1.1 pills	25.46 mg	32.75 mg	13.11 mg
Daily cost (£)	2.15	0.47	1.34	0.18
Monthly cost (£)	64.35	14.19	40.04	5.40

TABLE 83 *Utility values used in the cost–utility model submitted by Eli Lilly*

Health state	N	Mean	SD
Treatment with ATX; responder; no side-effects	83	0.959	0.077
Treatment with ATX; responder; side-effects	83	0.937	0.096
Treatment with ATX; non-responder; no side-effects	83	0.902	0.133
Treatment with ATX; non-responder; side-effects	83	0.886	0.148
Treatment with IR-MPH; responder; no side-effects	83	0.913	0.128
Treatment with IR-MPH; responder; side-effects	83	0.904	0.137
Treatment with IR-MPH; non-responder; no side-effects	83	0.889	0.154
Treatment with IR-MPH; non-responder; side-effects	83	0.875	0.164
Treatment with ER-MPH; responder; no side-effects	83	0.930	0.107
Treatment with ER-MPH; responder; side-effects	83	0.912	0.124
Treatment with ER-MPH; non-responder; no side-effects	83	0.898	0.130
Treatment with ER-MPH; non-responder; side-effects	83	0.884	0.143
No medication; responder	23	0.880	0.133
No medication; non-responder	23	0.880	0.133

then used to calculate the probability that an adverse event experienced by a patient on IR-MPH was insomnia, and this was estimated to be 46%. It is likely that the proportion of adverse events that are insomnia would be available directly from clinical trials of IR-MPH, and so the need for this indirect calculation is not clear. Adverse events other than insomnia are given a 47.3% chance of persisting to the next cycle for the first four cycles in the model and a 100% chance of persisting thereafter. Insomnia is given a 95.3% chance of persisting to the next cycle for the first four cycles in the model and a 100% chance thereafter. These estimates are a modelling assumption made with consideration of expert opinion.

Summary of resource utilisation and cost data

The model includes only the costs of the active medication and excludes all other costs. The estimated daily dose of each medication was taken from published sources (IMS BPI/HPAI database 2003, reference not provided in submission). The source of the unit costs of each medicine is unclear. As ATX is flat-priced regardless of dose, the submission assumes that 90% of patients will take one tablet per day and 10% will take two. The drug costs used in the model are shown in *Table 82*.

Summary of utility data

The utility data were based on a study previously published as a poster.[145] This study obtained utility values for 14 hypothetical health states from 83 parents as proxies for their children with ADHD using SG. The 18 health states were differentiated according to treatment received, response and side-effects, and the vignettes describing each state were designed to maximise the differences between the treatment options. The results of this utility study are shown in *Table 83*.

DEX was not included in the utility study, and so the model assumes that the values for treatment with IR-MPH are applicable. Some of these utility values appear inconsistent, for example, the utility for a non-responder to ATX who is experiencing side effects with treatment is higher than that of a person receiving no medication. The health state descriptions shown to parents in the elicitation study are shown in Appendix 10. The main difference between ATX and the stimulant therapies is related to treatment coverage in the early morning and late evening. This translates into a difference in utility of approximately 0.04 between responders to ATX and IR-MPH. This is a relatively large difference in utility in this population. As the results of this study are only available in poster format, it is not possible to

TABLE 84 *Cost-effectiveness results from cost–utility model submitted by Eli Lilly*

Subgroup	MPH	QALYs: strategy with ATX	Cost: strategy with ATX (£)	QALYs: strategy without ATX	Cost: strategy without ATX (£)	ICER (£)
1	ER	0.9341	599.78	0.9140	334.07	13,241
1	IR	0.9308	534.09	0.9040	125.76	15,224
2	NA	0.9217	480.94	0.8800	0.00	11,523
3	NA	0.9268	488.26	0.8967	39.48	14,945
4	NA	0.9120	395.98	0.8800	0.00	12,370
5	ER	0.9331	595.32	0.9126	316.32	13,609
5	IR	0.93	531.52	0.9033	121.49	15,355

NA, not applicable.

assess the quality of the methodology or the suitability of the sample of parents from whom the valuations were elicited. The sample consisted of parents of children with ADHD, and so the current treatment of their children could potentially introduce bias into the results. As such, the results of this utility elicitation study should be interpreted with caution.

Summary of cost-effectiveness

The submission states that owing to the use of patient-level simulation, a probabilistic sensitivity analysis was not practical, and so the model is run deterministically. As a result, the model cannot provide an estimate of the uncertainty around the estimated costs and effects. The cost-effectiveness results are shown in *Table 84*. Subgroups 1 and 5 are associated with two sets of results because the treatment strategies include MPH, of which there are two formulations, extended and instant release.

No detail is given of the pseudo-standard errors one would expect from a patient-level simulation, so it is not possible to judge whether enough patients were simulated to ensure stable estimates. The two pair-wise comparisons in subgroups 1 and 5 can be reduced to one four-way comparison by computing the ICERs using the rules of dominance and extended dominance (see p. 95). Using this method, the use of ER-MPH without ATX is ruled out by extended dominance in both subgroups. The ICER for IR-MPH with ATX compared with IR-MPH without ATX is £15,236 in subgroup 1 and £15,357 in subgroup 2 and the ICER for ER-MPH with ATX compared with IR-MPH with ATX is £19,906 in subgroup 1 and £20,581 in subgroup 2.

Several one-way sensitivity analyses were conducted. As expected, the results of the model were affected predominately by the utility values used.

Comments on methodology

As the electronic model was not submitted within the time frame for this review, it was not possible to verify or clarify further the information provided in the submission. It is also not possible to re-analyse the model for any further sensitivity analyses. The use of ATX is shown to be cost-effective, this result being driven by the utility values employed and the assumptions regarding the persistence of side-effects. Like the others, the submission did not consider long-term effects of medication for ADHD. Without examining the electronic model, the need for a patient-level simulation rather than cohort structure is unclear.

Chapter 6
Economic model

The review of the economic evidence from the literature and the manufacturers' submissions highlighted a number of potential limitations in existing studies assessing the cost-effectiveness of MPH, DEX and ATX in children and adolescents diagnosed with ADHD, including HKD. In particular, the review highlighted limitations in estimating treatment effectiveness and associated utility values. In an attempt to overcome these limitations, a new economic model was developed for this report. The scope of this review is to identify the most cost-effective treatment strategy for children and adolescents with ADHD, once one has assessed there to be a need for medical management. The scope specifically excludes the choice between medical management and non-drug interventions, for example MPH compared with BT without concurrent medication.

Methods

A new model was developed to assess the cost-effectiveness of IR-MPH (3–4 hour action), ER-MPH (8 and 12 hour action), DEX and ATX for the treatment of ADHD and HKD in children and adolescents. The model assesses the use of these drugs alone and in combination with a behavioural therapy element (combination therapy). The model is probabilistic, meaning that relevant input parameters are entered as probabilistic distributions rather than point estimates in order to represent the uncertainty around each point estimate.[146] The following sections of the report outline the structure of the model, the key assumptions made and the data sources used to populate the model.

Overview

The model has been developed to estimate costs from the perspective of the UK NHS and Personal Social Services (PSS), and health outcomes in terms of QALYs. The model was developed in Excel and the evidence synthesis used to calculate clinical effectiveness parameters was conducted in WinBUGS.[147] The model considers a hypothetical cohort of children aged 6 years. For the base case analysis, a 1-year time horizon was selected. As noted in the review of the literature and the manufacturers' submissions, this time span excludes the long-term outcomes associated with ADHD. It is known that patients can remain on treatment for more than 1 year, but there is a lack of data about the mechanism that determines the length of treatment. In particular, there is a lack of data for discriminating between treatments in terms of length of treatment for responders. Similarly, there is a lack of data regarding the relative effect of the alternative treatments on other long-term outcomes, including long-term adverse events and cost offsets. These issues will be discussed further in following sections of the report.

In a secondary analysis, we explore a limited extrapolation of the model beyond 1 year using an estimate of the age-dependent decline of symptoms with ADHD.[148]

Treatment strategies

The model considers alternative sequences of treatments. Patients who withdraw or fail on each treatment are assumed to move to the next in line, until they reach no treatment at the end of the sequence. It is assumed that medication is received as part of a comprehensive treatment plan that includes visits to child psychiatrists and paediatricians. The model separately assesses three formulations of MPH, and it is assumed that individuals who withdraw from one formulation would not be offered one of the alternative formulations, as they contain the same active ingredient.

Clearly, treatment sequences could be composed of strategies featuring one, two or three active treatments. Conducting such an analysis allows us to estimate the incremental cost-effectiveness of adding a second or third active treatment option. Such an analysis was conducted (see Appendix 8), and the results show that strategies with three active treatments are cost-effective. Subsequently, the results presented for the base case analysis and the sensitivity analyses concern only those treatment strategies featuring three active treatments. The benefit of omitting these extra strategies from the base case analysis and other sensitivity analyses is to simplify greatly the presentation of results (19 strategies instead of 38, without considering combination therapy). The

TABLE 85 *Treatment sequences compared in economic model*

Treatment sequences	1	2	3	4	5	6
1st line	MPH	MPH	ATX	ATX	DEX	DEX
2nd line	ATX	DEX	MPH	DEX	MPH	ATX
3rd line	DEX	ATX	DEX	MPH	ATX	MPH
4th line	No treatment	No treatment	No treatment	No treatment	No treatment	No treatment
	×3 to represent each formulation of MPH = 18 ×2 to include combination therapy = 36 + no treatment = 37					

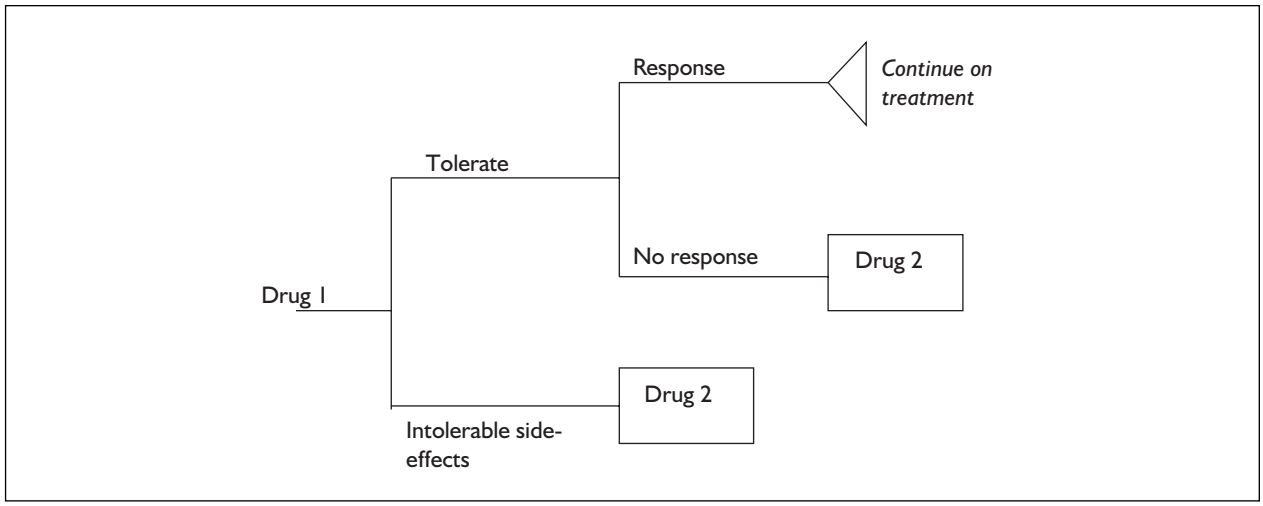

FIGURE 22 *Representation of economic model structure. Once all treatment options are exhausted, patients are assumed to remain non-responders on no treatment.*

reduction in the number of strategies aids interpretation of the model results. The consequence is that by removing a number of strategies, the decision uncertainty is underestimated.

Each treatment sequence is composed of a formulation of MPH (IR-MPH or ER-MPH8 or ER-MPH12), DEX and ATX, followed by no treatment last in sequence. This results in 18 treatment strategies to be considered in the model, all of which can be compared on the basis of pharmacotherapy only, or as part of combination therapy. In addition, there is a no (drug) treatment option, so there are 37 sequences for comparison. *Table 85* provides more information on the sequences for comparison.

Model structure

Upon entering the model, patients begin titration on the first-line treatment. This titration period is assumed to last for 1 month. The purpose of this titration period is to determine the optimal dose, in terms of adverse events and response to treatment. During the titration period, patients can withdraw from treatment if they experience intolerable side-effects and they are then assumed to enter the titration period for the next drug in sequence. The model assumes that patients tolerating treatment will continue with that treatment if they experience a response. Those patients who do not respond to treatment by the end of the titration period are assumed to move to titration for the next treatment in sequence. In the base case analysis, it is assumed that responders remain on therapy and continue to be responsive for the rest of the year. Another assumption of the model is that, although responders may experience side-effects with treatment, these will be relatively minor and tolerable; hence they will not develop intolerable side-effects beyond the titration period. This assumption was considered reasonable following consultation with a clinical expert. In summary, in the base case analysis, patients only withdraw owing to side-effects during the titration period, and patients are moved to the next treatment in sequence if they fail to respond by the end of the titration period. *Figure 22* provides a simple summary of the model structure.

Extrapolation

A secondary analysis extends the time horizon from 1 year to when the cohort reaches 18 years of age. In this secondary analysis, it is assumed that patients on active medication are given an annual drug-free period of 2 weeks to assess the ongoing need for medication. A proportion of patients, whose symptoms are found to be in remission, do not resume medication following this 2-week drug-free period. The model also incorporates the proportion of patients on no treatment who experience remission from symptoms, and hence are no longer defined as non-responders. The model makes the simple assumption that patients not in remission will return to their pre-drug-free period medication, that this medication will be tolerated and that the patient will continue to respond on medication as before. Patients in remission are assumed to be identical to responders in terms of utility and non-drug health expenditure.

In this extended analysis, costs are discounted at an annual rate of 6%, and health benefits are discounted at an annual rate of 1.5%, in accordance with NICE guidance.

Clinical effectiveness

As identified in the clinical effectiveness review in Chapter 4, there is huge variation in the instruments used and the outcomes reported regarding the clinical effectiveness of alternative treatment options. This reflects the lack of consensus on what constitutes successful treatment of ADHD in the absence of a biological marker and hampers between-study comparisons. The clinical effectiveness review addressed this issue of disparity by identifying the most valid and reliable measure in consultation with a clinical expert and adopting a standard method of presentation. Thus Chapter 4 presents an overview of the change in mean score on the Conners' Teachers Hyperactivity Subscale (CTRS-H) and Conners' Parent Hyperactivity Subscale (CPRS-H). Although this measure facilitates comparison across a large number of studies, there are limitations in its use in a decision-analytic model. As noted in the literature review in Chapter 4, if this measure is used, a gain of one point on the scale is valued the same, regardless of where one begins on that scale, so the relative value of different effect sizes is not readily interpretable. In addition, no published studies were available to provide a link between mean CTRS-H or CPRS-H score and utility data. In order to identify the most optimal treatment strategy in a decision-analytic model, one must be able to **value** the differences in outcome, and this is not currently possible with mean CTRS-H or CPRS-H score.

Alongside mean scores on various rating scales, a proportion of studies also report response rates to treatment. These indicate the percentage of children who reach a specified level of improvement. Response rates would be preferred from an economic evaluation perspective for two reasons. First, they explicitly identify a clinically meaningful change on the rating scale used to determine effectiveness. Second, the utility data currently available for patients with ADHD pertain to the states of 'responder' and 'non-responder'. Therefore, an economic model based on response can estimate a cost per QALY, which is more interpretable and generalisable than a cost per point gain in CTRS-H or CPRS-H. On the other hand, there are limitations with the use of response rate as a measure of clinical effectiveness, primarily owing to the lack of an agreed definition of response to treatment for ADHD. This makes comparisons between studies difficult as they may use different definitions.

Hence the measure of clinical effectiveness in the economic model is response rate to treatment. This reflects the approach used in the existing economic literature and the manufacturers' submissions, but must be interpreted according to the caveats used in calculating response rates. The model considers a number of different sets of response rates, each estimated from the clinical studies with different inclusion criteria. The first set of response rates was estimated using the most common definition of response in the included studies, namely a score of 1 or 2 (much improved or improved) on the clinician-rated Clinical Global Impression **improvement** subscale (CGI-I). These rates are used in the base case analysis. This allows a comparison of all relevant treatment strategies without making assumptions about the comparability of different definitions of response. The second definition of response is a score of 1 or 2 on the clinician-rated Clinical Global Impression **severity** subscale (CGI-S). There was no estimate available for the response rate to DEX using this definition. A third group of trials defined response as a reduction of ≥ 25% on the parent-rated ADHD-RS. Measures of response according to this criterion were only available for placebo, ATX and ER-MPH12. Hence for this third definition of response, further modelling was required in order to compare all relevant treatment strategies [details follow in the section 'Sensitivity to structural assumption regarding MPH' (p. 117)]. Finally, estimates of response

TABLE 86 *Response rates used in the base case analysis: response defined as score of 1 or 2 on CGI-I*

Trial	Treatment	Responders (%)	No. in group
Sharp, 1999[149a]	IR-MPH	26 (81)	32
	DEX	27 (84)	32
	Placebo	5 (16)	32
Greenhill, 2002[59]	ER-MPH8	125 (81)	154
	Placebo	78 (50)	156
Kemner, 2004[99]	ER-MPH12	583 (69)	850
	ATX	250 (53)	473
Steele, 2004[90]	ER-MPH12	58 (83)	70
	IR-MPH	45 (62)	73
Pliszka, 2000[83]	IR-MPH	13 (65)	20
	Adderall	18 (90)	20
	Placebo	5 (28)	18
Klein, 1997[65]	IR-MPH + BT	28 (97)	29
	IR-MPH	23 (79)	29
	Placebo + BT	14 (50)	28

[a] Not currently reviewed in Chapter 4.

defined as a score of ≤ 1 on the SNAP-IV scale were used in the MTA trial. The problems with interpreting the results of this trial have been described in more detail in Chapter 4, but nevertheless it is an important trial in this disease area. As such, it was felt appropriate to include a scenario using response rates defined according to the definition used in the MTA trial.

The base case analysis uses a consistent definition of response to compare all relevant options. Because this excluded a number of trials, and hence reduced the amount of available data, sensitivity analyses were conducted by relaxing the definition of response to include more trials and to assess the impact of different definitions of response on the estimates of cost-effectiveness.

Table 86 displays the source trials used to estimate response rate in the base case analysis. Further detail about each trial has been provided in Chapter 3, where the trial concerned was included in the effectiveness review. A number of studies excluded from the effectiveness review, for reasons of data presentation, were nevertheless found to provide information on response rate. These studies were therefore included in the calculation of response rate for the cost-effectiveness analysis. Further details of these excluded studies are given in Appendix 3. All of the trials were set in North America (five in the USA and one in Canada[90]), and most recruited children aged between 6 and 12 years (one study recruited from age 6 to 16 years[59]). Four used the DSM-IV diagnostic criteria, and the remaining two used other diagnostic interviews.[65,83] The average daily dose of IR-MPH and ER-MPH12 varied between the trials, and this is not reflected in the calculation of response rates. It is important to note that in the clinical trials, patients were titrated to the 'best' dose, which reflects our model structure, but does allow average dose to differ between trials. Three of the trials excluded subjects who were known non-responders to stimulant therapy,[59,90,99] and this is also not reflected in the calculation of response rates. This heterogeneity between trials must be borne in mind when interpreting the results of the model.

Table 86 excludes one trial[84] **[Confidential information removed]**. An important assumption in the base case model is that the treatment effects are independent of treatments previously received. In other words, the response rate to IR-MPH is the same if it is received as first-line therapy as when it is received following failure on DEX or ATX. This assumption was necessary as data were not available to calculate response rates conditional on specified previous treatments.

Ideally, the relative treatment effects of no treatment, IR-MPH, ER-MPH8, ER-MPH12, ATX and DEX would be estimated in a single, direct head-to-head RCT. However, such a trial does not exist, and instead we have a number of trials assessing the treatment effects of different subsets of the full set of relevant comparators. Clearly, the absolute response rates differ by trial, but the

economic model rests on the assumption that the relative treatment effects will be the same across trials. This is a common assumption used in any routine meta-analysis. As *Table 86* shows, there is not a common comparator between all the trials. Therefore, in order to pool the data, a mixed treatment comparison (MTC) model was used.[150,151] An MTC provides an explicit analytical framework to combine all the evidence simultaneously in order to estimate a set of response rates for the economic model. The framework requires few additional assumptions over those routinely made in simple meta-analyses.

Mixed treatment comparison

This section provides a brief overview of the principles underlying an MTC. Suppose there are three clinical trials comparing three treatments of interest, A, B and C. Each clinical trial assesses a different pair-wise comparison, AB, AC and BC. A simplistic method might be to compare direct treatment effects against a common baseline, for example A, and merely discard the information provided by the BC comparison. This is in accordance with the view that indirect comparisons of A and C based on comparisons of AB and BC represent a lower level of evidence. However, it is evident that, based on the principle of transitivity, if the true differences between AB, AC and BC are (on the appropriate scale) θ_{AB}, θ_{AC} and θ_{BC}, then we expect

$$\theta_{AC} = \theta_{AB} + \theta_{BC}$$

Hence the information provided by the BC comparison need not be discarded and can be used to update the direct comparisons of AB and AC. Higgins and Whitehead[150] have shown how the use of 'external' AB and BC evidence can substantially reduce uncertainty about an AC comparison of primary interest. For example, with reference to this report, the estimate of the effect of ER-MPH12 compared with IR-MPH from Steele and colleagues[90] can be combined with an estimate of the effect of IR-MPH relative to placebo in order to obtain an estimated relative treatment effect for ER-MPH12 compared with placebo. This estimate would be otherwise unavailable in this dataset.

