Cost-effectiveness of methylphenidate versus AMP/DEX mixed slats for the first-line treatment of ADHD

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of methylphenidate (MPH) versus amphetamine/dextroamphetamine mixed salts (AMP/DEX) as first-line agents for the treatment of attention deficit hyperactivity disorder (ADHD) was studied.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of male children aged 9 years and weighing 28 kg, with uncomplicated ADHD.

Setting
The setting was the community and primary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence was derived from studies published between 1991 and 2002. The cost data were derived from studies published between 2001 and 2002. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A decision tree model was used to estimate the costs and benefits associated with the three interventions assessed (i.e. MPH, AMP/DEX and no treatment) for the first-line treatment of ADHD. The time horizon of the analysis was one year because of the lack of long-term data. Decisions (branches of the model) occurred in monthly cycles. According to the model, treatment was initiated at month 1, and patients either responded to treatment, did not respond to treatment, or dropped out of therapy. Those who responded were assessed for side effects during the month after response, and their compliance was then assessed at month 6. Those who did not respond began treatment with another stimulant agent at month 2. Lack of response at month 2 resulted in a new (third) treatment with a stimulant. The stimulants used as second- and third-line treatment included MPH, AMP/DEX and DEX.

All treatment decisions were assumed to be finalised for each patient within 6 months. The results obtained at month 6 were extrapolated to the 12-month period, assuming that those who responded to treatment would continue to...
experience the same benefit and expect the same cyclical costs projected to one year.

**Outcomes assessed in the review**
The outcomes assessed were:

- the response rates,
- the side effect rates,
- the drop-out rates due to toxicity,
- the compliance rates, and
- the school administration rates associated with the use of MPH and AMP/DEX for the treatment of ADHD.

**Study designs and other criteria for inclusion in the review**
No study designs were reported. However, the studies used to assess efficacy rates included those that assessed response to therapy at a minimum of 1 month and a maximum of 8 weeks.

**Sources searched to identify primary studies**
HealthSTAR and MEDLINE were searched for primary studies using the keywords "attention deficit hyperactivity disorder", "methylphenidate", "amphetamine / dextroamphetamine mixed salts", "adverse events", "compliance rates", "school administration", "economic burden", "utility scores" and "quality of life".

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Approximately 9 primary studies were included in the review. One study was a weighted meta-analysis.

**Methods of combining primary studies**
The results of the primary studies were combined using a narrative method. No differential weights were placed on each of the studies. The full range of parameters was included in the sensitivity analysis.

**Investigation of differences between primary studies**
Potential differences between the primary studies were not discussed.

**Results of the review**
The immediate release response rate was 78.7% (95% confidence interval, CI: 74.7 - 82.4) for MPH and 82.7% (95% CI: 66.5 - 98.9) for AMP/DEX.

Other general stimulant response rates reported varied between 77 and 90%. The side effect rate was 61% for MPH and 86% for AMP/DEX.
The drop-out rate due to toxicity was common to both agents and was 6.9%.

The compliance rate at 6 months was 61.3% for MPH and 90.3% for AMP/DEX.

An overall stimulant compliance rate at 6 months was also reported (35%).

The school administration rate was 88% for MPH and 52% for AMP/DEX.

**Measure of benefits used in the economic analysis**

The measure of benefits used was the number of quality-adjusted life-years (QALYs) gained by adopting each intervention under assessment. The utility weights were estimated from a study that assessed the quality of life in paediatric patients by using the Index of Health-Related Quality of Life (IHRQOL) scale and converting the components of physical, mental and emotional sub-sets into a questionnaire that could be used in children (the Children's Health Questionnaire). For the base-case analysis, it was assumed that patients with untreated ADHD would have the reported utility of ADHD patients, while adequately treated patients would achieve the utility of patients documented as being free from ADHD symptoms. The treatment utilities were estimated on a monthly basis. Patients with side effects were assumed to drop down to the no treatment utility for 1 month and then to achieve the treatment utility score in the subsequent month, assuming they stayed on therapy.

**Direct costs**

The direct costs consisted of health care costs and school administration costs. The health care costs were for the drugs, outpatient visits, laboratory tests and out-of-pocket expenses. The school administration costs were associated with in-school dosing of ADHD medication (by school nurses or office assistants) and involved tasks such as medication inventory, paperwork, communications with parents or physician, state-required locked storage of medication, dispensing medication, and finding the child if they forgot to come for medication. The costs and the quantities were not analysed separately. Resource use was based on national surveys performed in school districts. The total costs were derived using modelling. The costs were adjusted to 2003 prices using the medical care component of the Consumer Price Index. Discounting was not carried out since the costs were incurred within one year.

**Statistical analysis of costs**

The costs were treated deterministically. No statistical analysis of the costs was undertaken.

**Indirect Costs**

Although it was stated that a societal perspective was adopted, indirect costs, reflecting productivity losses, were not included in the analysis.

**Currency**

US dollars ($).

**Sensitivity analysis**

One-way sensitivity analyses were used to test the robustness of the base-case results under the variability in effectiveness and cost data reported in the literature. The range of values used was based on the highest and lowest values reported for each model parameter.

