Cost-effectiveness of dexamphetamine and methylphenidate for the treatment of childhood attention deficit hyperactivity disorder


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 dexamphetamine (DEX) and methylphenidate (MPH) to treat childhood attention deficit hyperactivity disorder (ADHD). The two treatment protocols were accurately described. The drug dosages were as follows. During the titration period (4 weeks), the patients received DEX 5 mg/day (week 1), 10 mg/day (week 2), 15 mg/day (weeks 3 and 4) or MPH 10 mg/day (week 1), 20 mg/day (week 2), 30 mg/day (weeks 3 and 4). During the maintenance period (10 months), DEX was administered at a dose of 15 mg/day and MPH was administered at a dose of 30 mg/day.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised the cohort of children aged 4 to 17 years, who were suffering from ADHD but not receiving any psychostimulant medication, in Australia in the year 2000.

Setting
The setting was secondary care. The economic study was carried out in Australia.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1981 and 2001. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Outcomes assessed in the review
The outcomes estimated from the literature were:

- the prevalence of ADHD,
- the proportion of patients that underwent consultations and did not receive stimulants,
- the reductions in disability weight (DW), and
the adherence rate.

**Study designs and other criteria for inclusion in the review**

The inclusion criteria used to identify relevant studies were:

- Psychostimulant medication and placebo had to be administered for at least 6 consecutive days;

- The trial participants had to be aged between 4 and 17 years, with a DSM-III, DSM-III-R or DSM-IV diagnosis of ADHD; and

- The mean and standard deviations for the outcome measures either had to be reported or be available from the authors.

Primary studies were excluded if patient participation was dependent on the presence of co-morbidities (e.g. learning disorders, Tourette's syndrome) or prior positive response to medication, or if results were only presented for positive medication responders. Only randomised clinical trials were included. Other data were derived from Australian statistics.

**Sources searched to identify primary studies**

Three published meta-analyses, the Cochrane Controlled Trials Register, MEDLINE, and reference lists in review articles were searched for relevant studies.

**Criteria used to ensure the validity of primary studies**

The selection of randomised clinical trials only ensured the validity of the primary studies.

**Methods used to judge relevance and validity, and for extracting data**

The authors applied several statistical methods to judge the validity of the data extraction process.

**Number of primary studies included**

Approximately 28 primary studies provided the evidence.

**Methods of combining primary studies**

A meta-analysis was used to combine the primary estimates.

**Investigation of differences between primary studies**

A heterogeneity test was used to investigate differences among the primary studies. Heterogeneity was not significant at the p<0.01 level.

**Results of the review**

The results of the review were used to populate model distributions.

The mean prevalence of ADHD (normal distribution in the model) was 3.5% (standard error, SE=0.3).

The proportion of patients that consulted and did not receive stimulants (normal distribution) was 16.4% (SE=3.4).

The reductions in DW (triangular distribution) were 0.039 (lower limit 0.010; upper limit 0.051) with DEX and 0.038 (lower limit 0.031; upper limit 0.042) with MPH.

The adherence rate (uniform distribution) ranged from 56% (minimum) to 81% (maximum).
Measure of benefits used in the economic analysis

The summary benefit measure used was the number of disability-adjusted life-years (DALYs). Since there was no evidence for a difference in mortality with or without psychostimulant medication, only a change in the years lived with disability (YLD) component was considered. The YLD were calculated as the average DW multiplied by disease prevalence. Discounting was not applied because of the short timeframe of the analysis.

Direct costs

Discounting was not relevant since the costs were incurred during one year. In general, the unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were DEX, MPH, and visits to general practitioners, paediatricians and psychiatrists. The cost/resource boundary of the government and the patient was adopted. Some categories of costs were derived from the Medicare Benefits Schedule and other Australian sources. Resource use was derived from clinical practice guidelines and published data. It was assumed that the cost of non-adherence was comparable to current practice in patients currently not receiving stimulants. The costs incurred with current practice were subtracted from the intervention and non-adherence costs to obtain the incremental costs. The costs were presented in 2000 values.

Statistical analysis of costs

The costs were treated deterministically in the base-case.

Indirect Costs

The indirect costs were not included in the economic evaluation.

Currency

Australian dollars (Aus$).

Sensitivity analysis

The issue of uncertainty around the costs, benefits, and cost-utility ratios was addressed using a Monte Carlo simulation with 2,000 iterations. Median values were calculated because of the non normal distribution of costs, and 95% uncertainty intervals (UI) were derived from 2.5 and 97.5 percentile values.

Estimated benefits used in the economic analysis

In the whole cohort of 21,000 eligible Australian children in the year 2000, the estimated number of YLD was 435 (95% UI: 190 - 690) with DEX and 480 (95% UI: 250 - 750) with MPH.