Based on these general principles, a Bayesian meta-analysis of the proportion of responders assuming random treatment effects was conducted using Markov Chain Monte Carlo (MCMC) implemented in WinBUGS.[147] The WinBUGS model used to estimate the proportions of responders assumes a regression-like structure, with the logit of the proportion of responders for any treatment k, depending on a 'baseline' term μ_i in trial i, $i = 1, 2, \ldots, 6$, and a treatment effect δ_i^k. The trial-specific baselines are drawn from a common random normal distribution, whose parameters must be estimated from the data, given vague priors. Formally, this can be expressed as

$$\begin{aligned}
&\text{logit}(\rho_i^k) = \mu_i + \delta_i^k \\
&\mu_i \sim N(\mu, \tau a) \qquad \mu \sim N(0, 0.0001), \\
&\qquad\qquad\qquad\quad sa^2 \sim \text{uniform}(0,10) \\
&\tau a = 1/sa^2
\end{aligned}$$

The trial-specific treatment effects δ_i^k are assumed to be drawn from a common random normal distribution around the 'true' treatment effect δ^k. A binomial likelihood is assumed from the available data points:

$$\begin{aligned}
&\delta_i^k \sim N(\delta^k, \tau b) \quad \delta^k \sim N(0, 0.0001), \\
&\qquad\qquad\qquad\quad sb^2 \sim \text{uniform}(0,10) \\
&\tau b = 1/sb^2 \\
&r_i^k \sim \text{Bin}(p_i^k, n_i^k),
\end{aligned}$$

where k denotes all treatment indices in study i, r_i denotes the observed number of responses and n_i denotes the total number in the group.

The WinBUGS code for the model is reported in Appendix 9. The code represents an extension of the Higgins and Whitehead 1996 model[150] to more general MTC structures. The output from the model incorporates the uncertainty around the estimated response rates and also any correlation between treatments. However, for simplicity, three-arm trials were treated as two two-arm trials with a common comparator.

Combination therapy

As noted in the clinical effectiveness review in Chapter 4, where behavioural therapies are used in combination with pharmacotherapy, they vary between trials. As such, there is no one ADHD combination therapy that we could assess in comparison with drug monotherapy. However, some of the trials did show a (non-statistically significant) favourable effect of combination therapy compared with drug monotherapy. The data do not allow us to compare a single consistent behavioural therapy component in combination with all of the relevant treatment comparators. Instead, we can only estimate the relative increase in response rate associated with IR-MPH and BT compared with IR-MPH alone.[65,133] Hence combination therapy was considered in a secondary analysis, where the relative increase in response rate for IR-MPH with BT compared with

IR-MPH was assumed to apply to all drug treatments. However, owing to the variation in programmes, this analysis can tell us little about combination therapy in practice in the UK.

Adverse events

The model assumes that patients who fail to tolerate treatment during the titration period will discontinue that treatment if dose modification does not address the problem, and that any side-effects will dissipate upon treatment cessation. Hence the main consequence of adverse events in the model is discontinuation of treatment, and intolerable side-effects are not associated with an additional utility decrement. The cost and utility estimates for responders (i.e. patients continuing on treatment) take account of the minor side-effects that commonly accompany treatment for ADHD. However, it must be noted that they do not discriminate between treatments in this respect. As noted in the clinical effectiveness review in Chapter 4, there is little trial evidence to discriminate between the active therapies in terms of tolerable side-effects. Of the events assessed, insomnia may be more common with stimulant therapy in comparison with ATX, so this must be considered when interpreting the model results. Another important factor is the lack of data regarding long-term adverse events beyond the period observed in the clinical trials.

In the clinical trials, patients withdrew from treatment for many reasons, including lack of efficacy and intolerable adverse events. The reasons given differed between trials, and in some cases the reason for withdrawal was not stated. As a result, the withdrawal rates for the model were calculated to include all reported withdrawals, regardless of the reason given. This approach was chosen to maintain consistency between trials with differing definitions of withdrawal, and it is also a conservative approach from the point of view of NICE. This is because a higher rate of withdrawal will increase the cost-effectiveness ratios associated with active treatment, and so a treatment that appears cost-effective using this broad definition of withdrawal would appear even more cost-effective under a more precise definition. However, it must be noted that in four of the 10 trials shown in *Table 87*,[63,83,90,94] a proportion of withdrawals were attributed to non-response. This demonstrates that although the approach taken may be conservative and consistent in calculating withdrawal rates, it may include some double counting of non-responders. The degree of double counting is difficult to quantify because, as noted in the clinical effectiveness review in Chapter 4, none of the four trials calculated response in an ITT analysis.

The probability of withdrawal was calculated in the same way as the response rates, hence the same model applies, as shown in Appendix 9. Owing to the lack of reported data on withdrawal, one set of rates was calculated including all studies that provided an estimate of response rate, regardless of definition of response. *Table 87* details the data used to calculate withdrawal rates for the economic model. These data apply to all analyses, regardless of definition of response.

In the secondary analysis including combination therapy, it was assumed that withdrawal would only be induced by pharmacotherapy, and so the same withdrawal rates are applied as to drug monotherapy.

As noted earlier in this chapter, few data are available on adverse events associated with long-term use of pharmacotherapy for ADHD. Therefore, the adverse events reflected in the model are limited to those observed during the treatment phase of the included clinical trials.

Compliance

Compliance can be thought of as the ability of patients to take the required number of doses of medication, or of the ability of patients to take pills within the correct time frame; these are dose-taking and dose-timing compliance, respectively. This section of the report refers to dose-taking compliance. If patients take fewer pills than prescribed by their doctor, they will be receiving a lower dose of medication. In their submissions, Janssen-Cilag and Celltech both put forward the argument that compliance to a midday dose of treatment will be lower than compliance to an early morning dose. They argue that double-blind, double-dummy trials do not capture the effect of improved compliance to the once-daily extended-release formulations of MPH as both comparator groups must take more than one pill per day (the extra pills being placebo in the ER-MPH groups). In explanation, in a double-blind, double-dummy trial, patients are blinded to treatment and receive the same number of doses of medication per day in each arm. Dummy pills (placebo) are used to prevent patients identifying the treatment to which they have been allocated by counting the number of doses they receive. This means that in a double-blind, double-dummy trial of IR-MPH TID versus ER-MPH12, patients in both arms would receive three pills each day. In the IR-MPH arm, all the pills would contain an active dose of IR-

TABLE 87 *Data used in calculating withdrawal rates for the economic model*

Trial	Treatment	Withdrawals (%)	No. in group
Sharp, 1999[149a]	IR-MPH	1 (3)	32
	DEX	0 (0)	32
	Placebo	0 (0)	32
Greenhill, 2002[59]	ER-MPH8	20 (13)	158
	Placebo	32 (20)	163
Kemner, 2004[99]	ER-MPH12	41 (5)	850
	ATX	26 (5)	473
Steele, 2004[90]	ER-MPH12	12 (16)	73
	IR-MPH	12 (16)	74
Pliszka, 2000[83]	IR-MPH	1 (5)	20
	Adderall	2 (10)	20
	Placebo	2 (11)	18
Klein, 1997[65]	IR-MPH + BT	0 (0)	29
	IR-MPH	1 (3)	31
	Placebo + BT	2 (7)	29
Kelsey, 2004[63]	ATX	26 (20)	133
	Placebo	17 (27)	64
Michelson, 2002[74]	ATX	12 (14)	85
	Placebo	11 (13)	86
Weiss, 2004[94]	ATX	17 (17)	101
	Placebo	4 (8)	52
Spencer, 2002[89]	ATX	8 (6)	129
	Placebo	7 (6)	124

[a] Not currently reviewed in Chapter 4.

MPH. In the ER-MPH12 arm, only the first pill would contain active medication and the second and third doses each day would consist of placebo. In our base case analysis, it is assumed that the trial data adequately capture the effect of compliance on response to treatment. In other words, the daily dose received by patients taking ER-MPH would not be reduced if patients comply poorly with a lunchtime dose (as this is placebo in this group). Therefore, the improved effectiveness, due to better compliance to the morning dose, should be adequately captured. The clinical trials used to estimate response rate include open-label trials, and these should capture any effect of compliance on clinical outcomes. In an open-label trial, patients are not blind to treatment and may not receive the same number of doses of medication per day. In an open-label trial of IR-MPH TID versus ER-MPH12, patients in the IR-MPH arm would receive three pills per day, whereas patients in the ER-MPH12 arm would receive one pill per day. The open-label nature of the trial removes the need to include dummy, or placebo, pills.

For the argument that double-blind, double-dummy trials do not capture the effects of compliance to hold, the assumption must be that taking three pills per day has a deleterious effect on compliance to the morning dose, rather than that compliance to a midday dose is lower than to a morning dose. A systematic review of compliance to different dosing regimens in a range of disease areas has shown that compliance does appear to fall as the number of doses per day increases.[152] However, these data on average compliance per day cannot resolve the issue of whether patients' reduced compliance to twice- or three-times daily schedules is the result of taking fewer pills at each dose timing or as a result of taking fewer pills at the later dose timings (i.e. lunchtime and evening). Also, none of the studies in the SR of compliance looked specifically at ADHD, and instead the emphasis is on medication for adults. The exploration of the effects of non-compliance would involve a number of assumptions: the assumption that RCT data capture none of the effects of compliance; the application of a selected estimate of compliance from a source outside of the clinical trials; and an assumption regarding the distribution of reduced compliance between morning, lunchtime and evening doses of medication. It was felt that these modelling

TABLE 88 *Resource use and unit cost data used to populate the economic model*

Item	Average per year	Lower CI limit	Upper CI limit	Unit cost (£)
Responders:				
Consultations				
Psychiatrist	3.5	2.3	4.7	109.5
Paediatrician	2.25	0.6	3.7	188
GP	3	1.3	4.7	24
Tests				
Blood test	0.05	0	0.1	7
Non-responders:				
Consultations				
Psychiatrist	5.75	4.3	7.4	109.5
Paediatrician	2.5	0.9	3.7	188
GP	2.75	0.6	4.7	24
Tests				
Blood test	0.35	0.06	0.76	7
ECG	0.33	0	0.79	29.48
EEG	0.43	0.06	0.85	111.93
Allergy test	0.5	0.09	0.91	67

assumptions would not be reasonable given the lack of available data, which would render the results of any sensitivity analysis around compliance uninformative to decision-makers.

Resource utilisation and cost data

As identified in the review of existing economic evaluations, there are few observed data on the resource use associated with ADHD. In the absence of readily available data, it was necessary to base the resource use in the model on estimates obtained from expert opinion. Hence the resource use in the model is based on that used in the submission by Janssen-Cilag, reviewed in Chapter 5. The study from which these estimates were obtained[129] has been reviewed in more detail in Chapter 5. The estimates of resource use were obtained from a Delphi panel, in which the UK-based experts were asked to specify their drug treatment programmes according to treatment used, response status and presence of adverse events. These data are updated with current, UK-specific price data (NHS reference costs 2003).[153] The resource use includes visits to psychiatrists and paediatricians to reflect a more comprehensive treatment programme than drug therapy alone. Current guidance[1] recommends IR-MPH as part of a comprehensive treatment programme. The details of such a programme are not defined, but it does not need to include specific psychological treatment, that is, what we refer to as BT.

The uncertainty around the estimated resource use was characterised using a gamma distribution. *Table 88* shows the resource use and unit costs employed in the economic model.

The impact of using alternative estimates of resource use for children and adolescents with ADHD was assessed in a sensitivity analysis. As noted earlier in this chapter, the review found no data on resource use associated with long-term use of ADHD. In order to extrapolate the model beyond 1 year, it was assumed that patients who come off therapy due to remission of symptoms would incur the same non-drug resource use as responders. This acknowledges the fact that patients in remission of symptoms are not 'cured' of ADHD, but likely overestimates the costs in the long run.

The average dose for each active medication was taken from the trials used in calculating response rates. Although these doses may not reflect exactly current UK practice, they are the doses at which the effectiveness data were obtained. As we only have clinical trial data for treatment effectiveness, it is not possible to determine the effectiveness at the current average UK dose. Hence the drug costs are consistent with the effectiveness data used in the model. The drug prices were obtained from published UK pricing lists,[29] where available. ER-MPH8 is not currently priced in the UK, so the model employs the prices reported in the manufacturer's submission.[154] *Table 89* displays the dose and unit cost data employed in the economic model. The unit cost data for IR-MPH are based on the generic formulation (note that the cost of 10-mg Ritalin is the same as that for 10-mg generic IR-MPH).

The data regarding average drug dose are entered deterministically, which means that the model is

TABLE 89 *Average dose and unit cost used in economic model: IR-MPH, ER-MPH8, ER-MPH12, ATX and DEX*

Treatment	Average dose per day during titration (mg)	Average dose per day following titration (mg)	Cost per day titration period (£)	Cost per day after titration period (£)
IR-MPH	22	39	0.36	0.64
ER-MPH8	25	41	1.27	1.58
ER-MPH12	27	35	1.33	1.76
ATX	28	45	2.15	2.19
DEX	14	22	0.19	0.42

not fully probabilistic. The average daily drug doses correspond to the moderate/high dose trials in the clinical effectiveness review in Chapter 4.

Utility data

The review of the literature in Chapter 5 illustrated that there are few sources of data on utility for children and adolescents with ADHD. Two of the manufacturers' submissions used utility values obtained using an SG technique from parents of children with ADHD, providing proxy valuations for their children. These utility estimates were available in the public domain as poster presentations. The first set of utility values[136,155] provided an estimate of the utility of a responder to treatment (mean 0.837, standard error 0.039) and a non-responder to treatment for ADHD (mean 0.773, standard error 0.039), independent of the treatment being received. These values are used in the base case analysis. The second set of available utility values[145,156] provided estimates of the utility of responders and non-responders, with and without side-effects, that were treatment-specific. There were some concerns over the validity of these estimates, as detailed in Chapter 5, so these are employed in a sensitivity analysis. None of the available utility values were obtained with the use of a generic health valuation measure valued with public preferences, as recommended in guidance from NICE.[157] This is a common problem when assessing QoL in children.

The uncertainty around these estimated utility values was characterised using a beta distribution, as it was felt reasonable to assume that the values would not drop below zero.

Results

Response and withdrawal rates in the base case analysis

In the base case analysis, the definition of response was defined as a score of 1 or 2 on the CGI-I. This restricted the number of included trials to six of the 65 identified in the clinical effectiveness review in Chapter 4. The estimated response rates were subject to large uncertainty, which is unsurprising given the small size of some of the included studies, the restricted amount of data available and the heterogeneity between trials. The output of the WinBUGS model is shown in *Table 90*.

The estimated response rates are all in the expected direction given the trial evidence. However, it must be noted that the volume of trial data is small and varies between treatments. Data on the effectiveness of IR-MPH were available in four trials (154 patients), ER-MPH8 in one trial (154 patients), ER-MPH12 in two trials (920 patients), ATX in one trial (473 patients) and DEX in one trial (32 patients). The uncertainty in the calculated response rates incorporates the size of the evidence base for each treatment.

Cost-effectiveness results for the base case analysis

The base case analysis assessed the cost-effectiveness of alternative treatment strategies, comprising drug monotherapies followed by no treatment. Nineteen relevant strategies were compared, including a no treatment option (see *Table 85*), over a time horizon of 1 year. The results from this analysis identified a dominant treatment strategy, number 13, which was associated with the lowest costs and the highest QALY gains relative to other comparators. However, the difference in QALY gains between the active treatment strategies was very small. This is unsurprising given the uncertainty surrounding the relative clinical effectiveness of the active treatments. Also, the loss of QoL by trying an ineffective treatment before a relatively more effective one will endure for only 1 month before non-responders move to the next treatment in sequence. *Table 91* shows the results from the base case economic analysis, employing the response and withdrawal rates shown in *Table 90*. The results should therefore be interpreted with

TABLE 90 *Response and withdrawal rates estimated in MTC model in WinBUGS: response defined as score of 1 or 2 on CGI-I*

Treatment	Response rate (SD)	Withdrawal rate (SD)
Placebo	0.28 (0.04)	0.11 (0.02)
IR-MPH	0.68 (0.30)	0.09 (0.05)
ER-MPH8	0.57 (0.33)	0.08 (0.06)
ER-MPH12	0.75 (0.32)	0.12 (0.04)
ATX	0.67 (0.37)	0.11 (0.06)
DEX	0.75 (0.32)	0.02 (0.05)

TABLE 91 *Results of the base case analysis of the economic model*

Strategy	Order of treatments received	Cost	QALYs
1	IR-MPH – ATX – DEX – No treatment	1,233	0.8279
2	ER-MPH8 – ATX – DEX – No treatment	1,470	0.8273
3	ER-MPH12 – ATX – DEX – No treatment	1,479	0.8278
4	ATX – IR-MPH – DEX – No treatment	1,480	0.8278
5	ATX – ER-MPH8 – DEX – No treatment	1,550	0.8277
6	ATX – ER-MPH12 – DEX – No treatment	1,563	0.8274
7	IR-MPH – DEX – ATX – No treatment	1,140	0.8283
8	ER-MPH8 – DEX – ATX – No treatment	1,336	0.8277
9	ER-MPH12 – DEX – ATX – No treatment	1,410	0.8284
10	ATX – DEX – IR-MPH – No treatment	1,466	0.8281
11	ATX – DEX – ER-MPH8 – No treatment	1,485	0.8281
12	ATX – DEX – ER-MPH12 – No treatment	1,488	0.8278
13	**DEX – IR-MPH – ATX – No treatment**	**1,098**	**0.8289**
14	DEX – ER-MPH8 – ATX – No treatment	1,157	0.8287
15	DEX – ER-MPH12 – ATX – No treatment	1,159	0.8287
16	DEX – ATX – IR-MPH – No treatment	1,158	0.8288
17	DEX– ATX – ER-MPH8 – No treatment	1,177	0.8288
18	DEX– ATX – ER-MPH12 – No treatment	1,180	0.8285
19	No treatment	1,223	0.7727

reference to the caveats used in calculating these treatment effects.

In order to display the decision uncertainty, *Figure 23* shows the CEACs[137] for all 19 strategies compared. However, the CEACs cannot be used to determine the optimal treatment strategy. The optimal treatment strategy is the one with the highest expected net benefit at a given value of willingness to pay per QALY. If the distribution of incremental net benefits is skewed, the optimal treatment strategy may not have the highest probability of being cost-effective.[137] The results of this analysis showed that strategy 13 (shown in bold in *Table 91*) had the highest expected net benefit over the full range of values of willingness to pay per QALY considered (£0 to £60,000).

At any value of willingness to pay per QALY within the range explored, strategy 13 is the most optimal treatment strategy. If the societal willingness to pay were £30,000 per additional QALY, strategy 13 has a 31% probability of being the most cost-effective (see Appendix 8). However, the CEAC shown here includes only a subset of relevant treatment strategies: those featuring three active treatments. Hence the probability that strategy 13 is optimal shown in *Figure 23*(60%) is higher than the true probability because half as many treatment strategies are compared. The result reflects the fact that the trial data provide little evidence for discriminating between the alternative medications for ADHD in terms of effectiveness, but that DEX, followed by IR-MPH, are much cheaper than the other comparators.

The manufacturer's submissions consistently considered DEX as second-line therapy and never as a first-line treatment option. The licence for DEX specifies its use for refractory hyperkinetic states in children. Hence for patients who have previously failed BT or remedial measures, DEX could be considered as first-line drug therapy. However, if the term refractory refers to previous medical management, then DEX may only be suitable as second-line therapy. If this assumption

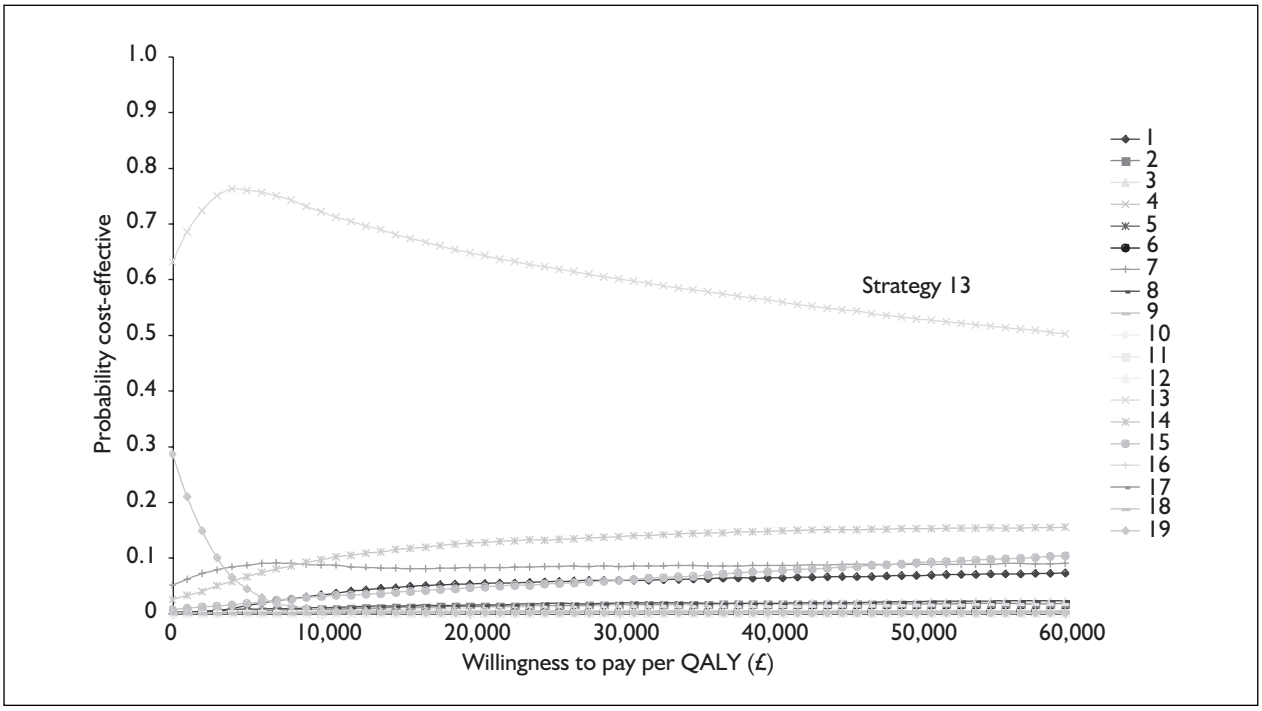

FIGURE 23 *CEACs for 19 strategies compared in the base case analysis*

is reasonable, then strategies 13–18 are no longer relevant, and the optimal treatment strategy is then number 7 (first-line IR-MPH, second-line DEX, third-line ATX). Strategy 7 does not dominate all the remaining alternatives. Strategy 9 (first-line ER-MPH12, second-line DEX, third-line ATX) is more costly and more effective, with a cost per QALY gained of £5,595,829 compared with strategy 7. If society were willing to pay £30,000 per additional QALY, strategy 7 would have an 84% probability of being most cost-effective. Again, this probability only includes uncertainty between treatment strategies featuring three active treatments. There is less uncertainty than when DEX is considered suitable as first-line therapy because there are six fewer treatment strategies being compared (13 compared with 19).