**Estimated benefits used in the economic analysis**

The one-year benefits per patient for each intervention under assessment were:

for MPH, 0.838 QALYs;
for APM/DEX, 0.889 QALYs; and
for no treatment, 0.798 QALYs.

The incremental benefit of APM/DEX versus no treatment was 0.091 QALYs.

The side effects of treatment were dealt with at the estimation of QALYs.

**Cost results**
The one-year costs per patient for each intervention under assessment were $3,053 for MPH, $3,000 for APM/DEX, and $994 for no treatment.

The incremental cost of APM/DEX versus no treatment was $2,007.

Costs associated with the treatment of side effects were not considered in the analysis.

**Synthesis of costs and benefits**
The costs and benefits were combined in the form of cost-effectiveness ratios, which expressed the cost per QALY gained for each option assessed.

The estimated cost-effectiveness ratios were $3,642/QALY for MPH, $3,374/QALY for APM/DEX, and $1,245/QALY for no treatment.

In addition, an incremental analysis was performed and an incremental cost-effectiveness ratio (ICER) calculated. The ICER expressed the incremental costs required to achieve an additional unit of benefit (QALY). MPH was excluded from the incremental analysis as it was dominated by APM/DEX (i.e. MPH was both more expensive and less effective than APM/DEX). The ICER of APM/DEX versus no treatment was $21,957/QALY.

The sensitivity analysis demonstrated that dominance of APM/DEX over MPH was robust to changes in cost, but was sensitive to changes in response and compliance rates of the two agents. However, even when APM/DEX was no longer dominant, its ICER in comparison with MPH was relatively low. For example, using the lowest response rate reported for APM/DEX resulted in an ICER of APM/DEX versus MPH of $6,535/QALY.

The ICER of APM/DEX versus no treatment was very sensitive to the utility weights. Varying the treatment utility by +/- 5% of the base-case value led to the ICER changing between a 233% increase ($73,162/QALY) and a 33% decrease ($14,758/QALY).

**Authors' conclusions**
Treatment with either methylphenidate (MPH) or amphetamine/dextroamphetamine mixed salts (AMP/DEX) was quite cost-effective in comparison with no treatment. APM/DEX was more cost-effective than MPH.

**CRD COMMENTARY - Selection of comparators**
The two agents examined had been recommended as first-line treatment options for ADHD. The choice of no treatment as a comparator allowed the active value of the pharmacological agents to be assessed. You should consider whether any of the alternative options evaluated reflects widely used practice in your own setting.

**Validity of estimate of measure of effectiveness**
It is likely that the review of the literature was conducted systematically. However, the methodology adopted was not described in detail. The effectiveness estimates were combined using narrative methods. The authors reported that they did not place differential weights on the studies included in the review, but the full range of parameters was tested in a sensitivity analysis. Potential differences between the primary studies were not discussed.
**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The decision tree used for this purpose was appropriate, as it incorporated a wide range of states or events associated with treatment of ADHD. However, owing to a lack of available effectiveness data, the time horizon of the analysis was limited to one year. Consequently, an estimation of the long-term benefits was not possible.

**Validity of estimate of costs**
Although it was stated that the study adopted a societal perspective, the indirect costs associated with productivity losses were not included in the analysis. The costs comprised health care costs (including parents’ out-of-pocket expenses) and school administrative costs. However, it appears that some relevant costs, such as outpatient and mental health visits and emergency room visits due to injuries, have been. With the exception of drug costs, which were provided separately, the health care costs were presented aggregated. The costs and the quantities were not reported separately, which hinders the reproducibility of the results. A sensitivity analysis of the costs was performed, although the ranges of values used were not provided. Since all of the costs were incurred during one year, discounting was unnecessary and was not carried out. The price year was stated and this increases the generalisability of the results. The authors did not report any further limitations.

**Other issues**
The authors did not compare their findings with those of other studies. The issue of generalisability to other settings was also not addressed. The results of the study were adequately reported. The authors' conclusions reflect the scope of the analysis.

**Implications of the study**
It was suggested that, in cases where use of stimulants is among the treatment options for ADHD patients, clinicians should initiate stimulant treatment in the short term, targeting patients to the therapy that would most likely precipitate the best therapeutic response and considering alternative stimulants if the initial therapy fails. Until further clinical evidence on differences in the effectiveness of stimulant therapy in various paediatric populations becomes available for guidance purposes, the choice of the stimulant should be influenced by the environmental factors surrounding the patient, such as the dosing interval, in-school dosing administration and oversight of the parent or guardian in treatment. The authors emphasised the need for further research on the long-term outcomes of stimulant therapy and its impact on co-morbidities such as anxiety, mood disorder, depression, conduct disorder and oppositional-defiant disorder. They also recommended that future research should focus on the identification and estimation of indirect and other non-medical costs associated with ADHD.

**Source of funding**
None stated.

**Bibliographic details**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Amphetamines /therapeutic use /economics; Attention Deficit Disorder with Hyperactivity /drug therapy; Child; Cost-Benefit Analysis; Humans; Methylphenidate /therapeutic use /economics; Models, Economic

**AccessionNumber**