Methylphenidate in children with hyperactivity: review and cost-utility analysis

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Authors' objectives
To examine the effectiveness and cost-effectiveness of methylphenidate in children with hyperkinetic disorder.

Searching
The following sources were searched: MEDLINE (from 1966 to 1997), EMBASE (from 1980 to 1997), the Social Sciences Citation Index (from 1981 to 1997), the Science Citation Index (from 1981 to 1997), the British Education Index (from 1976 to 1997), the Cochrane Controlled Trials Register and PsycLIT (from 1974 to 1997). Major journals published around the time of the review were searched for additional studies that were not yet listed on the databases. Unpublished material was sought by contacting Portsmouth Hospital's information service, the manufacturers of methylphenidate and the ADD/ADHD Family Support Group. In addition, experts were asked for details of other important studies or conference proceedings.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and crossover trials with a placebo control treatment group were eligible if they recruited more than 15 children and had clear entry criteria. Studies that included children with co-morbid anxiety were only included if they analysed results for this subgroup separately. The review also reports adverse reactions presented in two less rigorous studies that did not meet the inclusion criteria.

Specific interventions included in the review
Comparisons of methylphenidate with placebo were eligible. Methylphenidate was given in doses ranging from 5 to 90 mg/day, to 0.15 to 0.8 mg/kg twice or thrice daily. The co-interventions included: behaviour modification; parent training and support; individual and group psychotherapy; individual education therapy; reading therapy; parent and family psychotherapy; imipramine; and stimulants.

Participants included in the review
Children aged 6 to 12 years with a primary diagnosis of attention deficit hyperactivity disorder (ADHD or ADDH) according to the American Psychiatric Association's DSM criteria for pervasive ADHD/ADDH or Barkley's Research Criteria (see Other Publications of Related Interest no.1), and who were otherwise normal, were eligible. Children with conduct, oppositional defiant or learning disorders were also eligible.

Outcomes assessed in the review
Studies that assessed inattention, impulsivity and hyperactivity, academic performance, and mother-child relationships were eligible. The included studies used the following measures to assess the outcomes: school situations questionnaire; Conners parent rating scale including the Iowa and revised versions; Home situations questionnaire; observational methods; and laboratory methods including the Gordon diagnostic system, continuous performance test, and matching familiar figures test. In addition, adverse effects were assessed using Barkley's side effects rating scale and the subject treatment emergent symptoms scale. The outcomes were evaluated after one week to 6 months on methylphenidate.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Study validity was assessed using the following criteria: whether patients who entered the trial were adequately accounted for at its conclusion; the degree of blinding of the patients, health workers and study personnel; baseline
comparability of the treatment groups; adequate measurement of confounding factors; equal treatment of allocation groups other than the experimental intervention; outcome measures relevant, valid and reliable; and estimation of confidence limits. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The information tabulated in the full report of the review (see Other Publications of Related Interest no.2) included study design, sample size, characteristics of population, intervention details, outcomes measures used and results.

**Methods of synthesis**

How were the studies combined?
The studies were categorised as short-term (end points assessed after 1 to 4 weeks), medium-term (trials lasting up to 1 year) or long-term (follow-up beyond 1 year), and a narrative synthesis was undertaken.

How were differences between studies investigated?
Differences between the studies were discussed in the text of the review.

**Results of the review**

Nine placebo-controlled RCTs (691 children) were included.

The methodological flaws included: losses to follow-up; failure to analyse by intention-to-treat; inadequate means of dealing with confounding factors; unrepresentative samples; lack of comparison of side-effects between the active treatment and placebo groups; and the use of multiple significance testing.

Short-term studies (8 RCTs, 760 children).
All of the studies were good-quality double-blind crossover studies that included an assessment of inter-observer reliability where this was appropriate. In all studies, the use of methylphenidate was evaluated after 1 to 4 weeks on the drug. All 5 RCTs that assessed individual features of attention, impulsivity and hyperactivity showed significant benefit for methylphenidate compared with placebo. All 6 RCTs that assessed academic effects showed significant benefit for methylphenidate compared with placebo. One study excluded children with co-morbid conduct disorder. Both RCTs, conducted by the same researcher, which assessed the effects of the mother-child relationship showed significant benefit for methylphenidate in comparison with placebo.