Medication as part of combination therapy

The trials used to estimate response rates for the base case included a trial comparing IR-MPH alone with IR-MPH combined with BT. This trial was used to estimate the relative change in response rate of adding BT to medication. This relative effect was then applied to all of the drug treatments, yielding the same **relative** change in response rate across all treatments. This simplification was necessary as trials were not available assessing combination therapy with each of the relevant drug comparators. Also, had such trials been available, it is likely that the behavioural component would differ between trials, as highlighted in the section 'Combination therapy' (p. 105). Hence this sensitivity analysis represents a simplistic analysis of the cost-effectiveness of drug therapy in combination with BT.

The results of this sensitivity analysis indicate that strategy 13 remains the optimal treatment strategy. However, strategy 13 does not dominate the strategies that include combination therapy. This is because the drugs in combination with BT are marginally more effective than when given alone. By calculating the ICERs, according to the rules of dominance and extended dominance, the only alternative not ruled out is strategy 36 (combination therapy with first-line DEX, second-line ATX, third-line ER-MPH8). The cost per QALY gained with strategy 36 compared with strategy 13 is £1,241,570, hence combination therapy does not appear cost-effective in this sensitivity analysis. Increasing the number of strategies from 19 to 37 increases the decision uncertainty. If society were willing to pay £30,000 per additional QALY, strategy 13 has a 40% probability of being the optimal strategy (compared with 60% in the base case excluding combination therapy).

If DEX is not suitable as a first-line therapy, then strategy 7 (first-line IR-MPH, second-line DEX, third-line ATX) is the optimal treatment strategy.

TABLE 92 *Alternative utility values used in sensitivity analysis of the economic model*

Health state	Utility value (SE)
Responder to ATX, no side-effects	0.959 (0.077)
Responder to IR-MPH, no side-effects	0.913 (0.128)
Responder to ER-MPH, no side-effects	0.930 (0.107)
Non-responder, no medication	0.880 (0.133)

SE, standard error.

Sensitivity to estimated utility values

The base case analysis employs estimates of the utility associated with response to treatment and non-response to treatment that are independent of the treatment received. A responder to ATX therefore receives the same utility value as a responder to MPH or DEX. The submission by Eli Lilly utilised a different set of utility estimates derived using SG methodology. These estimates valued response (and non-response) to treatment dependent on the medication received. Hence separate values were available for response (and non-response) to ATX, IR-MPH and ER-MPH, also separated by the presence or absence of treatment side-effects. The review of the company submissions highlighted some concerns about the validity of these estimates, particularly the fact that the utility of a non-responder without side-effects differs between treatments. For example, the utility associated with non-response to ATX, without side-effects, is estimated to be 0.902, which compares with an estimated utility of 0.880 associated with non-response and no medication. A difference in utility of 0.022 is relatively large in this population, particularly between health states with identical characteristics.

A sensitivity analysis was conducted using these alternative estimates of utility. The reason for the differences in utility of non-response by treatment (including no treatment) is unclear, so the sensitivity analysis uses the utility of non-response associated with no medication. Our model does not separate responders into those with side-effects and those without, so we conducted the sensitivity analysis including the utility of response without side-effects. *Table 92* shows the utility values used in this sensitivity analysis.

The health state descriptions used to obtain these valuations are shown in Appendix 10. These vignettes were designed to maximise the differences between treatments. The results of this sensitivity analysis rely on the validity of these health state descriptions. No estimate was available for DEX, so the utility associated with IR-MPH was applied to patients responding to DEX, in accordance with the assumption made in the submission by Eli Lilly.

The results of the sensitivity analysis are shown in *Table 93*. Strategy 13 remained the cheapest strategy, but it no longer dominated the other strategies. By calculating the ICERs, according to the rules of dominance and extended dominance (p. 95), we see that strategies 5, 10, 11 and 16 are not ruled out by dominance or extended dominance. Strategies 5, 10 and 11 all feature ATX as first-line therapy. This is unsurprising given that a response to ATX is associated with a utility gain of 0.046 over a response to IR-MPH (and DEX). Response to ATX is associated with a utility gain of 0.079 compared with non-response with no treatment, whereas response to IR-MPH entails a gain of only 0.033 over non-response with no treatment. For comparison, in the base case analysis, response is associated with a utility gain of 0.064 compared with non-response.

Figure 24 shows the cost-effectiveness acceptability frontier for the optimal strategies in this sensitivity analysis. If society were willing to pay £30,000 per additional QALY, strategy 11 is the optimal strategy with a 3% probability of being the optimal strategy.

The discontinuities in the frontier in *Figure 24* illustrate that the distribution of incremental net benefit is skewed. Strategies 13 and 6 have a higher probability of being cost-effective than strategies 5, 10, 11 and 16 for values of willingness to pay per QALY >£11,000, but they do not have the highest expected net benefit.

Co-morbid conditions

The base case analysis does not include the additional costs of the common co-morbid conditions of CD and ODD. Estimates of the additional cost of common co-morbid conditions were available from the same source that provided

TABLE 93 *Results of sensitivity analysis employing treatment-specific utility values*

Strategy	Order of treatments received	Cost (£)	QALYs	Cost per QALY (£) (compared with)
1	IR-MPH – ATX – DEX – no treatment	1,237	0.9141	ED
2	ER-MPH8 – ATX – DEX – no treatment	1,474	0.9264	D
3	ER-MPH12 – ATX – DEX – no treatment	1,481	0.9228	D
4	ATX – IR-MPH – DEX – no treatment	1,484	0.9329	D
5	**ATX – ER-MPH8 – DEX – no treatment**	**1,554**	**0.9361**	**31,107 (vs 11)**
6	ATX – ER-MPH12 – DEX – no treatment	1,566	0.9359	D
7	IR-MPH – DEX – ATX – no treatment	1,144	0.9085	D
8	ER-MPH8 – DEX – ATX – no treatment	1,340	0.9176	ED
9	ER-MPH12 – DEX – ATX – no treatment	1,413	0.9190	ED
10	**ATX – DEX – IR-MPH – no treatment**	**1,470**	**0.9330**	**15,448 (vs 16)**
11	**ATX – DEX – ER-MPH8 – no treatment**	**1,489**	**0.9340**	**20,173 (vs 10)**
12	ATX – DEX – ER-MPH12 – no treatment	1,491	0.9287	D
13	**DEX – IR-MPH – ATX – no treatment**	**1,103**	**0.9088**	**–**
14	DEX – ER-MPH8 – ATX – no treatment	1,161	0.9117	D
15	DEX – ER-MPH12 – ATX – no treatment	1,163	0.9107	D
16	**DEX – ATX – IR-MPH – no treatment**	**1,162**	**0.9131**	**13,539 (vs 13)**
17	DEX– ATX – ER-MPH8 – no treatment	1,181	0.9140	ED
18	DEX– ATX – ER-MPH12 – no treatment	1,183	0.9138	D
19	No treatment	1,228	0.8780	D

D, ruled out by dominance; ED, ruled out by extended dominance.

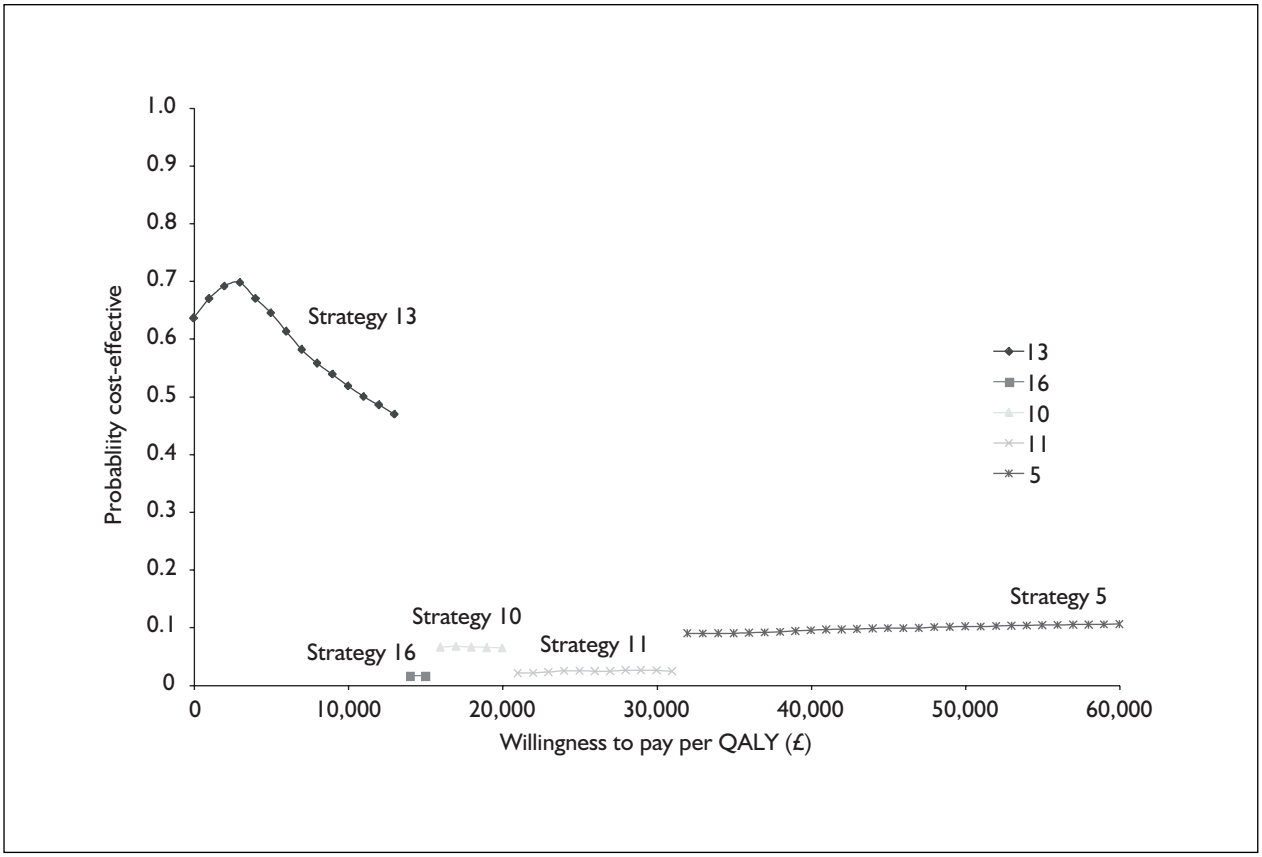

FIGURE 24 *Cost-effectiveness acceptability frontier showing the optimal strategies in a sensitivity analysis employing treatment-specific utility values*

TABLE 94 *Additional resource use data attributed to co-morbid conditions in patients with ADHD*

Item	Average per year	Lower CI limit	Upper CI limit
Consultations			
Psychiatrist	2.25	1.30	3.00
Paediatrician	0.25	0.00	0.70
GP	2.25	1.30	3.40
Tests			
Blood test	0.53	0.00	1.43
ECG	0.03	0.00	0.07

the non-drug costs used in the base case analysis. *Table 94* presents the additional cost of these co-morbid conditions.

When the model is re-analysed to include these additional costs, strategy 13 remains the dominant strategy, with a cost of £1491 and 0.8281 QALYs per patient over a time horizon of 1 year. This compares with a cost of £1098 and 0.8289 in the base case (difference in QALYs due to random variation). This sensitivity analysis relies on the assumption that the relative treatment effects on ADHD are independent of the presence of co-morbid conditions.

If DEX is not suitable as first-line therapy, strategy 7 (first-line IR-MPH, second-line DEX, third-line ATX) is optimal. In this analysis strategy 9 (first-line ER-MPH12, second-line DEX, third-line ATX) is more costly and more effective compared with strategy 7, but the cost per QALY gained is £5,697,763.

The base case analysis also does not consider patients with co-morbid conditions that make them unsuitable for treatment with stimulants, such as severe tics or Tourette's syndrome. In these patients, MPH and DEX may be unsuitable, leaving ATX as the only available pharmacotherapy. The submission by Eli Lilly used data from an unpublished trial comparing ATX with placebo in children with Tourette's syndrome and severe tics. The response rate to ATX was found to be 66.67%, defined as a reduction of ≥25% on the parent-rated ADHD-RS, which compares with a response rate of 65.08% in children and adolescents without these contraindications to treatment with stimulants.

No published trials were available comparing ATX with placebo in patients with severe tics or Tourette's syndrome. As such, a sensitivity analysis was conducted based on the assumption that the relative treatment effect of ATX on ADHD is independent of the presence of tics or Tourette's syndrome. Using the base case estimates of response rates (estimated from trials that excluded patients with severe tics and Tourette's syndrome), the cost per QALY gained with ATX compared with no treatment (strategy 19) is £7951. Hence treatment with ATX appears cost-effective in patients who are contraindicated to treatment with stimulants. If society were willing to pay £30,000 per additional QALY, treatment with ATX would have an 86% probability of being cost-effective.

Sensitivity to time horizon

The base case model considers a time horizon of 1 year. At the end of this year, the cohort is divided into responders on various medications and non-responders on no medication. It is unlikely that the proportion of patients in each of the health states at the end of 1 year will remain the same indefinitely. Unfortunately, there is a lack of long-term data in this area that might inform the model in terms of long-term adverse events with treatment, length of treatment and long-term benefits of treatment. As such, no extrapolation was considered in the base case analysis.

Two studies were identified that explored the age-dependent decline of symptoms of ADHD.[148,158] The data provided by Hill and Schoener[148] were transformed into a yearly probability of remission of 13% (50% over 5 years). This estimate of 50% remission over 5 years was calculated using a non-linear regression analysis on cohorts of children who received a mixture of treatments for ADHD. The yearly rate was applied to patients in each health state, including non-responders. Patients in remission were assumed to be identical with medication responders, without the cost of medication itself. The long-term model has been described in the section 'Extrapolation' (p. 103).

Figure 25 illustrates the simple structure, which employs a 1-year cycle length. *Table 95* shows the results from the extrapolation. Strategy 13 remains

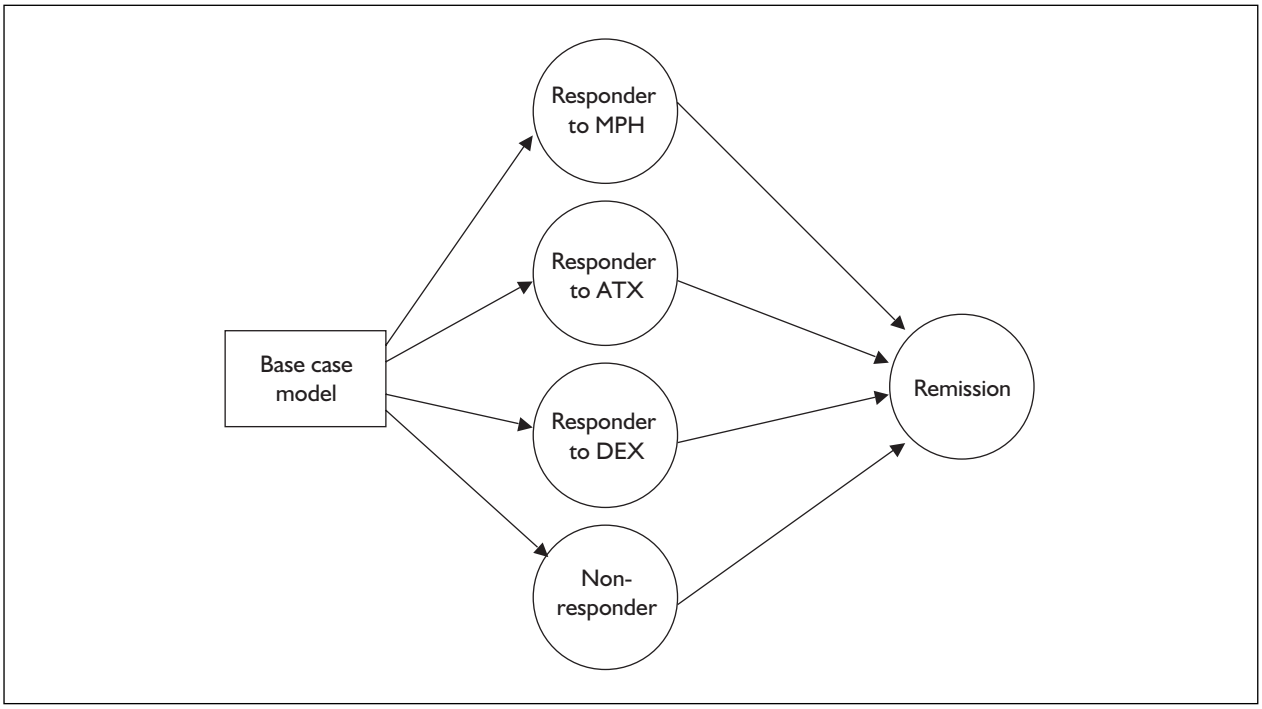

FIGURE 25 *Representation of the long-term extrapolation model*

TABLE 95 *Results of the sensitivity analysis extrapolating the model to when the cohort reaches 18 years of age*

Strategy	Order of treatments received	Cost (£)	QALYs	Cost per QALY (£) (compared with)
1	IR-MPH – ATX – DEX – no treatment	9,514	9.2403	D
2	ER-MPH8 – ATX – DEX – no treatment	10,649	9.2395	D
3	ER-MPH12 – ATX – DEX – no treatment	10,696	9.2386	D
4	ATX – IR-MPH – DEX – no treatment	10,646	9.2402	D
5	ATX – ER-MPH8 – DEX – no treatment	11,002	9.2398	D
6	ATX – ER-MPH12 – DEX – no treatment	11,009	9.2382	D
7	**IR-MPH – DEX – ATX – no treatment**	**9,016**	**9.2597**	**7,128**
8	ER-MPH8 – DEX – ATX – no treatment	10,553	9.2590	D
9	**ER-MPH12 – DEX - ATX – no treatment**	**10,882**	**9.2597**	**37,802,566**
10	ATX – DEX – IR-MPH – no treatment	11,554	9.2594	D
11	ATX – DEX – ER-MPH8 – no treatment	11,574	9.2594	D
12	ATX – DEX – ER-MPH12 – no treatment	9,036	9.2592	D
13	**DEX – IR-MPH – ATX – no treatment**	**8,885**	**9.2413**	**–**
14	DEX – ER-MPH8 – ATX – no treatment	9,187	9.2408	D
15	DEX – ER-MPH12 – ATX – no treatment	9,196	9.2394	D
16	DEX – ATX – IR-MPH – no treatment	9,172	9.2412	D
17	DEX– ATX – ER-MPH8 – no treatment	9,277	9.2409	D
18	DEX– ATX – ER-MPH12 – no treatment	9,291	9.2393	D
19	No treatment	9,580	8.8896	D

D, dominated.

the cheapest alternative, and strategies 7 and 9 are not dominated. For values of willingness to pay per QALY of more than £7128, strategy 7 (first-line IR-MPH, second-line DEX, third-line ATX) appears cost-effective. The cost per QALY gained with strategy 9 (first-line ER-MPH12, second-line DEX, third-line ATX) compared with strategy 7 is £37,802,566. If the societal value of willingness to pay per additional QALY were £30,000, strategy 7 would have a 19% probability of being the optimal strategy. Again, the distribution of incremental net benefit is skew, and so at £30,000 per QALY, strategy 13 has a 51% probability of being the optimal strategy, but it does not have the highest

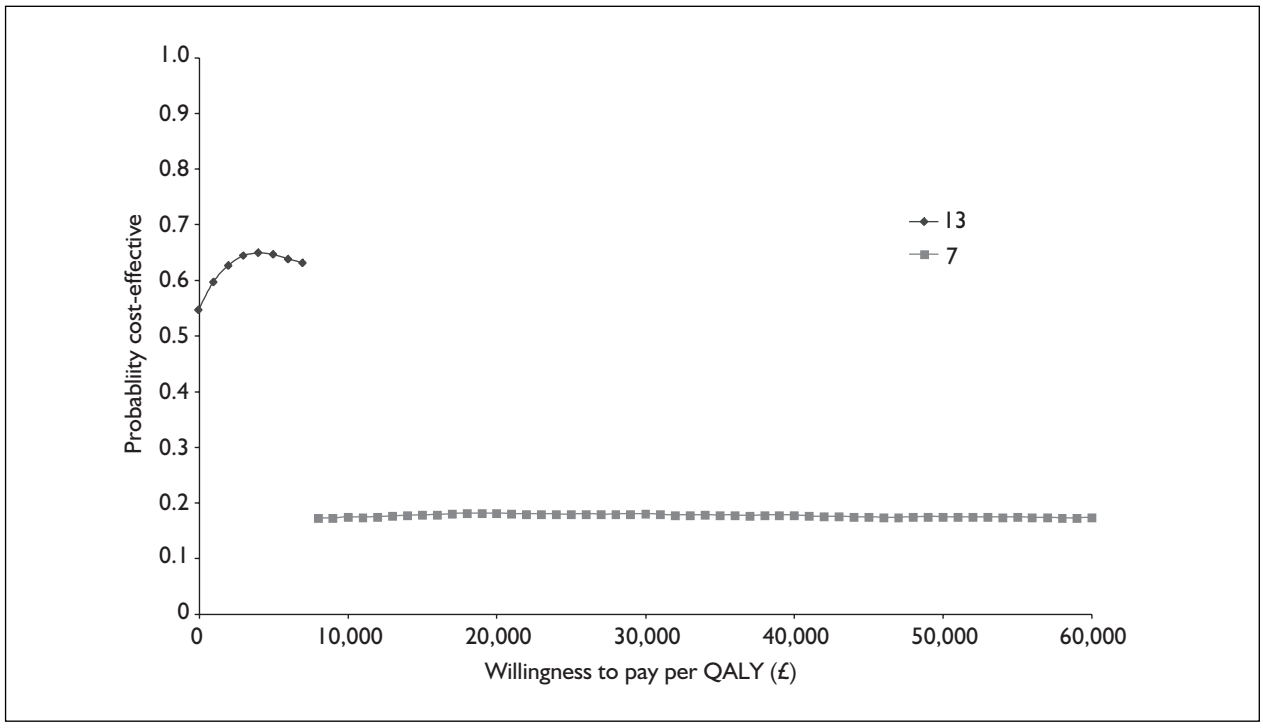

FIGURE 26 *Cost-effectiveness acceptability frontier showing the optimal strategies in a sensitivity analysis of long-term extrapolation*

expected net benefit. The cost-effectiveness frontier for this sensitivity analysis is shown in *Figure 26*. Strategy 7 appears cost-effective for values of willingness to pay per QALY above £7128, and strategy 9 does not appear to be cost-effective.