The percentage of YDL with the intervention was 23 (95% UI: 10 - 36) with DEX and 25 (95% UI: 13 - 39) with MPH.

Cost results

All the costs were determined in comparison with current practice.

The estimated government costs (in millions) were Aus$2.8 (95% UI: 0.9 - 5.0) with DEX and Aus$0.93 (95% UI: -0.86 - 3.2) with MPH.

The estimated patient costs (in millions) were -Aus$1.0 (95% UI: -2.1 - 0.13) with DEX and Aus$6.2 (95% UI: 3.2 - 10) with MPH. Therefore, the total costs over current practice were Aus$1.7 (95% UI: -1.0 - 4.7) with DEX and Aus$7.0 (95% UI: 3.3 - 12.5) with MPH.
Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and benefits of the interventions under examination. The incremental cost per DALY in comparison with current practice was Aus$4,100 (95% UI: negative - 14,000) with DEX and Aus$15,000 (95% UI: 9,100 - 22,000) with MPH.

The authors considered four criteria to ensure the validity, applicability, and generalisability of their findings:

- strength of evidence (assessment of the robustness of the estimators used in the analysis),
- equity (capacity of the interventions to affect inequity in distribution of mental disorder and access or utilisation issues),
- feasibility (availability of an appropriate workforce with appropriate training to implement the intervention), and
- acceptability to stakeholders (including consumers and their family or carers, clinicians, policy-makers, the general community, and third-party payer).

The analysis revealed that the acceptability of stakeholders was the most critical issue, as ADHD represents a disease difficult to diagnose and some children could be medicated unnecessarily. Further, some parents were less prone to use psychostimulants to treat their children.

Authors' conclusions
Both psychostimulant medications had a cost-utility ratio well below the commonly used threshold for cost-effectiveness. Dexamphetamine (DEX) was more costly for the government, while methylphenidate (MPH) was more costly for the patient. In general, DEX was more cost-effective since the disability-adjusted life-years (DALYs) were quite comparable, but the costs were significantly higher with MPH than with DEX.

CRD COMMENTARY - Selection of comparators
The choice of the comparators appears to have been appropriate as both the new interventions were compared with current practice in the authors' setting. The protocols of treatment used with the two psychostimulants were described in detail. You should decide whether current practice is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a well-conducted review of the literature. Inclusion and exclusion criteria were reported, and the authors described the approaches used to identify, select and then combine the relevant studies. In general, the methods and conduct of the review were satisfactorily reported. The issue of differences among primary studies was addressed by testing for heterogeneity. The selection of only clinical trials ensured the validity of the primary sources. The strength of the evidence was considered good and all uncertainty was managed in the probabilistic sensitivity analysis (Monte Carlo simulation).

Validity of estimate of measure of benefit
The benefit measure was selected so as to reflect the impact of the interventions on the most important aspect of patient health, namely disability. Although DALYs are not as common as quality-adjusted life-years, they were appropriately selected as summary benefits of the psychostimulant treatments. No impact on survival was assumed, thus no discounting was applied. The method used to elicit the impact of the interventions on disability was described and justified.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted in the study. It appears that all the relevant categories of costs have been considered in the analysis. The costs relevant to the two main payers (government and patient) were presented separately. Further, the unit costs were given and there was sufficient information on resource usage. It could,
therefore, be possible to replicate the results of the analysis in other contexts. The source of the economic data was reported for all items. The treatment protocols associated with the two psychostimulants were described in detail and reflected local treatment patterns. The price year was reported, which aids reflation exercises in other settings. No statistical tests of the costs were carried out in the base-case, but all the cost inputs were varied in the stochastic sensitivity analysis.

Other issues
The authors reported the results of a Canadian study comparing the cost-effectiveness of MPH and DEX, which found that MPH dominated DEX, possibly because of the higher cost of DEX compared with MPH in Canada. The issue of the generalisability of the study results to other settings was addressed by performing a stochastic sensitivity analysis. Moreover, the authors highlighted the methodological rigour used in the analysis, as a unique strength of their work. However, the authors noted that the greatest limitation was the definition of the method used to determine the change in DW. Similarly, the analysis did not consider any disorders frequently experienced alongside ADHD. In general, caution is required when extrapolating the results of the current analysis to all patients with ADHD because the patient groups might differ. Finally, the authors admitted that the use of psychostimulants did not represent the perfect solution in ADHD patients.

Implications of the study
The results of the study showed that if MPH were listed on the Medicare Benefits Schedule at a similar price to DEX, as is common with drugs of similar efficacy, then MPH would be as cost-effective as DEX. The authors stated that the restriction of prescriptions appears appropriate only if access to providers is not limited.

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