Medium-term studies (3 RCTs with end points between 16 weeks and 6 months were identified, but only 1 RCT met all the inclusion criteria).
All 3 RCTs showed significant positive effects of methylphenidate, compared with placebo, on teacher ratings of behaviour and the three cardinal features of hyperkinetic disorder (p<0.01 to p<0.005). The one RCT that met the inclusion criteria assessed the outcomes at 6 months and showed a significant effect of methylphenidate on learning ability, but not memory.

Long-term studies.
No well-designed long-term studies were identified. The one identified RCT had a drop-out rate of 59% making interpretation problematical. One retrospective cohort study, one prospective cohort study and one unplanned prospective cohort study were found.

Adverse effects (6 RCTs).
Five RCTs (only 3 appear to have met the inclusion criteria) compared the incidence of side-effects in the treatment
and control groups. The 2 excluded studies reported adverse events in greater detail and found that the most common side-effects were decreased appetite, insomnia, stomachache and headache. These reactions occurred at higher rates in the methylphenidate-treated groups than in the placebo groups. The rates were 15 to 37% higher for low-dose and 10 to 40% higher for high-dose methylphenidate. These 2 RCTs reported a significant decrease in weight, but not in height, at 4 months and one year. These 2 RCTs were longer term and they reported evidence of growth suppression.

**Cost information**
Yes. A cost-utility analysis was performed from a NHS perspective, according to methodology developed by the former South and West Development Evaluation Committee (see Other Publications of Related Interest no.3). The number of quality-adjusted life-years (QALY) gained was estimated using the Index of Health Related Quality of Life to model treatment. The costs per QALY were estimated to be £7,400 to £9,200 at 1997 prices.

**Authors' conclusions**
Short-term treatment of hyperkinetic children with methylphenidate is effective and cost-effective.

**CRD commentary**
The aims were clearly stated and the inclusion criteria were rigorously defined in terms of the participants, study design, intervention and outcome. Several relevant sources of literature were searched and attempts were made to locate unpublished material, but the methods used to select the studies were not described. Validity was assessed using predefined criteria, and the methodological strengths and weaknesses of the included studies were presented in the data extraction tables. Relevant data were extracted and tabulated in the full report, but the methods used to extract the data and assess validity were not described. A narrative review was appropriate given the small number of studies, and the results were discussed in relation to the quality of the studies. This is a structured and well-presented review that only lacks a description of the methods used to conduct the review. The evidence presented supports the authors' conclusions.

**Implications of the review for practice and research**
Practice: The authors state that short-term treatment (over weeks and months) of hyperkinetic children with methylphenidate is effective and cost-effective. Recommendations apply only to the use of methylphenidate as monotherapy in the treatment of hyperkinetic disorder as defined by ICD-10 criteria. Treatment should be integrated into existing educational and psychosocial protocols. The optimum duration of treatment is unknown and children should be reviewed regularly.

Research: The authors state that research is required to provide better evidence on adolescent and adult outcomes, the efficacy and safety of follow-up in different settings, and the impact of treatment on parents and family quality of life.

**Bibliographic details**

**PubMedID**
11499858

**DOI**
10.1002/pds.564

**Other publications of related interest**
3. Best L, Stevens A, Colin-Jones D. Rapid and responsive health technology assessment: the development and evaluation process in the South and West region of

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Subject indexing assigned by NLM

MeSH
Attention Deficit Disorder with Hyperactivity /drug therapy /economics; Child; Costs and Cost Analysis; Great Britain; Humans; Methylphenidate /economics /therapeutic use; Quality-Adjusted Life Years; Randomized Controlled Trials as Topic; Sensitivity and Specificity; Sympathomimetics /economics /therapeutic use

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.