Clearly, this model does not incorporate long-term adverse effects of pharmacotherapy, as the data were not available to include this, and this is an important omission from the model. The model also does not include long-term benefits of treatment, which could perhaps be avoidance of prison, lower numbers of exclusions from school and improved peer relations. However, this omission is less critical, because the inclusion of these benefits would only improve the cost-effectiveness of active treatment.

Sensitivity to estimated resource use

In the base case model, the no treatment option (strategy 19) is dominated by an active treatment option. This is due in part to the estimates of resource use employed in that model, in particular the fact that a non-responder is more costly in terms of non-drug resource use compared with a responder. In the submission by Celltech, an alternative assumption was used regarding resource use. They followed the Wessex DEC evaluation[124] in assuming that responders to treatment had six visits to a psychiatrist per year and six visits to a GP per year. Non-responders were assumed to have only two visits to a GP per year, and were therefore less costly than responders in terms of non-drug resource use.

In this sensitivity analysis, we evaluate the impact on the model results of employing this alternative source of resource use. The uncertainty surrounding the resource use was characterised using a gamma distribution. The 95% CI for the numbers of psychiatrist and GP visits for responders was assumed to be 3 to 9 per year. The 95% CI around the number of GP visits for non-responders was assumed to be 0 to 4 per year. The results of this analysis are shown in *Table 96*. Strategy 19 (no treatment) is no longer dominated.

The cost per QALY gained with strategy 13 (first-line DEX, second-line IR-MPH, third-line ATX) compared with strategy 19 is £14,939. Strategy 13 remains the optimal treatment strategy in this sensitivity analysis with radically different estimates of resource use.

If DEX is not suitable as first-line therapy, strategy 7 (first-line IR-MPH, second-line DEX, third-line ATX) remains the optimal treatment strategy, with a cost per QALY gained of £15,662 compared with

TABLE 96 *Results of the sensitivity analysis employing alternative estimates of resource use*

Strategy	Order of treatments received	Cost (£)	QALYs	Cost per QALY (£) (compared with)
1	IR-MPH – ATX – DEX – no treatment	1006	0.8279	D
2	ER-MPH8 – ATX – DEX – no treatment	1233	0.8273	D
3	ER-MPH12 – ATX – DEX – no treatment	1250	0.8278	D
4	ATX – IR-MPH – DEX – no treatment	1250	0.8278	D
5	ATX – ER-MPH8 – DEX – no treatment	1320	0.8277	D
6	ATX – ER-MPH12 – DEX – no treatment	1327	0.8274	D
7	IR-MPH – DEX – ATX – no treatment	920	0.8283	D
8	ER-MPH8 – DEX – ATX – no treatment	1105	0.8277	D
9	ER-MPH12 – DEX – ATX – no treatment	1190	0.8284	D
10	ATX – DEX – IR-MPH – no treatment	1242	0.8281	D
11	ATX – DEX – ER-MPH8 – no treatment	1261	0.8281	D
12	ATX – DEX – ER-MPH12 – no treatment	1259	0.8278	D
13	**DEX – IR-MPH – ATX – no treatment**	**887**	**0.8288**	**14,939**
14	DEX – ER-MPH8 – ATX – no treatment	944	0.8287	D
15	DEX – ER-MPH12 – ATX – no treatment	945	0.8286	D
16	DEX – ATX – IR-MPH – no treatment	946	0.8288	D
17	DEX– ATX – ER-MPH8 – no treatment	965	0.8288	D
18	DEX– ATX – ER-MPH12 – no treatment	963	0.8285	D
19	**No treatment**	**48**	**0.7727**	**–**

D, dominated.

TABLE 97 *Cost-effectiveness of ER-MPH8, ER-MPH12, ATX and no treatment in patients for whom a midday dose of medication is unsuitable*

Strategy	Order of treatments received	Cost (£)	QALYs	Cost per QALY (£) (compared with)
19	No treatment	1223	0.7731	–
20	ATX only	1517	0.8093	D
22	ER-MPH8 only	1360	0.8053	4251 (vs 19)
23	ER-MPH12 only	1427	0.8140	7670 (vs 22)

D, dominated.

no treatment. Again, strategy 9 is not ruled out by dominance or extended dominance, but the cost per QALY gained compared with strategy 7 is outside the range normally considered cost-effective (£5,808,184).

Sensitivity to structural assumption regarding MPH

A major structural assumption in the model is that a patient who has failed treatment with one formulation of MPH would not then receive a different formulation of the same drug. However, if failure on IR-MPH was due to non-compliance, or because a midday dose was simply unworkable for the patient, ER-MPH may be a relevant treatment option. The effect of compliance on response rates to IR-MPH and ER-MPH is reflected in the model. However, the model, and the trial data, do not identify the proportion of non-responders that fail owing to lack of compliance. As such, this sensitivity analysis considers a hypothetical cohort of patients for whom a midday dose of medication is considered unsuitable. This includes patients who have failed on IR-MPH or DEX where the clinician can identify that the reason for failure is non-response. Also included are patients for whom the clinician judges a midday dose of medication to be unworkable.

The model is a simple comparison of ER-MPH8, ER-MPH12 and ATX and no treatment. The results of the analysis are shown in *Table 97*. They show that in this selected patient population, ATX is dominated by ER-MPH12. Hence in those patients for whom a midday dose of medication is unsuitable, through non-compliance or for other reasons, ER-MPH12 would precede ATX in any

TABLE 98 *Response rates defined as score of 1 or 2 on CGI-S*

Trial	Treatment	Responders (%)	No. in group
Greenhill, 2002[59]	ER-MPH8	98 (63)	154
	Placebo	41 (26)	156
Steele, 2004[90]	ER-MPH12	**[Confidential information removed]**	
	IR-MPH		
Kelsey, 2004[63]	ATX	34 (27)	126
	Placebo	3 (5)	60
Michelson, 2002[74]	ATX	24 (29)	84
	Placebo	8 (10)	83
Weiss, 2004[94]	ATX	**[Confidential information removed]**	
	Placebo		

treatment strategy. Whether it is possible to identify such patients in practice is a challenge for the clinician in charge.

Sensitivity to estimated response rates

The section 'Clinical effectiveness' (p. 103) illustrated the numerous definitions of response available in the trial data. In order to utilise different definitions of response, it was necessary to model a relationship between the alternative definitions. This was achieved by extending the base case MTC model. As a reminder, the base case model assumes a binomial likelihood from the available data points, r and n, and the proportion of responders, p, is estimated in a regression-like structure, with the logit of the proportion of responders dependent on a study-specific baseline, μ, and a treatment effect, δ:

$$r_i^k \sim \text{Bin}(p_i^k, n_i^k)$$
$$\text{logit}(p_i^k) = \mu_i + \delta_i^k$$

To extend this model, let us assume that response defined as a score of 1 or 2 on the CGI-I is response **1**, which is modelled as follows:

$$r\mathbf{1}_i^k \sim \text{Bin}(p\mathbf{1}_i^k, n\mathbf{1}_i^k)$$
$$\text{logit}(p\mathbf{1}_i^k) = \mu\mathbf{1}_i + \delta\mathbf{1}_i^k$$

Response defined as a score of 1 or 2 on the CGI-S is response **2**, and response on this scale is modelled to be conditional on the estimated response rate on scale 1:

$$r\mathbf{2}_i^k \sim \text{Bin}(p\mathbf{2}_i^k, n\mathbf{2}_i^k)$$
$$\text{logit}(p\mathbf{2}_i^k) = \mu\mathbf{2}_i + \delta\mathbf{2}_i^k$$

If both measures capture the same effect, $\delta\mathbf{2}$ may be random error. If the measures capture different effects, the relationship between the measures is estimated according to this model, and the correlation between the two is reflected. Because we have trials that report response on more than one measure, the relationship between the different measures is estimated from the data. Through this relationship, trials that report response only on scale 2 can inform the estimate of response on scale 1. By selecting which definition of response is to be the baseline in the model (scale 1), we can infer response rates on that scale, strengthened by information about response on different scales. The code for this extended model is given in Appendix 11.

Using the framework described above, we could bring in trials reporting response on the CGI-S, in order to synthesise all clinician-rated response data. Two of the trials reporting response on CGI-I for the base case analysis also reported response defined as a score of 1 or 2 on the CGI-S. Three more trials reported response on CGI-S, but not on CGI-I. The additional information provided by these trials is shown in *Table 98*.

The three additional trials were all set in the USA and used DSM-IV diagnostic criteria. They recruited patients of varying age ranges (6–12, 6–16 and 8–12 years), and this again is not reflected in the model. The output from 2 WinBUGS models, using CGI-I and CGI-S as baseline, respectively, is shown in *Table 99*. Where CGI-I is used as the baseline response definition, the results are slightly higher than the base case analysis and the uncertainty around the estimated treatment effects is reduced. Using the same information, but specifying CGI-S as the baseline scale, the order of the treatment effects remains stable, but the absolute effects are lower. This reflects the lower absolute response rates reported using CGI-S in comparison with CGI-I.

TABLE 99 *Response rates estimated in extended MTC model in WinBUGS: response defined as score of 1 or 2 on CGI-I or CGI-S*

Treatment	Response rate, CGI-I baseline (SD)	Response rate, CGI-S baseline (SD)
Placebo	0.36 (0.09)	0.15 (0.09)
IR-MPH	0.76 (0.14)	0.53 (0.22)
ER-MPH8	0.68 (0.20)	0.43 (0.25)
ER-MPH12	0.85 (0.13)	0.65 (0.22)
ATX	0.72 (0.14)	0.43 (0.19)
DEX	0.89 (0.14)	0.74 (0.24)

TABLE 100 *Response rates defined as reduction of ≥ 25% on the ADHD-RS*

Trial	Treatment	Responders (%)	No. in group
Kelsey, 2004[63]	ATX	79 (63)	126
	Placebo	20 (33)	60
Michelson, 2002[74]	ATX	50 (60)	84
	Placebo	26 (31)	83
Kemner, 2004[99]	ER-MPH12	**[Confidential information removed]**	
	ATX		
Weiss, 2004[94]	ATX		
	Placebo		
Spencer, 2002 (reported results of 2 trials)[89]	ATX	42 (65)	65
	Placebo	15 (24)	62
Spencer, 2002[89]	ATX	38 (59)	64
	Placebo	25 (40)	62

The same method for synthesising the clinician-rated response rates can be used to estimate the relationship between response defined on a clinician-rated scale and response defined on a parent-rated scale. This allows us to overcome the lack of parent-rated response rate data for ER-MPH8 and DEX. As highlighted in the section 'Clinical effectiveness' (p. 103), a group of six trials reported response defined as a reduction of ≥ 25% on the parent-rated ADHD-RS. Three of the six trials also reported response defined as a score of 1 or 2 on CGI-S, and one reported response defined as a score of 1 or 2 on CGI-I. The additional data provided on this new definition of response is shown in *Table 100*.

The trials reported by Spencer and colleagues[89] recruited patients aged between 7 and 13 years, using DSM-IV diagnostic criteria in a US setting. At this stage, we can also incorporate the results of the MTA trial,[133] but only by assuming that the medical management group in that trial represents treatment with IR-MPH. The review in Chapter 4 highlighted that although the majority of the medication in the MTA trial was IR-MPH, a proportion consisted of other medications. The definition of response in the MTA trial was a score of ≤ 1 on the SNAP-IV scale. In order to calculate response rates, investigators averaged over the teacher and parent ratings for each item on the scale. The trial by Steele and colleagues[90] also reported response defined as a score of ≤ 1 on the SNAP-IV scale. *Table 101* shows the response rate information available on the SNAP-IV scale (assuming that medical management in the MTA trial is equal to IR-MPH). The nature of the treatment received in the community comparison arm of the MTA trial is still unclear, and as a result these data are omitted from the analysis.

Hence in the final estimation of response rates, we include all of the data from *Tables 86*, *98*, *100* and *101*. In other words, we synthesise response defined on the CGI-I scale, CGI-S scale, ADHD-RS and SNAP-IV scale, by estimating the relationships between response defined on the different scales. This final analysis also incorporates data reported in Quinn[84] and the results from Elia and colleagues.[51] **[Confidential information removed]**. The study by Elia and colleagues[51] used DSM-III diagnostic criteria and defined response as a score of 1, 2 or 3 on CGI-I. This increases the heterogeneity between studies synthesised in this estimate of treatment effects.

TABLE 101 *Response rates defined as score of ≤ 1 on the SNAP-IV scale*

Trial	Treatment	Responders (%)	No. in group
Steele, 2004	ER-MPH12 IR-MPH	**[Confidential information removed]**	
Swanson, 2001[a]	IR-MPH IR-MPH + BT Community comparison	81 (56) 99 (68) 37 (25)	144 145 146

[a] Results for BT alone omitted as not relevant to this review.

TABLE 102 *Response rates estimated in extended MTC model in WinBUGS: response defined on CGI-I, CGI-S, ADHD-RS or SNAP-IV*

Treatment	Response rate, CGI-I baseline (SD)	Response rate, ADHD-RS baseline (SD)
Placebo	0.29 (0.07)	0.39 (0.10)
IR-MPH	0.64 (0.12)	0.74 (0.11)
ER-MPH8	0.59 (0.14)	0.69 (0.13)
ER-MPH12	0.79 (0.10)	0.85 (0.09)
ATX	0.60 (0.11)	0.70 (0.11)
DEX	0.89 (0.10)	0.93 (0.07)

The ADHD-RS is chosen as the baseline response rate, in order to obtain parent-rated estimates of treatment effect. The results of this analysis are compared to the same model using a CGI-I baseline, to aid comparison with the base case results. These data are shown in *Table 102*.

Again, the new information has altered the response rates somewhat, but the order in terms of treatment effect remains the same. Response defined on the ADHD-RS produces a higher absolute number of responders than response defined on the CGI-I scale.

Results using all clinician-rated response

Table 103 shows the results of the model using the response rates reported in *Table 98*. The new sets of response rates alter the results slightly because strategy 13 no longer dominates all the other strategies. Instead, strategy 15 (first-line DEX, second-line ER-MPH12, third-line ATX) is more effective, but at a higher cost. The point estimate of response to ER-MPH12 is higher than the point estimate of response to IR-MPH in the base case and in the extended MTC, but in the latter model the relative difference in treatment effects is more favourable towards ER-MPH12.

The cost per QALY gained with strategy 15 compared with strategy 13 falls when responses are estimated on the CGI-S scale in comparison to the CGI-I scale. This is because overall the response rates are lowered when measured on CGI-S, and there is greater potential to increase the number of responders by switching to a more effective treatment. In the analysis using response measured on CGI-I, a much larger proportion of patients will have responded to first-line DEX, so the potential for increasing the number of responders by altering the second- or third-line therapies is reduced. In both cases, the cost per QALY gained with strategy 15 compared with strategy 13 is probably outside the range of values normally considered to be cost-effective, so strategy 13 remains optimal.

For both of these analyses, if DEX is not considered suitable as first-line therapy, the optimal strategy is number 7 (first-line IR-MPH, second-line DEX, third-line ATX). Strategy 9 is not ruled out by dominance or extended dominance, but the cost per QALY gained compared with strategy 7 is outside the range normally considered cost-effective (>£150,000 per QALY).

Results using parent-rated response: synthesising all response rates

Table 104 shows the results of the model using the response rates reported in *Table 102*. The results are very similar to those using only clinician-rated response data (*Table 101*). Strategy 13 is no longer the dominant treatment strategy, but the cost per QALY gained to move to the next most effective strategy, number 15, is outside the range normally considered cost-effective.

TABLE 103 *Results of the economic model using all response rates estimated on clinician-rated scales*

Strategy	Order of treatments received	CGI-I scale baseline			CGI-S scale baseline		
		Cost (£)	QALY	ICER (£)	Cost (£)	QALY	ICER (£)
1	IR-MPH – ATX – DEX – no treatment	1,223	0.8322	D	1,239	0.8244	D
2	ER-MPH8 – ATX – DEX – no treatment	1,468	0.8315	D	1,413	0.8230	D
3	ER-MPH12 – ATX – DEX – no treatment	1,507	0.8328	D	1,456	0.8261	D
4	ATX – IR-MPH – DEX – no treatment	1,496	0.8319	D	1,378	0.8238	D
5	ATX – ER-MPH8 – DEX – no treatment	1,569	0.8315	D	1,460	0.8229	D
6	ATX – ER-MPH12 – DEX – no treatment	1,598	0.8321	D	1,510	0.8250	D
7	IR-MPH – DEX – ATX – no treatment	1,119	0.8326	D	1,140	0.8254	D
8	ER-MPH8 – DEX – ATX – no treatment	1,341	0.8320	D	1,293	0.8242	D
9	ER-MPH12 – DEX – ATX – no treatment	1,426	0.8331	D	1,378	0.8269	D
10	ATX – DEX – IR-MPH – no treatment	1,478	0.8322	D	1,356	0.8247	D
11	ATX – DEX – ER-MPH8 – no treatment	1,488	0.8320	D	1,378	0.8241	D
12	ATX – DEX – ER-MPH12 – no treatment	1,491	0.8324	D	1,387	0.8256	D
13	**DEX – IR-MPH – ATX – no treatment**	**1,065**	**0.8334**	**–**	**1,102**	**0.8267**	**–**
14	DEX – ER-MPH8 – ATX – no treatment	1,098	0.8332	D	1,142	0.8260	D
15	**DEX – ER-MPH12 – ATX – no treatment**	**1,102**	**0.8337**	**177,000**	**1,150**	**0.8278**	**46,000**
16	DEX – ATX – IR-MPH – no treatment	1,101	0.8334	D	1,131	0.8266	D
17	DEX – ATX – ER-MPH8 – no treatment	1,111	0.8332	D	1,153	0.8260	D
18	DEX – ATX – ER-MPH12 – no treatment	1,114	0.8336	D	1,162	0.8275	D
19	No treatment	1,225	0.7741	D	1,224	0.7727	D

D, dominated.

TABLE 104 *Results of the economic model using all response rates defined on CGI-I, CGI-S, ADHD-RS or SNAP-IV*

Strategy	Order of treatments received	CGI-I scale baseline			ADHD-RS scale baseline		
		Cost (£)	QALY	ICER (£)	Cost (£)	QALY	ICER (£)
1	IR-MPH – ATX – DEX – no treatment	1,240	0.8304	D	1,225	0.8316	D
2	ER-MPH8 – ATX – DEX – no treatment	1,449	0.8298	D	1,464	0.8312	D
3	ER-MPH12 – ATX – DEX – no treatment	1,492	0.8317	D	1,507	0.8324	D
4	ATX – IR-MPH – DEX – no treatment	1,444	0.8301	D	1,487	0.8313	D
5	ATX – ER-MPH8 – DEX – no treatment	1,527	0.8298	D	1,565	0.8311	D
6	ATX – ER-MPH12 – DEX – no treatment	1,568	0.8308	D	1,596	0.8316	D
7	IR-MPH – DEX – ATX – no treatment	1,117	0.8311	D	1,115	0.8321	D
8	ER-MPH8 – DEX – ATX – no treatment	1,312	0.8306	D	1,339	0.8318	D
9	ER-MPH12 – DEX – ATX – no treatment	1,405	0.8322	D	1,424	0.8328	D
10	ATX – DEX – IR-MPH – no treatment	1,423	0.8308	D	1,467	0.8317	D
11	ATX – DEX – ER-MPH8 – no treatment	1,435	0.8306	D	1,475	0.8316	D
12	ATX – DEX – ER-MPH12 – no treatment	1,439	0.8312	D	1,478	0.8319	D
13	**DEX – IR-MPH – ATX – no treatment**	**1,068**	**0.8325**	**–**	**1,059**	**0.8333**	**–**
14	DEX – ER-MPH8 – ATX – no treatment	1,096	0.8323	D	1,082	0.8331	D
15	**DEX – ER-MPH12 – ATX – no treatment**	**1,101**	**0.8330**	**63,690**	**1,085**	**0.8335**	**108,747**
16	DEX – ATX – IR-MPH – no treatment	1,095	0.8325	D	1,083	0.8332	D
17	DEX – ATX – ER-MPH8 – no treatment	1,106	0.8323	D	1,091	0.8331	D
18	DEX – ATX – ER-MPH12 – no treatment	1,111	0.8329	D	1,094	0.8334	D
19	No treatment	1,225	0.7739	D	1,227	0.7735	D

D, dominated.

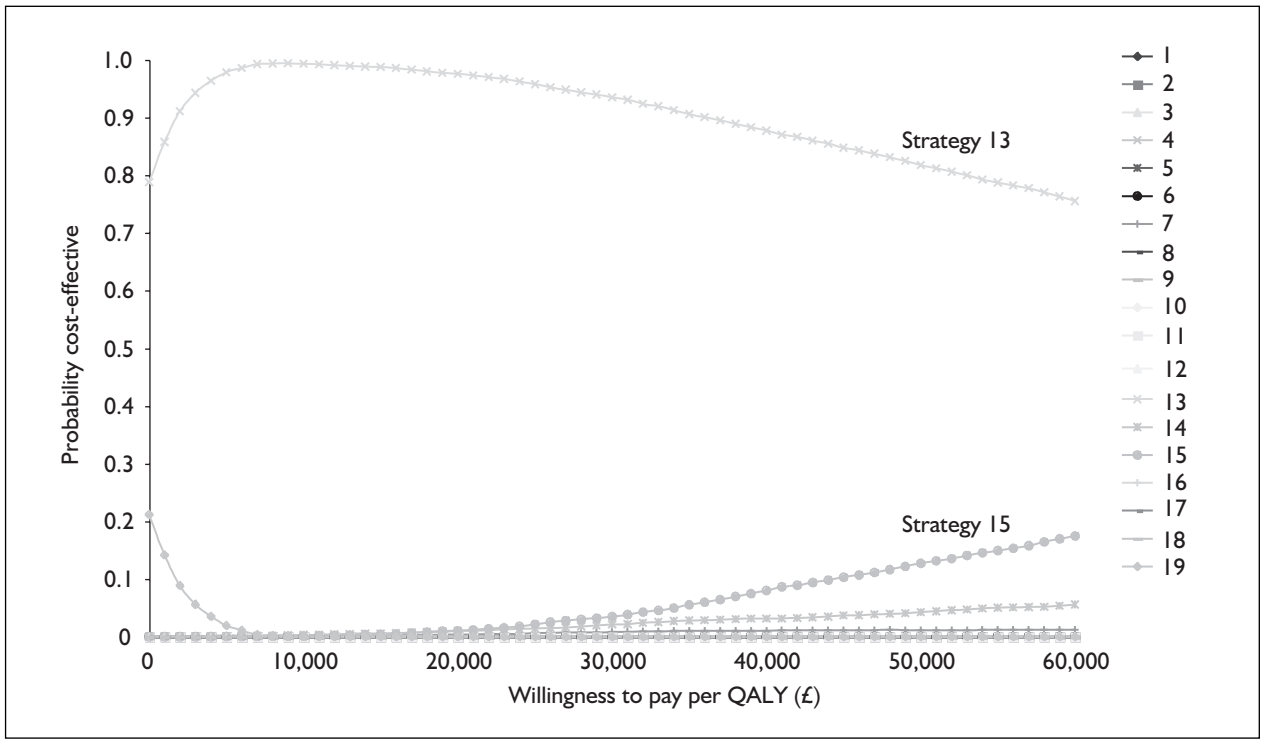

FIGURE 27 *CEACs for 19 strategies compared: synthesising all response rates against an ADHD-RS baseline*

The CEACs from the synthesis of all response rates are very similar whether they are based on CGI-I or ADHD-RS. *Figure 27* shows the CEACs when the response rates are synthesised against an ADHD-RS baseline.

If society were willing to pay £30,000 per additional QALY, strategy 13 has a 93% probability of being most cost-effective (among strategies including three active treatments). This gain in certainty compared with the base case reflects the incorporation of more trial data.

For both of these analyses, if DEX is not suitable as first-line therapy, the optimal treatment strategy is number 7 (first-line IR-MPH, second-line DEX, third-line ATX). In the analysis with all response rates synthesised against the parent-rated ADHD-RS baseline, if society were willing to pay £30,000 per additional QALY, strategy 7 has a 100% probability of being the optimal treatment strategy. Again, the uncertainty is decreased by the incorporation of more trial data. Also, the uncertainty is reduced compared to the case where DEX is considered suitable as first-line therapy because there are six fewer strategies being compared. Strategy 9 is not ruled out by dominance or extended dominance, but the cost per QALY gained compared with strategy 7 is outside the range normally considered cost-effective (>£250,000 per QALY).

[Following this appraisal in 2004, the price of dexamfetamine rose, in 2005, from £1.92 to £3.00 per 28 5-mg tablets. Despite this price increase, it remained the cheapest of the alternative drug treatments, and the results of the economic analysis were robust to this price increase.]

Discussion

This study sought to answer the question of which treatment or treatment strategy is most cost-effective once one has assessed there to be a need for medical management in children and adolescents with ADHD. A very simple economic model was constructed to assess the cost-effectiveness of alternative treatment options. The model was necessarily simple owing to a lack of data relating to, in particular, clinically meaningful response rates, long-term effects of treatment and response to treatment conditional on factors such as previous treatment, ADHD subtype, gender and age. Some of these data deficiencies were explored in scenario analyses by specifying modelling assumptions.

In the base case analysis, response rates were calculated by using only few additional assumptions above those found in a typical meta-analysis. However, this severely reduced the number of trials informing the model to only six

of the 64 identified in the clinical effectiveness review. This analysis showed that a treatment strategy of first-line DEX, followed by second-line IR-MPH for treatment failures, followed by third-line ATX for repeat treatment failures was optimal. This strategy remained optimal when including the additional costs of co-morbid conditions, extrapolating the model to age 18 years, and using alternative estimates of resource use in ADHD. A sensitivity analysis employing alternative estimates of the utility values associated with ADHD did alter the results, but problems in interpreting these alternative utility values mean that the result may not be valid. It is interesting that, despite using a different measure of efficacy to that used in the clinical effectiveness review in Chapter 4, the conclusions are broadly similar. Chapters 4 and 6 indicate the superiority of drugs over no drug therapy, but show no significant difference in terms of efficacy or side-effects between the active therapies. This lack of significant difference could be due simply to the lack of available evidence in both cases. The main additional feature of this chapter in comparison with Chapter 4 is the consideration of costs. Given the lack of evidence for differences in efficacy between active therapies, the results of the economic model are largely driven by drug cost, in which there are marked differences between the relevant comparators.

It is possible that DEX may not be considered suitable as a first-line therapy; if the interpretation of its licence is that it can only be used following failure on another medication for ADHD, or if concerns about its abuse potential (not reflected in the model) are so much greater than concerns about MPH. In this case, the model identified an optimal treatment strategy of first-line IR-MPH, followed by second-line DEX for treatment failures, followed by third-line ATX for repeat treatment failures. However, data on the relative abuse potential of MPH and DEX are scarce, and the costs and dis-benefits associated with such abuse would be hard to quantify in this simple model. As such, we presented results for the case where DEX is considered suitable as first-line therapy, and the case where it is not, leaving the reader to decide whether strategies with DEX first-line therapy are relevant comparators.

It is feasible that factors in the school environment or characteristics of particular patients with respect to compliance make a midday dose of medication unworkable. If this is the case, the analysis in the section 'Sensitivity to structural assumption regarding MPH' (p. 117) indicates that ER-MPH12 would be preferred to ATX, and so would precede ATX in any treatment strategy.

In order to increase the number of trials used in calculating response rate, the MTC model used to synthesise the data in the base case analysis was extended to estimate a relationship between responses defined by different criteria. Bringing in additional trials increased the certainty around the model results, and a three-treatment strategy (first-line DEX, second-line IR-MPH, third-line ATX) remained cost-effective. However, even this extended analysis only employs data from 14 out of 64 trials. The model also relies on non-drug resource use data estimated using an expert panel. This increases the uncertainty in the model results, but the model was robust to using very different estimated resource use.

For a decision taken now, with current available data, the results of the economic evaluation clearly identify an optimal treatment strategy. However, the model is not without limitations, and new data on long-term outcomes associated with medical management of ADHD could change the analysis significantly. The model considers a broadly defined set of patients with ADHD, as the data did not allow us to discriminate between patients in terms of ADHD subtype, gender, age or previous treatment. The resource use data are based on expert opinion, which may not reflect resource use in practice in the UK. Similarly, resource use and monitoring in UK practice may be lower than that observed in clinical trials, which could translate to lower effectiveness in practice compared with that observed in clinical trials. The effectiveness data used in the model are based on trials set in North America, owing to the lack of data specific to the UK. Although there are many trials in this area, the outcome measures used, and the way in which results are reported, vary widely. As such, the treatment effects used to populate the economic model are based on a subset of the clinical evidence, predominantly recent trials. An analysis of treatment effects that included all the available trial data would involve many assumptions regarding the clinical value of mean difference in different rating scales, the role of baseline mean score in relation to mean difference, the distribution of mean score and mean difference on each rating scale and the utility associated with mean score on different rating scales. Such assumptions would go beyond what is justified by the data, so it was felt that a more robust synthesis, based on a subset of the available evidence, would be more appropriate.

Chapter 7
Discussion

Effectiveness evidence

This review presents a comprehensive overview of studies (that meet our inclusion criteria) on MPH, DEX and ATX published up to July/August 2004. Overall, the systematic review of effectiveness studies represents an archive of data for reference. The results are presented separately for low, medium and high doses. Although we acknowledge that this may be less relevant for clinical practice, because the dose will be established by titration for individual patients, this approach was chosen for the SR because most of the evidence was presented by dose.

The majority of included studies were of poor quality. Only five out of the 60 non-confidential studies properly reported the method used to assign participants to patient groups. Nine out of the 60 non-confidential studies reported that the sequence of allocation was truly random. Most studies were blinded, but none of the included studies reported whether blinding was successful. Eleven out of the 60 non-confidential studies reported to have used an ITT analysis and 18 out of the 60 non-confidential studies provided a complete description of withdrawals. For most of the crossover trials the statistical analysis was either not clearly reported or not appropriate; for parallel trials the quality of the analysis was better reported.

It should be noted that some of the quality items reflect the quality of reporting and not necessarily the quality of the actual trial. However, given the poor scores on these quality items, the reliability of the study results is unknown.

As reported in the previous NICE report[4] and the AHRQ[28] and CCOHTA[30] reviews, the plethora of MPH studies suggest that MPH (both immediate- and extended-release) is effective at reducing hyperactivity, and improving QoL (as determined by CGI – either the Improvement or Severity subscale) in children. It was noted, however, that the majority of studies that evaluated the effectiveness of MPH did not adequately report their study methodology. There appears to be little evidence of a statistically significant difference in the effectiveness of IR-MPH and ER-MPH.

Similarly, DEX also appears to be effective at reducing hyperactivity and improving QoL. However, there were generally very few high-quality studies that evaluated the effectiveness of DEX. As with MPH, some of the results were variable.

There was consistent evidence that ATX was superior to placebo for hyperactivity and CGI. These more recent studies on ATX had well-reported study methodologies and the results are likely to be reliable.

Very few studies made head-to-head comparisons between the drugs. The previous NICE report[4] stated that there appeared to be little difference in the effectiveness of MPH and DEX. No recent studies were found in our updated search. While the studies reported variable results, the one study that reported no statistically significant differences between drugs was deemed to be of good quality, whereas the quality of the others was uncertain, given the poor reporting of study methodologies.

One study that compared MPH and ATX reported no statistically significant difference between the drugs for hyperactivity or CGI. However, this study did not adequately report on their study methodology. Hence there is insufficient evidence to judge the relative effectiveness of these drugs.

Few studies were included in the review that examined a non-drug intervention in combination with MPH, DEX or ATX. Generally, the results were variable. The studies were, however, heterogeneous regarding the type of non-drug interventions examined and the scales used to measure outcomes.

Adverse events

Upon examination of the evidence, it is clear that adequate and informative data regarding the potential adverse effects of MPH, DEX and ATX are lacking. Of the 64 studies included in the clinical effectiveness section of this review, 38 contributed some data to the analysis of adverse events. However, this contribution was minimal in the majority of cases: only eight studies, for example, provided usable data regarding the

impact of active drug treatment on participant weight loss/gain.

The analysis of adverse events was focused on the most commonly reported complaints of individuals receiving treatment for ADHD, which were identified by examining previous literature. Several studies presented mean severity ratings for adverse events without accompanying data indicating the numbers of participants actually suffering from such effects, thus making adverse impact difficult to quantify. Furthermore, a distinction between numbers of adverse events and numbers of participants suffering from adverse events was often not clearly stated. Total numbers of participants included in safety analyses were often unclear, requiring assumptions to be made which could have underestimated effect sizes. Measures of variance were not always reported, making calculation of relative risks impossible. Although standardised reporting was employed by many authors, some studies appeared to rely upon spontaneous reporting of somatic complaints, which may also have introduced considerable bias into the results. Some trials reported the mean weights of participants across treatment groups at follow-up rather than mean weight change; for crossover trials, this information was not informative owing to the likelihood of carryover effects.

Overall, higher dosages of IR-MPH appear to be associated with the occurrence of headache, loss of appetite, stomach ache and insomnia compared with placebo. ER-MPH appears to be associated with decreased appetite and increased insomnia. However, a systematic review[114] highlighted the need for further research into somatic complaints, which may be associated with the disorder itself rather than MPH treatment. Similarly, high doses of DEX appear to be associated with decreased appetite and increased sleeping problems. ATX of any dose may impair appetite.

As previously highlighted, head-to-head comparisons have not often been examined and, together with poor reporting of adverse events outcomes, data are very sparse. One study comparing immediate- and extended-release formulations of MPH reported a higher occurrence of headache in the latter group. No statistically significant differences in adverse events were detected in the studies comparing MPH with DEX. However, participants assigned to ER-MPH were found to suffer from decreased appetite and increased insomnia compared with those assigned to ATX.

No studies compared ATX with DEX.

Economic evidence

This review presents a comprehensive overview of existing economic evaluations of MPH, ATX and DEX for children and adolescents with ADHD, including three submissions from manufacturers of these medications. The review highlighted a number of potential limitations in the existing literature. In particular, the review highlighted limitations in estimating treatment effectiveness and associated utility values. These limitations may stem from a lack of available data.

A new economic model was developed for this report. Pooling was limited in the clinical effectiveness review, owing to heterogeneity between trials. However, some degree of pooling is necessary to proceed with an economic model. The issue of heterogeneity was overcome by basing the base case on trials that are more similar in terms of how they measure the outcome of interest. In a series of sensitivity analyses, more trials were included by relaxing the criterion of similarity in outcome measurement. Data on resource use associated with ADHD in the UK were lacking, so the model relies on estimates from experts.

Given the lack of available evidence for statistically significant differences in efficacy between the alternative drugs, the results of the economic model were largely driven by drug cost, in which there are marked differences. For a decision taken now, with current available data, the results of the economic evaluation clearly identified an optimal treatment strategy, that is, first-line DEX, followed by second-line IR-MPH for treatment failures, followed by third-line ATX for repeat treatment failures. If DEX is considered not suitable as a first-line therapy, the optimal strategy is first-line IR-MPH, followed by second-line DEX, and third-line ATX. For patients contraindicated to stimulants, ATX is preferred to no treatment. For patients in whom a midday dose of medication is unworkable, ER-MPH is preferred to ATX, and ER-MPH12 appears more cost-effective than ER-MPH8.

The model is not without limitations. As identified in the clinical effectiveness review, the reporting of studies was poor, there are few data to discriminate between the drugs in efficacy or adverse events and there are few data on long-term efficacy and adverse events associated with medical management of ADHD. The data do not allow discrimination between patients with ADHD in terms of ADHD subtype, age, gender or

previous treatment. These caveats must be borne in mind when interpreting the model results.

Limitations of the clinical effectiveness studies and need for further research

The limitations of the research base remain similar to those reported in the previous NICE review and in other SRs.

- Generally, the methodology used in the studies was poorly reported. Inadequate information makes it difficult to assess validity and reliability of the studies.
- The literature is dominated by studies of MPH, although the quality of these studies is generally poor. For DEX, both the quantity and quality of studies are poor. For ATX, there are few studies, but most are of better quality. The quantity and quality of studies evaluating MPH, DEX and ATX should be a consideration for future research. Researchers should use the CONSORT approach to study design.[159]
- Very few studies compared MPH and DEX directly. No studies compared ATX and DEX directly. More head-to-head studies may be beneficial.
- Most of the studies report short-term outcomes. More long-term studies are needed to establish clinical effectiveness and adverse events.
- There is an almost total absence of research investigating the effectiveness of MPH and other interventions for children with a diagnosis of hyperactivity disorder, rather than the broader diagnosis of ADHD. This may have implications for the generalisability of these studies in the UK where HKD makes up most of the cases.
- The majority of studies have been conducted on children between the ages of 5 and 13 years. More studies in adolescents may be useful.
- It appears that, in some cases, parents are less likely than teachers to rate children as being improved.
- It may be useful when possible to collect data from the children to obtain a better understanding of treatment from a patient's perspective and to estimate patient-based measures of clinical outcome.
- The studies used a number of outcomes and scales to measure behaviour, including hyperactivity, making comparisons of results difficult. It would be beneficial if research groups selected a core set of validated and clinically relevant outcomes to be measured in all studies, and to be consistent in analysing and reporting the results.
- A number of studies used a crossover design; however, the data were not always analysed using a method specific to paired data. Presenting within-patient differences (and associated SDs) would be useful.
- A number of the included studies have small sample sizes. Presenting sample size calculations would be useful in order to make sure the studies are not underpowered, so that clinically significant differences between interventions are detected. As part of sample size calculations, authors should clearly specify a clinically significant effect on a particular outcome measure.
- Very few studies included in the review presented usable data for analysing adverse events. Standardised reporting of data (e.g. presenting the numbers of adverse events, numbers of participants suffering from adverse events and total numbers of participants included in the safety analysis) is required to estimate prevalence.

Chapter 8
Conclusion

MPH, DEX and ATX improve hyperactivity and QoL (as assessed using CGI as a proxy) compared with placebo. The validity of the results is not known for studies of MPH and DEX, given the poor reporting of study methodology in the majority of these trials. The recent trials on ATX are likely to be more reliable.

There were very few head-to-head studies comparing MPH, DEX and ATX. No significant differences between the various drugs in terms of efficacy or side-effects were found, mainly owing to a lack of evidence.

The main conclusions from this report are:

- Drug therapy seems to be superior to no drug therapy.
- No significant differences between the various drugs in terms of efficacy or side-effects were found, mainly owing to a lack of evidence.
- The additional benefits from BT (in combination with drug therapy) are uncertain.

The main additional feature of the economic model is the consideration of costs. Given the lack of evidence for any differences in effectiveness between the drugs, the model tends to be driven by drug costs, which differ considerably.

Research recommendations

- Future trials examining MPH, DEX and ATX should include the assessment of tolerability and safety as a priority. Reporting should be standardised and transparent. Researchers should refer to the CONSORT approach to study design.[159]
- Longer term follow-up of individuals participating in trials could further inform policy makers and health professionals. Such data could potentially distinguish between these drugs in a clinically useful way.
- In addition, research examining whether somatic complaints are actually related to drug treatment or to the disorder itself would be informative.

Acknowledgements

We thank the expert advisory panel for their useful advice and constructive comments on the report. We also wish to thank Professor Stephen Senn, University of Glasgow, who provided statistical advice on crossover trials. Thanks are also due to Alison Brown, Ange Davison, and Sally Kingsley, University of York, who provided technical assistance with the report, and to Carol Forbes who produced some of the tables. Ailsa Snaith and Linda McIntyre were involved in data extraction.

Contribution of authors

Sarah King (Research Fellow) was the lead reviewer responsible for writing the protocol and final report and was involved in study selection, data extraction, validity assessment and synthesis of data. Susan Griffin (Research Fellow) was involved in the analysis of cost-effectiveness, writing the protocol, study selection, data extraction, development of the economic model and report writing. Zoé Hodges (Research Fellow) was the second reviewer involved in designing the Access database, study selection, data extraction, validity assessment and writing the final report. Helen Weatherly (Research Fellow) was involved in the analysis of cost-effectiveness, writing the protocol, study selection, data extraction, development of the economic model and report writing. Christian Asseburg (Research Fellow) was involved in the analysis of cost-effectiveness. Gerry Richardson (Research Fellow) was involved in the analysis of cost-effectiveness, data extraction, development of the economic model and commenting on drafts of the economic sections of the report. Su Golder (Information Officer) devised the search strategy and carried out the literature searches, wrote the search methodology sections of the protocol and final report and managed the Endnote library. Eric Taylor (Professor of Child and Adolescent Psychiatry) provided input and advice at all stages, commented on drafts of the protocol and final report and contributed to the discussion section of the report. Mike Drummond (Professor of Health Economics) provided input at all stages, commented on various drafts of the report and had overall responsibility for the cost-effectiveness section of the report. Rob Riemsma (Senior Research Fellow) was review manager responsible for overall management of the project and was also involved in study selection, data extraction, synthesis of data and writing the report.

Note

A number of sponsors submitted information to the National Institute for Health and Clinical Excellence in confidence and references to this information have been removed from the report. However, it should be noted that the Institute's Appraisal Committee has access to the full report when drawing up their guidance.

This report was commissioned by the NHS R&D HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme. Any errors are the responsibility of the authors.

References

1. National Institute for Clinical Excellence (NICE). *Guidance on the use of methyphenidate (Ritalin, Equasym) for attention deficit/hyperactivity disorder (ADHD) in childhood*. Report No. 13. London: NICE; 2000.
2. American Psychiatric Association. *Diagnostic and statistical manual for mental disorders, fourth edition (DSM-IV)*. Washington, DC: American Psychiatric Association; 1994.
3. Agency for Health Care Policy and Research. *Diagnosis of attention-deficit/hyperactivity disorder*. Rockville, MD: Agency for Health Care Policy and Research; 1999.
4. Lord J, Paisley S. *The clinical effectiveness and cost effectiveness of methylphenidate for hyperactivity in childhood*. London: NICE; 2000.
5. Ford T, Goodman R, Meltzer H. The British child and adolescent mental health survey 1999: the prevalence of DSM-IV disorders. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:1203–11.
6. Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis type 1. *Dev Med Child Neurol* 2002;**44**:164–70.
7. Dunn DW, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. *Dev Med Child Neurol* 2003;**45**:50–4.
8. Elgen I, Sommerfelt K, Markestad T. Population based, controlled study of behavioural problems and psychiatric disorders in low birthweight children at 11 years of age. *Arch Dis Child Fetal Neonatal Ed* 2002;**87**:F128–32.
9. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F445–50.
10. Rasmussen P, Gillberg C. Natural outcome of ADHD with developmental coordination disorder at age 22 years: a controlled, longitudinal, community-based study. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:1424–31.
11. Sturm H, Fernell E, Gillberg C. Autism spectrum disorders in children with normal intellectual levels: associated impairments and subgroups. *Dev Med Child Neurol* 2004;**46**:444–7.
12. Biederman J, Faraone SV. Current concepts on the neurobiology of attention-deficit/hyperactivity disorder. *J Atten Disord* 2002;**6** (Suppl 1):s7–16.
13. Bradley JD, Golden CJ. Biological contributions to the presentation and understanding of attention-deficit/hyperactivity disorder: a review. *Clin Psychol Rev* 2001;**21**:907–29.
14. World Health Organization. Behavioural and emotional disorders with onset usually occurring in childhood and adolescence. In *The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization; 1992. Chapter 5, pp. 260–6.
15. Clarke AR, Barry RJ, McCarthy R, Selikowitz M. Hyperkinetic disorder in the ICD-10: EEG evidence for a definitional widening? *Eur Child Adolesc Psychiatry* 2003;**12**:92–9.
16. Foreman DM, Foreman D, Prendergast M, Minty B. Is clinic prevalence of ICD-10 hyperkinesis underestimated? Impact of increasing awareness by a questionnaire screen in an UK clinic. *Eur Child Adolesc Psychiatry* 2000;**10**:130–4.
17. Mota VL, Schachar RJ. Reformulating attention-deficit/hyperactivity disorder according to signal detection theory. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:1144–51.
18. Hartman CA, Hox J, Mellenbergh GJ, Boyle MH, Offord DR, Racine Y, *et al*. DSM-IV internal construct validity: when a taxonomy meets data. *J Child Psychol Psychiatry* 2001;**42**:817–36.
19. Guardiola A, Fuchs FD, Rotta NT. Prevalence of attention-deficit hyperactivity disorders in students. Comparison between DSM-IV and neuropsychological criteria. *Arq Neuropsiquiatr* 2000;**58**(2-B):401–7.
20. Burns GL, Boe B, Walsh JA, Sommers-Flanagan R, Teegarden LA. A confirmatory factor analysis on the DSM-IV ADHD and ODD symptoms: what is the best model for the organization of these symptoms? *J Abnorm Child Psychol* 2001;**29**:339–49.
21. Byrne JM, Bawden HN, Beattie TL, DeWolfe NA. Preschoolers classified as having attention-deficit hyperactivity disorder (ADHD): DSM-IV symptom endorsement pattern. *J Child Neurol* 1999;**15**:533–8.
22. Rohde LA. ADHD in Brazil: the DSM-IV criteria in a culturally different population. *J Am Acad Child Adolesc Psychiatry* 2002;**41**:1131–3.
23. Graetz BW, Sawyer MG, Hazell PL, Arney F, Baghurst P. Validity of DSM-IVADHD subtypes in a nationally representative sample of Australian children and adolescents. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:1410–17.

24. Crystal DS, Ostrander R, Chen RS, August GJ. Multimethod assessment of psychopathology among DSM-IV subtypes of children with attention-deficit/hyperactivity disorder: self-, parent, and teacher reports. *J Abnorm Child Psychol* 2001;**29**:189–205.

25. Datapharm Communications. Electronic Medicines Compendium (eMC): summary of product characteristics. URL: http://emc.medicines.org.uk/. Accessed 18 November 2004.

26. Janssen-Cilag. Putting patients at the heart of everything we do. High Wycombe: Janssen-Cilag Limited: Bucks; 2004. URL: http://www.janssen-cilag.co.uk/index.asp. Accessed 9 December 2004.

27. Healthyplace. Atomoxetine HCl. Brand name: Strattera. 2002. URL: http://www.healthyplace.com/medications/strattera.htm. Accessed 9 December 2004.

28. Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. *Treatment of attention-deficit/hyperactivity disorder. Evidence Report: Technology Assessment No. 11*. Rockville, MD: Agency for Health Care Policy and Research; 1999.

29. Joint Formulary Committee. *British National Formulary*. 47th ed. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; 2004.

30. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). *A review of therapies for attention-deficit/hyperactivity disorder – systematic review*. Ottawa: Canadian Coordinating Office for Health Technology, Assessment (CCOHTA), 1998. URL: http://www.ccohta.ca

31. Centre for Reviews and Dissemination. *CRD Report No. 4. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*. 2nd ed. York: Centre for Reviews and Dissemination; 2001.

32. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, *et al*. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics* 2004;**113**:e206–16.

33. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;**31**:140–9.

34. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to BMJ. *BMJ* 1996;**313**:275–83.

35. Ahmann PA, Waltonen SJ, Olson KA, Theye FW, van Erem AJ, LaPlant RJ. Placebo-controlled evaluation of ritalin side effects. *Pediatrics* 1993;**91**:1101-6.

36. Arnold LE, Huestis RD, Smeltzer DJ, Scheib J, Wemmer D, Colner G. Levoamphetamine vs dextroamphetamine in minimal brain dysfunction. Replication, time response, and differential effect by diagnostic group and family rating. *Arch Gen Psychiatry* 1976;**33**:292–301.

37. Arnold LE, Christopher J, Huestis R, Smeltzer DJ. Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: controlled comparison by placebo washout design with Bayes' analysis. *Arch Gen Psychiatry* 1978;**35**:463–73.

38. Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, Tobin K. Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biol Psychiatry* 1989;**25**:222–8.

39. Barkley RA, McMurray MB, Edelbrock CS, Robbins K. Side effects of methylphenidate in children with attention deficit hyperactivity disorder: a systematic, placebo-controlled evaluation. *Pediatrics* 1990;**86**:184–92.

40. Barkley RA, Connor DF, Kwasnik D. Challenges to determining adolescent medication response in an outpatient clinical setting: comparing Adderall and methylphenidate for ADHD. *J Atten Disord* 2000;**4**:102–13.

41. Brown RT, Wynne ME, Medensis R. Methylphenidate and cognitive therapy: a comparison of treatment approaches with hyperactive boys. *J Abnorm Child Psychol* 1985;**13**:69–87.

42. Brown RT, Wynne ME, Boren KA, Clingerman SR, Geniesse R, Spunt AL. Methylphenidate and cognitive therapy in children with attention-deficit disorder: a double-blind trial. *J Dev Behav Pediatr* 1986;**7**:163–74.

43. Brown RT, Sexton SB. A controlled trial of methylphenidate in black adolescents. Attentional, behavioural, and physiological effects. *Clin Pediatr* 1988;**27**:74–81.

44. Buitelaar JK, van der Gaag R, Swaab-Barneveld H, Kuiper M. Pindolol and methylphenidate in children with attention-deficit hyperactivity disorder: clinical efficacy and side-effects. *J Child Psychol Psychiatry* 1996;**37**:587–95.

45. Conners CK, Taylor E, Meo G, Kurtz MA, Fournier M. Magnesium pemoline and dextroamphetamine: a controlled study in children with minimal brain dysfunction. *Psychopharmacologia* 1972;**26**:321–36.

46. Conners CK, Taylor E. Pemoline, methylphenidate, and placebo in children with minimal brain dysfunction. *Arch Gen Psychiatry* 1980;**37**:922–30.

47. Conrad WG, Dworkin ES, Shai A, Tobiessen JE. Effects of amphetamine therapy and prescriptive

tutoring on the behavior and achievement of lower class hyperactive children. *J Learn Disabil* 1971;**4**:509–17.

48. Dopfner M, Bonaschewski T, Schmidt J, Uebel H, Schmeck K, Gerber WD, *et al*. Long-acting methylphenidate preparation in children with ADHD – a multicenter study. *Nervenheilkd* 2003;**22**:85–92.

49. DuPaul GJ, Rapport MD. Does methylphenidate normalize the classroom performance of children with attention deficit disorder? *J Am Acad Child Adolesc Psychiatry* 1993;**32**:190–9.

50. Efron D, Jarman F, Barker M. Methylphenidate versus dexamphetamine in children with attention deficit disorder: a double-blind, crossover trial. *Pediatrics* 1997;**100**:e6.

51. Elia J, Borcherding BG, Rapoport JL, Keysor CS. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? *Psychiatry Res* 1991;**36**:141–55.

52. Fine S, Johnston C. Drug and placebo side effects in methylphenidate–placebo trial for attention deficit hyperactivity disorder. *Child Psychiatry Hum Dev* 1993;**4**:25–30.

53. Firestone P, Crowe D, Goodman JT, McGrath P. Vicissitudes of follow-up studies: differential effects of parent training and stimulant medication with hyperactives. *Am J Orthopsychiatry* 1986;**56**:184–94.

54. Fischer M, Newby RF. Assessment of stimulant response in ADHD children using a refined multimethod clinical protocol. *J Clin Child Psychol* 1991;**20**:232–44.

55. Fitzpatrick PA, Klorman R, Brumaghim JT, Borgstedt AD. Effects of sustained-release and standard preparations of methylphenidate on attention deficit disorder. *J Am Acad Child Adolesc Psychiatry* 1992;**31**:226–34.

56. Gillberg C, Melander H, von Knorring AL, Janols LO, Thernlund G, Hagglof B, *et al*. Long-term stimulant treatment of children with attention-deficit hyperactivity disorder symptoms. A randomized, double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1997;**54**:857–64.

57. Gittelman-Klein R, Klein DF, Katz S, Saraf K, Pollack E. Comparative effects of methylphenidate and thoridazine in hyperkinetic children. I. Clinical results. *Arch Gen Psychiatry* 1976;**33**:1217–31.

58. Greenberg LM, Deem MA, McMahon S. Effects of dextroamphetamine, chlorpromazine, and hydroxyzine on behavior and performance in hyperactive children. *Am J Psychiatry* 1972;**129**:532–9.

59. Greenhill LL, Findling RL, Swanson JM, Group AS. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2002;**109**:E39.

60. Handen B, Feldman HM, Lurier A, Murray PJ. Efficacy of methylphenidate among preschool children with developmental disabilities and ADHD. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:805–12.

61. Hoeppner JA, Hale JB, Bradley AM, Byrnes M, Coury DL, Lennie L, *et al*. A clinical protocol for determining methylphenidate dosage levels in ADHD. *J Attention Disord* 1997;**2**:19–30.

62. James RS, Sharp WS, Bastain TM, Lee PP, Walter JM, Czarnolewski M, *et al*. Double-blind, placebo-controlled study of single-dose amphetamine formulations in ADHD. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:1268–76.

63. Kelsey D, Sumner C, Casat CD, Coury DL, Quintana H, Saylor KE, *et al*. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behaviour: a double-blind, placebo controlled trial. *Pediatrics* 2004;**114**:e1–8.

64. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett S. *Treatment outcomes of OROS(R) methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized, prospective study*. Washington, DC: McNeil Consumer and Specialty Pharmaceuticals; 2004.

65. Klein RG, Abikoff H. Behavior therapy and methylphenidate in the treatment of children with ADHD. *J Atten Disord* 1997;**2**:89–114.

66. Klorman R, Coons HW, Borgstedt AD. Effects of methylphenidate on adolescents with a childhood history of attention deficit disorder: I. Clinical findings [published erratum appears in *J Am Acad Child Adolesc Psychiatry* 1987;**26**:820 (Ref. 304)]. *J Am Acad Child Adolesc Psychiatry* 1987;**26**:363–7.

67. Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD. Clinical effects of a controlled trial of methylphenidate on adolescents with attention deficit disorder. *J Am Acad Child Adolesc Psychiatry* 1990;**29**:702–9.

68. Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD, Strauss J. Clinical and cognitive effects of methylphenidate on children with attention deficit disorder as a function of aggression/oppositionality and age. *J Abnorm Psychol* 1994;**103**:206–21.

69. Kolko DJ, Bukstein OG, Barron J. Methylphenidate and behavior modification in children with ADHD and comorbid ODD or CD: main and incremental effects across settings. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:578–86.

70. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, *et al*. Atomoxetine and methylphenidate treatment in

children with ADHD: a prospective, randomized, open-label trial. *J Am Acad Child Adolesc Psychiatry* 2002;**41**:776–84.

71. Kupietz SS, Winsberg BG, Richardson E, Maitinsky S. Effects of methylphenidate dosage in hyperactive reading-disabled children: I. Behavior and cognitive performance effects. *J Am Acad Child Adolesc Psychiatry* 1988;**27**:70–7.

72. Manos MJ, Short EJ, Findling RL. Differential effectiveness of methylphenidate and Adderall® in school-age youths with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:813–19.

73. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, *et al*. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose–response study. *Pediatrics* 2001;**108**:E83.

74. Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, *et al*. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry* 2002;**159**:1896–901.

75. Michelson D, Buitelaar JK, Danckaerts M, Gillberg C, Spencer TJ, Zuddas A, *et al*. Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 2004;**43**:896–904.

76. Jensen PS, Arnold LE, Richters JE, Severe JB, Vereen D, Vitiello B, *et al*. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;**56**:1073–86.

77. Pelham WEJ, Sturges J, Hoza J, Schmidt C, Bijlsma JJ, Milich R, *et al*. Sustained release and standard methylphenidate effects on cognitive and social behavior in children with attention deficit disorder. *Pediatrics* 1987;**80**:491–501.

78. Pelham WEJ, Greenslade KE, Vodde-Hamilton M, Murphy DA, Greenstein JJ, Gnagy EM, *et al*. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release dextroamphetamine, and pemoline. *Pediatrics* 1990;**86**:226–37.

79. Pelham WEJ, Carlson C, Sams SE, Vallano G, Dixon MJ, Hoza B. Separate and combined effects of methylphenidate and behaviour modification on boys with attention deficit-hyperactivity disorder in the classroom. *J Consult Clin Psychol* 1993;**61**:506–15.

80. Pelham WE, Aronoff HR, Midlam JK, Shapiro CJ, Gnagy EM, Chronis AM, *et al*. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics* 1999;**103**:e43.

81. Pelham WE, Gnagy EM, Chronis AM, Burrows-MacLean L, Fabiano GA, Onyango AN, *et al*. A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 1999;**104**:1300–11.

82. Pelham WE, Gnagy EM, Burrows-Maclean L, Williams A, Fabiano GA, Morrisey SM, *et al*. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics* 2001;**107**:E105.

83. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:619–26.

84. Quinn D. *Celltech integrated clincial study report. A multi-centre, double-blind, three arm, parallel group study comparing the efficacy of immediate release methylphenidate (Ritalin®) and modified release methylphenidate with placebo in children with attention deficit/hyperactivity disorder*. Slough: Celltech Pharmaceuticals; 2003.

85. Rapport MD, DuPaul GJ, Kelly KL. Attention deficit hyperactivity disorder and methylphenidate: the relationship between gross body weight and drug response in children. *Psychopharmacol Bull* 1989;**25**:285–90.

86. Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioural, situational, and temporal effects of treatment of ADHD with methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:754–63.

87. Diamond IR, Tannock R, Schachar RJ. Response to methylphenidate in children with ADHD and comorbid anxiety. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:402–9.

88. Smith BH, Pelham WE, Evans S, Gnagy E, Molina B, Bukstein O, *et al*. Dosage effects of methylphenidate on the social behaviour of adolescents diagnosed with attention-deficit hyperactivity disorder. *Exp Clin Psychopharmacol* 1998;**6**:187–204.

89. Spencer T, Heiligenstein JH, Biederman J, Faries DE, Kratochvil CJ, Conners CK, *et al*. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2002;**63**:1140–7.

90. Steele M, Weiss M, Swanson J, Wang J, Riccardelli R, Binder C. *A randomized, controlled, effectiveness trial of OROS–methylphenidate compared to usual care with immediate-release-methylphenidate in attention-deficit-hyperactivity disorder*. A submission to the National Institute for Clinical Excellence. London, Ontario: Janssen-Ortho; 2004.

91. Stein MA, Blondis TA, Schnitzler ER, O'Brien T, Fishkin J, Blackwell B, *et al*. Methylphenidate dosing: twice daily versus three times daily. *Pediatrics* 1996;**98**:748–56.

92. Stein MA, Sarampote CS, Waldman ID, Robb AS, Conlon C, Pearl PL, *et al*. A dose–response study of OROS methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2003;**112**:E404–13.

93. Tervo RC, Azuma S, Fogas B, Fiechtner H. Children with ADHD and motor dysfunction compared with children with ADHD only. *Dev Med Child Neurol* 2002;**44**:383–90.

94. Weiss M, Tannock R, Kratochvil C, Dunn D, Velez-Borras J, Thomason C, *et al*. *A randomized, placebo-controlled study of once-daily atomoxetine in the school setting in children with ADHD*. A submission to the National Institute for Clinical Excellence. Indianapolis, IN: Lilley Research Laboratories; 2004.

95. Wernicke JF, Adler L, Spencer T, West SA, Allen AJ, Heiligenstein J, *et al*. Changes in symptoms and adverse events after discontinuation of atomoxetine in children and adults with attention deficit/hyperactivity disorder: a prospective, placebo-controlled assessment. *J Clin Psychopharmacol* 2004;**24**:30–5.

96. Werry JS, Aman MG, Diamond E. Imipramine and methylphenidate in hyperactive children. *J Child Psychol Psychiatry* 1980;**21**:27–35.

97. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, *et al*. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;**108**:883–92.

98. Zeiner P, Bryhn G, Bjercke C, Truyen K, Strand G. Response to methylphenidate in boys with attention-deficit hyperactivity disorder. *Acta Paediatr* 1999;**88**:298–303.

99. Kemner JE, Starr L, Ciccone PE, Hooper-Wood CG, Crockett S. *Treatment outcomes of OROS® methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized, prospective study*. A submission to the National Institute for Clinical Excellence. Fort Washington, PA: McNeil Consumer and Speciality Pharmaceuticals; 2004.

100. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:619–26.

101. Zeiner P. Do the beneficial effects of extended methylphenidate treatment in boys with attention-deficit hyperactivity disorder dissipate rapidly during placebo treatment? *Nord J Psychiatry* 1999;**53**:55–66.

102. Albaret JM, Soppelsa R, Marquet-Doleac J. Interest of the Matching Figure Test in the diagnostic of the impulsivity component in the attention deficit/hyperactivity disorder: comparative study. *Approche Neuropsychologique des Apprentissages chez l'Enfant* 2000;**12**:98–102.

103. Jensen PS. Fact versus fancy concerning the multimodal treatment study for attention-deficit hyperactivity disorder. *Can J Psychiatry* 1999;**44**:975–80.

104. Taylor E. Development of clinical services for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;**56**:1097–9.

105. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: the Multimodal Treatment Study of children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;**56**:1088–96.

106. Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Newcorn JH, Abikoff HB, *et al*. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:147–58.

107. Jensen P, Hinshaw S, Swanson J, Greenhill L, Conners C, Arnold L, *et al*. Findings from the NIMH multimodal treatment study of ADHD (MPA): implications and applications for primary care providers. *J Dev Behav Pediatr* 2001;**22**:60–73.

108. Vitiello B, Severe J, Greenhill L, Arnold L, Abikoff H, Bukstein O, *et al*. Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:188–96.

109. Greenhill LL, Swanson JM, Vitiello B, Davies M, Clevenger W, Wu M, *et al*. Impairment and deportment responses to different methylphenidate doses in children with ADHD: the MTA titration trial. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:180–7.

110. Rieppi R, Greenhil lLL, Ford RE, Chuang S, Wu M, Davies M, *et al*. Socioeconomic status as a moderator of ADHD treatment outcomes. *J Am Acad Child Adolesc Psychiatry* 2002;**41**:269–77.

111. Arnold LE, Elliot M, Sachs L, Bird H, Kraemer HC, Wells KC, *et al*. Effects of ethnicity on treatment attendance, stimulant response/dose, and 14-month outcome in ADHD. *J Consult Clin Psychol* 2003;**71**:713–27.

112. Galanter CA, Carlson GA, Jensen PS, Greenhill LL, Davies M, Li W, *et al*. Response to methylphenidate in children with attention deficit hyperactivity disorder and manic symptoms in the multimodal treatment study of children with attention deficit hyperactivity disorder titration trial. *J Child Adolesc Psychopharmacol* 2003;**13**:123–36.

113. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. *Pediatrics* 2004;**113**:754–61.

114. Rapport MD, Moffitt C. Attention deficit/hyperactivity disorder and methylphenidate. A review of height/weight, cardiovascular, and somatic complaint side effects. *Clin Psychol Rev* 2002;**22**:1107–31.

115. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford Medical Publications; 1997.

116. Markwardt FC. *Peabody Individual Achievement Test (PIAT)*. Circle Pines, MN: American Guidance Service; 1998.

117. Pelham WE, Bender ME, Caddell J, Booth S, Moorer SH. Methylphenidate and children with attention deficit disorder. *Arch Gen Psychiatry* 1985;**42**:948–52.

118. Conners CK, Epstein JN, March JS, Angold A, Wells KC, Klaric J, *et al*. Multimodal treatment of ADHD in the MTA: an alternative outcome analysis. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:159–67.

119. Rosser R, Cottee M, Rabin R, Selai C. Index of health related quality of life. In Hopkins A, editor. *Measures of the quality of life*. London: Royal College of Doctors; 1992.

120. Landgraf J, Abetz L, Ware J. *The Child Health Questionnaire user's manual*. Boston, MA: HealthAct; 1999.

121. Zwi M, Ramchandani P, Joughin C. Evidence and belief in ADHD. *BMJ* 2000;**321**:975–6.

122. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for the EurQol: results from a UK general population survey*. York: Centre for Health Economics, University of York; 1995.

123. Gilmore A, Milne R. Methylphenidate in children with hyperactivity: review and cost–utility analysis. *Pharmacoepidemiol Drug Saf* 2001;**10**:85–94.

124. Gilmore A, Best L, Milne R. *Methylphenidate in children with hyperactivity*. Report No. 78. Southampton: Wessex Institute for Health Research and Development; 1998.

125. Matza LS, Secnik K, Rentz AM, Mannix S, Revicki DA, Sallee FR. Development and assessment of health state utilities for attention deficit/hyperactivity disorder in children using parent proxy report. *Value Health* 2003;**6**:697–8.

126. Zupancic JAF, Miller A, Raina P, Lee SK, Klassen A, Olsen L. *A review of therapies for attention deficit/hyperactivity disorder*. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 1998.

127. Shukla VK, Otten N. *Assessment of attention deficit/hyperactivity disorder therapy: a Canadian perspective*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1999. URL: http://www.ccohta.ca/

128. Marchetti A, Magar R, Lau H, Murphy EL, Jensen PS, Conners CK, *et al*. Pharmacotherapies for attention-deficit/hyperactivity disorder: expected-cost analysis. *Clin Ther* 2001;**23**:1904–21.

129. Vanoverbeke N, Annemans L, Ingham M, Adriaenssen I. A cost analysis of the management of attention-deficit/hyperactivity disorder (ADHD) in children in the UK. *J Med Econ* 2003;**6**:79–94.

130. Barkley RA. Child behaviour rating scales and checklists. In Rutter M, Tuma AH, Lann IS, editors. *Assessment and diagnosis in child psychopathology*. New York: Guildford Press; 1988.

131. *Monthly index of medical specialities (MIMS) [August]*. London: Haymarket Medical Publications, 1997.

132. Foster N. *Comorbidity as a moderator of cost-effectiveness*. York: University of York; 2004.

133. Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, *et al*. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:168–79.

134. National Institute for Clinical Excellence (NICE). *Methylphenidate (Ritalin, Equasym) for attention deficit/hyperactivity disorder (ADHD) in childhood*. London: NICE; 2000. URL: http://www.nice.org.uk/article.asp?a=11667

135. Netten A, Curtis L. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit (PSSRU), University of Kent; 2003. URL: www.pssru.ac.uk

136. Coghill D, Spender Q, Barton J, Hollis C, Yuen C, Cleemput I, *et al*. Measuring quality of life in children with attention-deficit-hyperactivity-disorder in the United Kingdom. In *16th World Congress of the International Association of Child and Adolescent Psychiatry and Allied Professions (IACAPAP)*, 23–26 August 2004, Berlin. URL: http://www.iacapap-berlin.de/guest/?MIval=AbstractView&ABSID=4112

137. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–89.

138. Kauffman RE, Smith-Wright D, Reese CA, Simpson R, Jones F. Medication compliance in hyperactive children. *Pediatr Pharmacol* 1981;**1**:231–7.

139. Dirksen SJ, D'Imperio JM, Birdsall D, Hatch SJ. A postmarketing clinical experience study of Metadate CD. *Curr Med Res Opin* 2002;**18**:371–80.

140. Hill P, Taylor E. An auditable protocol for treating attention deficit/hyperactivity disorder. *Arch Dis Child* 2001;**84**:404–9.

141. Netten A, Curtis L. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit (PSSRU), University of Kent; 2002. URL: www.pssru.ac.uk

142. Biederman J, Heiligenstein JH, Faries DE, Galil N, Dittmann R, Emslie GJ, *et al*. Efficacy of atomoxetine versus placebo in school-age girls with attention-deficit/hyperactivity disorder. *Pediatrics* 2002;**110**:e75.

143. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997;**100**:662–6.

144. Weiss M, Tannock R, Kratochvil C, Dunn D, Velez-Boras J, Thomason C, *et al*. Placebo-controlled study of once-daily atomoxetine in the school setting. *Eur Neuropsychopharmacol* 2003;**13** (suppl 4):S456.

145. Secnik K, Cottrell S, Matza LS, Edgell E, Aristides M, Tilden D, *et al*. Assessment of health state utilities for attention-deficit/hyperactivity disorder in children using parent-based standard gamble scores. In *9th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)*, 16–19 May 2004, Arlington, VA.

146. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000; **17**:479–500.

147. Spiegelhalter DJ, Thomas A, Best NG, Gilks WR. BUGS: *Bayesian inference using Gibbs sampling, version 0.5, (version ii)*. Cambridge: MRC Biostatistics Unit; 1996.

148. Hill JC, Schoener EP. Age-dependent decline of attention deficit hyperactivity disorder. *Am J Psychiatry* 1996;**153**:1143–6.

149. Sharp WS, Walter JM, Marsh WL, Ritchie GF, Hamburger SD, Castellanos FX. ADHD in girls: clinical comparability of a research sample. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:40–7.

150. Higgins JPT, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Stat Med* 1996;**15**:2733–49.

151. Ades AE, Cliffe S. Markov Chain Monte Carlo estimation of a multi-parameter decision model: consistency of evidence and the accurate assessment of uncertainty. *Med Decis Making* 2002;**22**:359–71.

152. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;**23**:1296–310.

153. Netten A, Curtis L. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit (PSSRU), University of Kent; 2004. URL: www.pssru.ac.uk

154. Celltech Pharmaceuticals Limited. *Appraisal of drugs used in attention deficit hyperactivity disorder*. A submission to the National Institute for Clinical Excellence. Slough: Celltech Pharmaceuticals; 2004.

155. Janssen-Cilag. *For health technology appraisal: methylphenidate, atomoxetine and dexamphetamine for attention-deficit/hyperactivity disorder in children and adolescents, including review of existing guidance number 13*. A submission to the National Institute for Clinical Excellence. High Wycombe: Janssen-Cilag Limited; 2004.

156. Eli Lilly. *Atomoxetine for the treatment of ADHD*. A submission to the National Institute for Clinical Excellence. Basingstoke: Eli Lilly and Company Limited; 2004.

157. National Institute for Health and Clinical Excellence (NICE). *National Institute for Clinical Excellence methodological guidance: economic evaluations*. London: NICE; 2004.

158. Biederman J, Mick E, Faraone S. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry* 2000;**157**:816–18.

159. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**:1191–4.

160. Aggarwal A, Lillystone D. A follow-up pilot study of objective measures in children with attention deficit hyperactivity disorder. *J Paediatr Child Health* 2000;**36**:134–8.

161. Akhondzadeh S, Tavakolian R, Davari-Ashtiani R, Arabgol F, Amini H. Selegiline in the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;**27**:841–5.

162. Akhondzadeh S, Mohammadi MR, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial [ISRCTN64132371]. *BMC Psychiatry* 2004;**4**:9.

163. Allen AJ, Spencer TJ, Heiligenstein JH, Faries DE, Kelsey DK, Laws HF, *et al*. Safety and efficacy of tomoxetine for ADHD in two double-blind, placebo-controlled trials. *Biol Psychiatry* 2001;**49**:325–35.

164. Allen AJ, Michelson D, Harder Donald R, Trapp NJ, Kelsey DK. Efficacy of atomoxetine in children and adolescents with ADHD. In *155th Annual Meeting of the American Psychiatric Association*, 18–23 May 2002, Philadelphia, PA.

165. Aman MG, Langworthy KS. Pharmacotherapy for hyperactivity in children with autism and other pervasive developmental disorders. *J Autism Dev Disord* 2000;**30**:451–9.

166. Aman MG, Buican B, Arnold LE. Methylphenidate treatment in children with borderline IQ and mental retardation: analysis of three aggregated studies. *J Child Adolesc Psychopharmacol* 2003;**13**:29–40.

167. Baren M, Swanson JM, Wigal SB. Lack of effect of different breakfast conditions on the pharmacokinetics and efficacy of OROS® methylphenidate HCl extended-release tablets in children with ADHD. *Pediatr Res* 2000;**47**:129.

168. Bedard AC, Ickowicz A, Tannock R. Methylphenidate improves Stroop naming speed, but not response interference, in children with attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2002;**12**:301–9.

169. Bedard AC, Martinussen R, Ickowicz A, Tannock R. Methylphenidate improves visual-spatial memory in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2004;**43**:260–8.

170. Berman T. *Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder*. Thesis. Montreal: McGill University; 1998.

171. Berman T, Douglas VI, Barr RG. Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder. *J Abnorm Psychol* 1999;**108**:90–105.

172. Biederman J. Effectiveness and safety of the once-daily OROS formulation of methylphenidate in adolescents with attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol* 2003;**13**:S448.

173. Biederman J. Evaluation of once-daily OROS methylphenidate in children with attention-deficit/hyperactivity disorder: effects on sleep, appetite, and tics. *Eur Neuropsychopharmacol* 2003;**13** (suppl 4):S447–8.

174. Biederman J, Quinn D, Weiss M, Markabi S, Weidenman M, Edson K, *et al*. Efficacy and safety of Ritalin LA, a new, once daily, extended-release dosage form of methylphenidate, in children with attention deficit hyperactivity disorder. *Paediatr Drugs* 2003;**5**:833–41.

175. Caballero J, Nahata MC. Atomoxetine hydrochloride for the treatment of attention-deficit/hyperactivity disorder. *Clin Ther* 2003;**25**:3065–83.

176. Chen J, Chen YY, Wang XM. Clinical study on treatment of children attention deficit hyperactivity disorder by jiangqian granule. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2002;**22**:258–60.

177. Chronis AM, Pelham WEJR, Gnagy EM, Roberts JE, Aronoff HR. The impact of late-afternoon stimulant dosing for children with ADHD on parent and parent–child domains. *J Clin Child Adolesc Psychol* 2003;**32**:118–26.

178. Connor DF. Preschool attention deficit hyperactivity disorder: a review of prevalence, diagnosis, neurobiology, and stimulant treatment. *J Dev Behav Pediatr* 2002;**23** (Suppl 1):S1–9.

179. Connor DF, Barkley RA, Davis HT. A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. *Clin Pediatr* 2000;**39**:15–25.

180. Cox DJ, Merkel RL, Penberthy JK, Kovatchev B, Hankin CS. Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2004;**43**:269–75.

181. Davidovitch M, Manning-Courtney P, Hartmann LA, Watson J, Lutkenhoff M, Oppenheimer S. The prevalence of attentional problems and the effect of methylphenidate in children with myelomenigocele. *Pediatr Rehabil* 1999;**3**:29–35.

182. Denney CB, Rapport MD. Predicting methylphenidate response in children with ADHD: theoretical, empirical, and conceptual models. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:393–401.

183. Ding GA, Yu GH, Chen SF. Assessment on effect of treatment for childhood hyperkinetic syndrome by combined therapy of yizhi mixture and ritalin. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2002;**22**:255–7.

184. Donnelly M, Rapoport JL, Potter WZ, Oliver J, Keysor CS, Murphy DL. Fenfluramine and dextroamphetamine treatment of childhood hyperactivity: clinical and biochemical findings. *Arch Gen Psychiatry* 1989;**46**:205–12.

185. Duggan CM, Mitchell G, Nikles CJ, Glasziou PP, Del Mar CB, Clavarino A. Managing ADHD in general practice. N of 1 trials can help! *Aust Fam Physician* 2000;**29**:1205–9.

186. Ebell M. How safe and effective is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? *Evid Based Pract* 2002;**5**:9.

187. Eiland LS, Guest AL. Atomoxetine treatment of attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2004;**38**:86–90.

188. Firestone P, Musten LM, Pisterman S, Mercer J, Bennett S. Short-term side effects of stimulant medication are increased in preschool children with attention-deficit/hyperactivity disorder: a double-blind placebo-controlled study. *J Child Adolesc Psychopharmacol* 1998;**8**:13–25.

189. Francis S, Fine J, Tannock R. Methylphenidate selectively improves story retelling in children with attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2001;**11**:217–28.

190. Gadow KD, Nolan E, Sverd J, Sprafkin J, Paolicelli L. Methylphenidate in aggressive-hyperactive boys: I. Effects on peer aggression in public school settings. *J Am Acad Child Adolesc Psychiatry* 1990;**29**:710–18.

191. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Grossman S. Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Arch Gen Psychiatry* 1999;**56**:330–6.

192. Gadow KD, Nolan EE, Sverd J, Sprafkin J, Schwartz J. Anxiety and depression symptoms and response to methylphenidate in children with attention-deficit hyperactivity disorder and tic disorder. *J Clin Psychopharmacol* 2002;**22**:267–74.

193. Goldberg J. Clonidine and methylphenidate were effective for attention deficit hyperactivity disorder in children with comorbid tics. *Evid Based Ment Health* 2002;**5**:122.

194. Goldberg J. Clonidine and methylphenidate were effective for attention deficit hyperactivity disorder in children with comorbid tics. *ACP J Club* 2002;**137**:70.

195. Grcevich S. Review: Adderall may have a small advantage over methylphenidate in attention deficit hyperactivity disorder. *Evid Based Ment Health* 2003;**6**:43.

196. Greenhill LL. Efficacy and safety of once-daily methylphenidate HCl, standard methylphenidate and placebo in children with ADHD. In *153rd Annual Meeting of the American Psychiatric Association*, 13–18 May 2002, Chicago, IL.

197. Greenhill LL. Evaluation of the efficacy and safety of Concerta (methylphenidate HCl) extended-release tablets, ritalin, and placebo in children with ADHD. *Neurology* 2000;**54** (suppl 7):A420–1.

198. Greenhill LL, Halperin JM, Abikof H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:503–12.

199. Greenhill LL, Pliszka S, Dulcan MK, Bernet W, Arnold V, Beitchman J, *et al*. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2002;**41** (2 Suppl):26S–49S.

200. Gross-Tsur V, Shalev RS, Badihi N, Manor O. Efficacy of methylphenidate in patients with cerebral palsy and attention-deficit hyperactivity disorder (ADHD). *J Child Neurol* 2002;**17**:863–6.

201. Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J Autism Dev Disord* 2000;**30**:245–55.

202. Heiligenstein JH, Biederman J, Christopher J, Galil N, West Scott A, Emslie Graham J. Efficacy of tomoxetine versus placebo in school-age girls with ADHD. In *155th Annual Meeting of the American Psychiatric Association*, 18–23 May 2002; Philadelphia, PA.

203. Heiligenstein JH, Biederman J, Kratochvil CJ, Galil N, West SA, Emslie GJ. Efficacy of tomoxetine versus placebo in school-age girls with ADHD. In *Annual Meeting of the American Psychiatric Association* 5–10 May 2001, New Orleans, LA.

204. Heiligenstein JH, Dunn DW, Busner J, Stein M, McDougle CJ. Efficacy of tomoxetine versus placebo in school-age children with ADHD who failed psychostimulant treatment. In *Annual Meeting of the American Psychiatric Association* 5–10 May 2001, New Orleans, LA.

205. Heiligenstein JH, Wagner KD, Casat CD, Busner J, Newcorn JH, Saylor KE, *et al*. Efficacy of tomoxetine versus placebo in school-age children with ADHD: inattentive subtype. In *Annual Meeting of the American Psychiatric Association* 5–10 May 2001, New Orleans, LA.

206. Hoffman M, Pelham WE, Burrows-MacLean L. Dose-ranging studies demonstrating efficacy of once-daily transdermal methylphenidate, time-course of action, and effect in combination with behavioral modification in pediatric patients with ADHD. *Pediatr Res* 2003;**53**:556A.

207. Jadad AR, Boyle M, Cunningham C. Pharmacological interventions are more effective than non-pharmacological for attention deficit hyperactivity disorder. *Evid Based Med* 2000;**5**:179.

208. Kent MA, Camfield CS, Camfield PR. Double-blind methylphenidate trials – practical, useful, and highly endorsed by families. *Arch Pediatr Adolesc Med* 1999;**153**:1292–6.

209. Klein C, Fischer B, Fischer B, Hartnegg K. Effects of methylphenidate on saccadic responses in patients with ADHD. *Exp Brain Res* 2002;**145**:121–5.

210. Kollins SH, MacDonald EK, Rush CR. Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. *Pharmacol Biochem Behav* 2001;**68**:611–27.

211. Konrad K, Gunther T, Hanisch C, Herpertz-Dahlmann B. Differential effects of methylphenidate on attentional functions in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2004;**43**:191–8.

212. Kurlan R, Goldberg J. Clonidine and methylphenidate were effective for attention deficit hyperactivity disorder in children with comorbid tics. *Evid Based Med* 2002;**7**:157.

213. Lewis D, Linder S, Kurlan R, Winner P, Dunn D, Sallee FR, *et al*. Atomoxetine for the treatment of attention deficit hyperactivity disorder and comorbid tics in children. *Ann Neurol* 2003;**54** (Suppl 7):S106.

214. Li X, Chen Z. Clinical comparative observation on duodongning and Ritalin in treating child hyperkinetic syndrome. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1999;**19**:410–11.

215. Lieberman SG, Christophersen ER. The effect of an afternoon dose of methylphenidate on the accuracy and on-tack behavior of the homework completed by children with attention deficit hyperactivity disorder. *Pediatr Res* 2000;**47**:29A.

216. Loo SK, Specter E, Smolen A, Hopfer C, Teale PD, Reite ML. Functional effects of the DAT1 polymorphism on EEG measures in ADHD. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:986–93.

217. Lopez F, Silva R, Pestreich L, Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. *Paediatr Drugs* 2003;**5**:545–55.

218. Malone MA, Rosenfield JD, Roberts SW. Methylphenidate (Ritalin) effects on the grapho-motor artwork of children with attention deficit hyperactivity disorder. *Canadian Art Therapy Association Journal* 2002;**15**:7–13.

219. Mannuzza S, Klein RG, Moulton JL III. Does stimulant treatment place children at risk for adult substance abuse? A controlled, prospective follow-up study. *J Child Adolesc Psychopharmacol* 2003;**13**:273–82.

220. Manos MJ, Short EJ, Findling RL. Dose response curves across ADHD subtypes: differential effects between Adderall and methylphenidate. *Pediatr Res* 2000;**47**:172.

221. McBurnett K. Treatment of adolescent ADHD with OROS® methylphenidate. *Pediatr Res* 2003;**53**:3143.

222. Michelson D, Faries D, Wernicke J, Spencer T. Atomoxetine in the treatment of children with ADHD: a randomized, placebo-controlled, dose-response study. *Eur Neuropsychopharmacol* 2001;**11**:S319.

223. Michelson D, Faries DE, Wernicke JF, Spencer T. Atomoxetine in the treatment of children with ADHD: a randomized, placebo-controlled dose-response study. *Eur Neuropsychopharmacol* 2001;**11**:S319–20.

224. Mohammadi MR, Kashani L, Akhondzadeh S, Izadian ES, Ohadinia S. Efficacy of theophylline compared to methylphenidate for the treatment of attention-deficit hyperactivity disorder in children and adolescents: a pilot double-blind randomized trial. *J Clin Pharm Ther* 2004;**29**:139–44.

225. Montiel Nava C, Pena JA, Espina Marines G, Ferrer-Hernandez ME, Lopez-Rubio A, Puertas-Sanchez S, *et al*. A pilot study of methylphenidate and parent training in the treatment of children with attention-deficit hyperactivity disorder. *Rev Neurol* 2002;**35**:201–5.

226. Newcorn JH. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled dose–response study. *Curr Psychiatry Rep* 2003;**5**:85.

227. Nolan EE, Gadow KD, Sprafkin J. Stimulant medication withdrawal during long-term therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Pediatrics* 1999;**103**:730–7.

228. Overtoom CC, Verbaten MN, Kemner C, Kenemans JL, van Engeland H, Buitelaar JK, *et al*. Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with attention deficit hyperactivity disorder. *Behav Brain Res* 2003;**145**:7–15.

229. Palumbo DR, Starr HL. Impact of ADHD treatment with a once-daily OROS® formulation of methylphenidate on tics. *Pediatr Res* 2003; **53**:555A–6A.

230. Pearson DA, Santos CW, Roache JD, Casat CD, Loveland KA, Lachar D, *et al*. Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:209–16.

231. Pearson DA, Lane DM, Santos CW, Casat CD, Jerger SW, Loveland KA, *et al*. Effects of methylphenidate treatment in children with mental retardation and ADHD: individual variation in medication response. *J Am Acad Child Adolesc Psychiatry* 2004;**43**:686–98.

232. Pearson DA, Santos CW, Casat CD, Lane DM, Jerger SW, Roache JD, *et al*. Treatment effects of methylphenidate on cognitive functioning in children with mental retardation and ADHD. *J Am Acad Child Adolesc Psychiatry* 2004;**43**:677–85.

233. Pelham WE, Hoza B, Pillow DR, Gnagy EM, Kipp HL, Greiner AR, *et al*. Effects of methylphenidate and expectancy on children with ADHD: behavior, academic performance, and attributions in a summer treatment program and regular classroom settings. *J Consult Clin Psychol* 2002;**70**:320–35.

234. Rapport MD, Randall R, Moffitt C. Attention-deficit/hyperactivity disorder and methylphenidate: a dose–response analysis and parent-child comparison of somatic complaints. *J Attention Disord* 2002;**6**:15–24.

235. Rhodes SM, Coghill DR, Matthews K. Neuropsychological profile and response to methylphenidate in girls with hyperkinetic disorder (ADHD). *J Psychopharmacol* 2003;**17** (3 Suppl):A73.

236. Riyad CE, Skowronsk iGA, Turkall RM, Abdel-Rahman MS. A study of safety factors for risk assessment of drugs used for treatment of attention deficiency hyperactivity disorder in sensitive populations. *Hum Ecol Risk Assess* 2002;**8**:823–40.

237. Rubia K, Noorloos J, Smith A, Gunning B, Sergeant J. Motor timing deficits in community and clinical boys with hyperactive behavior: the effect of methylphenidate on motor timing. *J Abnorm Child Psychol* 2003;**31**:301–13.

238. Schachter HM, Pham B, King J, Langford S, Moher D. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ* 2001;**165**:1475–88.

239. Scheres A, Oosterlaan J, Swanson J, Morein-Zamir S, Meiran N, Schut H, *et al*. The effect of methylphenidate on three forms of response inhibition in boys with AD/HD. *J Abnorm Child Psychol* 2003;**31**:105–20.

240. Sharp WS, Walter JM, Marsh WL, Ritchie GF, Hamburger SD, Castellanos FX. ADHD in girls: clinical comparability of a research sample. In Hertzig ME, Farber EA, editors. *Annual progress in child psychiatry and child development 2000–2001*. New York: Brunner Routledge; 2003. pp. 263–77.

241. Shaughnessy A. Does Adderall produce similar results as methylphenidate in children with attention deficit-hyperactivity disorder? *Evid Based Pract* 1999;2:7.

242. Smith BH, Waschbusch DA, Willoughby MT, Evans S. The efficacy, safety, and practicality of treatments for adolescents with attention-deficit/hyperactivity disorder (ADHD). *Clin Child Fam Psychol Rev* 2000;**3**:243–67.

243. Smith R, Larsen D, Derby KM, McLaughlin TF, Weber KP, Brown K, *et al*. A comparison of teacher checklists used over 15 days and a one-day antecedent analysis to conduct a medication trial. *Psychol Schools* 2004;**41**:235–40.

244. Spencer TJ. Atomoxetine treatment in children with attention-deficit/hyperactivity disorder and comorbid tic disorders. *Biol Psychiatry* 2004;**55** (1S-242S):185.

245. Sunohara GA, Malone MA, Rovet J, Humphries T, Roberts W, Taylor MJ. Effect of methylphenidate on attention in children with attention deficit hyperactivity disorder (ADHD): ERP evidence. *Neuropsychopharmacology* 1999;**21**:218–28.

246. Swanson JM, Wigal SB, Lemer MA. Comparison of the efficacy and safety of OROS methylphenidate HCl with methylphenidate tid and placebo in children with ADHD. *Pediatr Res* 2000;**47**:34A.

247. Swanson JM. Evaluation of different methylphenidate (MPH) delivery patterns for the treatment of children with ADHD. *Neurology* 2000;**54** (Suppl 7):A420.

248. Swanson J, Wigal S, Greenhill L, Browne R, Waslick B, Lerner M, *et al*. Objective and subjective measures of the pharmacodynamic effects of Adderall® in the treatment of children with ADHD in a controlled laboratory classroom setting. *Psychopharmacol Bull* 1998;**34**:55–60.

249. Swanson JM, Wigal S, Greenhill LL, Browne R, Waslik B, Lerner M, *et al*. Analog classroom assessment of Adderall® in children with ADHD. *J Am Acad Child Adolesc Psychiatry* 1998; **37**:519–26.

250. Swanson JM, Gupta S, Williams L, Agler D, Lerner M, Wigal S. Efficacy of a new pattern of delivery of methylphenidate for the treatment of ADHD: effects on activity level in the classroom and on the playground. *J Am Acad Child Adolesc Psychiatry* 2002;**41**:1306–14.

251. Swanson J, Gupta S, Guinta D, Flynn D, Agler D, Lerner M, *et al*. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999;**66**:295–305.

252. Swanson J, Sadeh A, Lerner MA, Wigal SB. Comparison of the impact of OROS methylphenidate HCI with methylphenidate tid and placebo on the sleep of children with ADHD. *J Dev Behav Pediatr* 2000;**21**:387–8.

253. Swanson J, Wigal S, Lerner M. Treatment with a controlled-release formulation of methylphenidate for attention-deficit/hyperactivity disorder: onset and duration of effect. *Eur Neuropsychopharmacol* 2002;**12** (Suppl 3):S414.

254. Szobot CM, Ketzer C, Cunha RD, Parente MA, Langleben DD, Acton PD, *et al*. The acute effect of methylphenidate on cerebral blood flow in boys with attention-deficit/hyperactivity disorder. *Eur J Nucl Med Mol Imaging* 2003;**30**:423–6.

255. Tenreiro K. Methylphenidate–placebo: a trial for attention deficit disorders. *International Journal of Pharmaceutical Computing* 2001;**5**:21–2.

256. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial.comment. *Neurology* 2002;**58**:527–36.

257. Tillery KL, Katz J, Keller WD. Effects of methylphenidate (Ritalan) on auditory performance in children with attention and auditory processing disorders. *J Speech Lang Hear Res* 2000;**43**:893–901.

258. van der Meere J, Gunning B, Stemerdink N. The effect of methylphenidate and clonidine on response inhibition and state regulation in children with ADHD. *J Child Psychol Psychiatry* 1999;**40**:291–8.

259. Wernicke JF, Fouche DS, Spencer T, Dunn D, Faries DE, Kelsey DK, *et al*. Safety of atomoxetine in pediatric patients treated for ADHD. Eur *Neuropsychopharmacol* 2001;**11** (Suppl 3):S319.

260. Wernicke JF, Dunn D, Faries DE, Heiligenstein JH, Kelsey DK, Kendrick KL, *et al*. Safety of atomoxetine in placebo-controlled pediatric attention-deficit hyperactivity disorder trials. *Ann Neurol* 2001;**50** (Suppl 3):S123–4.

261. Wernicke JF, Allen AJ, Faries D, Heiligenstein JH, Kelsey D, Kendrick K, *et al*. Safety of tomoxetine in clinical trials. *Biol Psychiatry* 2001;**49**:159S.

262. Whalen CK, Henker B, Buhrmester D, Hinshaw SP, Huber A, Laski K. Does stimulant medication improve the peer status of hyperactive children? *J Consult Clin Psychol* 1989;**57**:545–9.

263. Wigal SB. OROS® formulation of methylphenidate in treatment for ADHD: duration of effect. *Pediatr Res* 2002;**51**:120.

264. Wigal SB, Swanson JM, Greenhill L, Waslick B, Cantwell D, Clevenger W, *et al*. Evaluation of individual subjects in the analog classroom setting: II. Effects of dose of amphetamine (Adderall®). *Psychopharmacol Bull* 1998;**34**:833–8.

265. Wigal SB, Sanchez DY, DeCory HH, D'Imperio JM, Swanson JM. Selection of the optimal dose ratio for a controlled-delivery formulation of methylphenidate. *J Appl Res* 2003;**3**:46–63.

266. Wigal S, Lerner M, Swanson J. Once-daily methylphenidate formulation: impact on academic productivity and activity levels of children with attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol* 2002;**12** (Suppl 3):S416.

267. Wigal T, Swanson JM, Regino R, Lerner MA, Soliman I, Steinhoff K, *et al*. Stimulant medications for the treatment of ADHD: efficacy and limitations. *Ment Retard Dev Disab Res Rev* 1999;**5**:215–24.

268. Wilens TE. Long-term safety and effectiveness of Concerta (methylphenidate HCI) in children with ADHD. *Neurology* 2000;**54** (Suppl 7):A420.

269. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics* 2003;**111**:179–85.

270. Wilens TE, Biederman J, Lerner M. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder. Results from a one-year follow-up study. *J Clin Psychopharmacol* 2004;**24**:36–41.

271. Wolraich ML. Evaluation of efficacy and safety of OROS® methylphenidate HCl (MPH) extended-release tablets, methylphenidate tid, and placebo in children with ADHD. *Pediatr Res* 2000;**47**:207.

272. Amery B, Minichiello MD, Brown GI. Aggression in hyperactive boys: response to D-amphetamine. *J Am Acad Child Adolesc Psychiatry* 1984;**23**:291–4.

273. Barrickmann LL, Perry PJ, Allen AJ, Kuperman S, Arndt SV, Herrmann KJ, *et al*. Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1995;**34**:649–57.

274. Castellanos FX, Giedd JN, Elia J, Marsh WL, Ritchie GF, Hamburger SD, *et al*. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:589–96.

275. Donnelly C, Faries D, Swensen A, Ruff D, Michelson D, Matza I, *et al*. The effect of atomoxetine on the social and family functioning of children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Eur Neuropsychopharmacol* 2002;**12** (Suppl 3):S437.

276. Gadow KD, Nolan E, Sverd J. Methylphenidate in hyperactive boys with comorbid tic disorder: II. Short-term behavioural effects in school settings. *J Am Acad Child Adolesc Psychiatry* 1992;**31**:462–71.

277. Gadow KD, Nolan E, Sprafkin J, Sverd J. School observations of children with attention-deficit hyperactivity disorder and comorbid tic disorder: effects of methylphenidate treatment. *J Dev Behav Pediatr* 1995;**16**:167–76.

278. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Ezor SN. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Arch Gen Psychiatry* 1995;**52**:444–55.

279. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Ezor SN. Erratum: Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Arch Gen Psychiatry* 1995;**52**:836.

280. Garfinkel BD, Webster CD, Sloman L. Responses to methylphenidate and varied doses of caffeine in children with attention deficit disorder. *Can J Psychiatry* 1981;**26**:395–401.

281. Gittelman-Klein R, Landa B, Mattes JA, Klein DF. Methylphenidate and growth in hyperactive children. *Arch Gen Psychiatry* 1988;**45**:1127–30.

282. Handen BL, Feldman H, Gosling A, Breaux AM, McAuliffe S. Adverse side effects of methylphenidate among mentally retarded children with ADHD. *J Am Acad Child Adolesc Psychiatry* 1991;**30**:241–5.

283. Hinshaw SP, Henker B, Whalen CK. Cognitive-behavioural and pharmacologic interventions for

hyperactive boys: comparative and combined effects. *J Consult Clin Psychol* 1984;**52**:739–49.

284. Hinshaw SP, Buhrmester D, Heller T. Anger control in response to verbal provocation: effects of stimulant medication for boys with ADHD. *J Abnorm Child Psychol* 1989;**17**:393–407.

285. Hinshaw SP, Henker B, Whalen CK, Erhardt D, Dunnington REJ. Aggressive, prosocial, and nonsocial behaviour in hyperactive boys: dose effects of methylphenidate in naturalistic settings. *J Consult Clin Psychol* 1989;**57**:636–43.

286. Klein RG, Abikoff H, Klass E, Ganeles D, Seese LM, Pollack S. Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Arch Gen Psychiatry* 1997;**54**:1073–80.

287. Long N, Rickert VI, Ashcraft EW. Bibliotherapy as an adjunct to stimulant medication in the treatment of attention-deficit hyperactivity disorder. *J Pediatr Health Care* 1993;**7**:82–8.

288. Lufi D, Parish-Plass J, Gai E. The effect of methylphenidate on the cognitive and personality functioning of ADHD children. *Isr J Psychiatry Relat Sci* 1997;**34**:200–9.

289. Matochik JA, Liebenauer LL, King C, Szymanski HV, Cohen RM, Zametkin AJ. Cerebral glucose metabolism in adults with attention deficit hyperactivity disorder after chronic stimulant treatment. *Am J Psychiatry* 1994;**151**:658–64.

290. McBride MC. An individual double-blind crossover trial for assessing methylphenidate response in children with attention deficit disorder. *J Pediatr* 1988;**113**:137–45.

291. Pelham WE, Hoza B, Kipp HL, Gnagy EM, Trane ST. Effects of methylphenidate and expectancy of ADHD children's performance, self-evaluations, persistence, and attributions on a cognitive task. *Exp Clin Psychopharmacol* 1997;**5**:3–13.

292. Quinn PO, Rapoport JL. One-year follow-up of hyperactive boys treated with imipramine or methylphenidate. *Am J Psychiatry* 1975;**132**:241–5.

293. Rapport MD, Carlson GA, Kelly KL, Pataki C. Methylphenidate and desipramine in hospitalized children: I. Separate and combined effects on cognitive function. *J Am Acad Child Adolesc Psychiatry* 1993;**32**:333–42.

294. Solanto MV, Wender EH, Bartell SS. Effects of methylphenidate and behavioral contingencies on sustained attention in attention-deficit hyperactivity disorder: a test of the reward dysfunction hypothesis. *J Child Adolesc Psychoparmacol* 1997;**7**:123–36.

295. Spencer T, Wilens T, Biedermanm J, Faraone SV, Ablon JS, Lapey K. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1995;**52**:434–43.

296. Wender PH, Reimherr FW, Wood D, Ward M. A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. *Am J Psychiatry* 1985;**142**:547–52.

297. Winsberg BG, Press M, Bialer I, Kupietz S. Dextroamphetamine and methylphenidate in the treatment of hyperactive-aggressive children. *Pediatrics* 1974;**53**:236–41.

298. Zametkin A, Rapoport JL, Murphy DL, Linnoila M, Ismond D. Treatment of hyperactive children with monoamine oxidase inhibitors: I, clinical efficacy. *Arch Gen Psychiatry* 1985;**42**:962–6.

299. Arnold LE, Pinkham SM, Votolato N. Does zinc moderate essential fatty acid and amphetamine treatment of attention-deficit/hyperactivity disorder? *J Child Adolesc Psychopharmacol* 2000;**10**:111–17.

300. Efron D, Jarman FC, Barker MJ. Methylphenidate vs dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind cross-over trial. *J Paediatr Child Health* 1997;**33**:A21.

301. Efron D, Jarman FC, Barker MJ. Child and parent perceptions of stimulant medication treatment in attention deficit hyperactivity disorder. *J Paediatr Child Health* 1998;**34**:288–92.

302. Castellanos FX, Elia J, Kruesi MJ, Marsh WL, Gulotta CS, Potter WZ, *et al*. Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 1996;**14**:125–37.

303. Handen BL, Feldman HM, Lurier A, Murray PJH. Efficacy of methylphenidate among preschool children with developmental disabilities and ADHD. In Hertzig ME, Farber E, editors. *Annual progress in child psychiatry and child development: 2000–2001*. New York: Brunner Routledge; 2003. pp. 247–62.

304. Klorman R, Coons HW, Borgstedt AD. Effects of methylphenidate on adolescents with a childhood history of attention deficit disorder: I. Clinical findings (Erratum). *J Am Acad Child Adolesc Psychiatry* 1987;**26**:820.

305. Dittmann R, Fouche DS, Kratochvil C, Heiligenstein J, Spencer T, Biederman J. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. *Eur Neuropsychopharmacol* 2001;**11** (Suppl 3):S318.

306. Findling RL, Short EJ, Manos MJ. Short-term cardiovascular effects of methylphenidate and Adderall. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:525–9.

307. Findling RL, Short EJ, Manos MJ. Developmental aspects of psychostimulant treatment in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:1441–7.

308. Faraone SV, Pliszka SR, Olvera RL, Biederman J. Adderall and methylphenidate in ADHD. In *2001 Annual Meeting of the American Psychiatric Association*, 5–10 May 2001, New Orleans, LA.

309. Faraone SV, Short EJ, Biederman J, Findling RL, Roe C, Manos MJ. Efficacy of Adderall and methylphenidate in attention deficit hyperactivity disorder: a drug–placebo and drug–drug response curve analysis of a naturalistic study. *Int J Neuropsychopharmacol* 2002;**5**:121–9.

310. Newcorn J, Spencer TJ, Biedermann J, Milton D, Michelson D. *Atomoxetine treatment in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder*. Indianapolis, IL: Eli Lilly and Company; 2004.

311. Matza LS, Rentz AM, Secnik K, Swensen AR, Revicki DA, Michelson D, *et al*. The link between health-related quality of life and clinical symptoms among children with attention-deficit hyperactivity disorder. *J Dev Behav Pediatr* 2004;**25**:166–74.

312. Dunn D, Michelson D, Allen AJ, Kelsey D, Wernicke JF. Once-daily atomoxetine treatment for children and adolescents with attention-deficit/hyperactivity disorder. *Ann Neurol* 2002;**52** (Suppl 3):S116.

313. Bukstein OG. Once-daily atomoxetine may reduce attention deficit hyperactivity disorder symptoms in children and adolescents. *Evid Based Ment Health* 2003;**6**:42.

314. Michelson D. Once-daily administration of atomoxetine: a new treatment for ADHD. In *155th Annual Meeting of the American Psychiatric Association*, 18–23 May 2002, Philadelphia, PA.

315. Michelson D, Buitelaar J, Danckaerts M, Gillberg C, Spencer TJ, Zuddas A, *et al*. Atomoxetine in the long-term prevention of relapse in ADHD. *Eur Neuropsychopharmacol* 2003;**13** (Suppl 4):S455–6.

316. Pelham WE, Hoffman MT, Lock T. Evaluation of once-a-day OROS methylphenidate HCI (MPH) extended-release tablets versus MPH tid in children with ADHD in natural school settings. *Pediatr Re*s 2000;**47**:31A.

317. Pelham WE, Hoffman MT, Lock T. Evaluation of once-a-day OROS® methylphenidate HCl (MPH) extended-release tablets vs MPH tid in children with ADHD in a laboratory setting. *Pediatr Res* 2000;**47**:180.

318. Connor D. Once a day Concerta methylphenidate was equivalent to 3 times daily methylphenidate in children with ADHD. *Evid Based Ment Health* 2002;**5**:20.

319. Pliszka SR, Wynne SK, Olvera RL, Browne RG. Comparing Adderall methylphenidate in ADHD. In *152nd Annual Meeting of the American Psychiatric Association*, 15–20 May 1999, Washington, DC.

320. Faraone SV, Pliszka SR, Olvera RL, Skolnik R, Biederman J. Efficacy of Adderall and methylphenidate in attention deficit hyperactivity disorder: a reanalysis using drug–placebo and drug–drug response curve methodology. *J Child Adolesc Psychopharmacol* 2001;**11**:171–80.

321. Law SF, Schachar RJ. Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder? *J Am Acad Child Adolesc Psychiatry* 1999;**38**: 944–51.

322. Evans SW, Pelham WE, Smith BH, Bukstein O, Gnagy EM, Greiner AR, *et al*. Dose-response effects of methylphenidate on ecologically valid measures of academic performance and classroom behavior in adolescents with ADHD. *Exp Clin Psychopharmacol* 2001;**9**:163–75.

323. Smith BH, Pelham WE, Jr., Gnagy E, Molina B, Evans S. The reliability, validity, and unique contributions of self-report by adolescents receiving treatment for attention-deficit/hyperactivity disorder. *J Consult Clin Psychol* 2000;**68**:489–99.

324. Stein M, Seymour K, Black D, Sarampote C, Robb A, Conlon C, *et al*. Effects and side effects of Concerta methylphenidate (MPH) in children with ADHD and comorbid internalizing symptoms. *Pediatr Res* 2003;**53**:555A.

325. Wolraich ML. Efficacy and safety of OROS® methylphenidate HCl (MPH) extended-release tablets (CONCERTA™), conventional MPH, and placebo in children with ADHD. *Int J Neuropsychopharmacol* 2000;**3** (Suppl 1):S329.

326. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, *et al*. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;**108**:883–92.

This version of HTA monograph volume 10, number 23 does not include the 220 pages of appendices. This is to save download time from the HTA website.

The printed version of this monograph also excludes the appendices.

View/download the appendices (800 kbytes).

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Lay Member, Bolton

Professor Max Bachmann Professor of Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist and Clinical Director of Pathology, Department of Clinical Microbiology, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, University Department of Radiology, University of Cambridge Clinical School

Dr David Elliman, Consultant Paediatrician/ Hon. Senior Lecturer, Population Health Unit, Great Ormond St. Hospital, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Professor William Rosenberg, Professor of Hepatology, Liver Research Group, University of Southampton

Dr Susan Schonfield, Consultant in Public Health, Specialised Services Commissioning North West London, Hillingdon Primary Care Trust

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr Margaret Somerville, PMS Public Health Lead, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Associate Dean for Education, Head of Department of Obstetrics and Gynaecology, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Chair Division A, The John Radcliffe Hospital, Oxford Radcliffe Hospitals NHS Trust

Professor Tony Avery, Head of Division of Primary Care, School of Community Health Services, Division of General Practice, University of Nottingham

Ms Anne Baileff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Consultant in Pharmaceutical Public Health, National Public Health Service for Wales, Cardiff

Mrs Sharon Hart, Head of DTB Publications, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, South Gloucestershire Primary Care Trust

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, The Royal Marsden Hospital, Sutton

Ms Barbara Meredith, Lay Member, Epsom

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician & Gynaecologist, Department of Obstetrics & Gynaecology, University of Cambridge

Dr Frances Rotblat, CPMP Delegate, Medicines & Healthcare Products Regulatory Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Department of Surgery, Royal Devon & Exeter Hospital

Dr Aileen Clarke,
Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, London

Dr Matthew Cooke, Reader in A&E/Department of Health Advisor in A&E, Warwick Emergency Care and Rehabilitation, University of Warwick

Dr Carl E Counsell, Clinical Senior Lecturer in Neurology, Department of Medicine and Therapeutics, University of Aberdeen

Ms Amelia Curwen, Executive Director of Policy, Services and Research, Asthma UK, London

Professor Gene Feder, Professor of Primary Care R&D, Department of General Practice and Primary Care, Barts & the London, Queen Mary's School of Medicine and Dentistry, London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of General Practice and Primary Care, South Tees Hospital NHS Trust, Middlesbrough

Ms Bec Hanley, Co-Director, TwoCan Associates, Hurstpierpoint

Ms Maryann L Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, Academic Department of Radiology, The Institute of Cancer Research, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Professor Neil McIntosh, Edward Clark Professor of Child Life & Health, Department of Child Life & Health, University of Edinburgh

Professor James Neilson, Professor of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University of Liverpool

Dr John C Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust

Karen Roberts, Nurse Consultant, Queen Elizabeth Hospital, Gateshead

Dr Vimal Sharma, Consultant Psychiatrist/Hon. Senior Lecturer, Mental Health Resource Centre, Cheshire and Wirral Partnership NHS Trust, Wallasey

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, Department of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman, Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond, Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson, Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, London

Mr John Dunning, Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick, Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field, Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher, Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs, Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Services, West Middlesex University Hospital, Isleworth

Dr Neville Goodman, Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray, Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson, Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little, Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok, Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant, Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall, General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire, Professor of Health Economics, London School of Economics

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick, Director, NHS Cancer Screening Programmes, Sheffield

Professor Tim Peters, Professor of Primary Care Health Services Research, Academic Unit of Primary Health Care, University of Bristol

Professor Chris Price, Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Eamonn Sheridan, Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein, Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown, Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

ISSN 1366-5278