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Title **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**

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Aim

To assess the clinical and cost effectiveness of oral methylphenidate hydrochloride (MPH), dexamfetamine sulphate (DEX), and atomoxetine (ATX) in children and adolescents diagnosed with attention deficit hyperactivity disorder (ADHD), including hyperkinetic disorder.

Conclusions and results

Sixty-five papers met the inclusion criteria. The results suggest that MPH and DEX are effective at reducing hyperactivity and improving quality of life (QoL), as determined by Clinical Global Impression, in children. However, the reliability of the MPH study is unknown, and there were few DEX studies. Consistently, 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. Few studies made direct head-to-head comparisons. Adequate and informative data regarding the potential adverse effects of the drugs were also lacking. Results of the economic evaluation clearly identified an optimal treatment strategy of DEX first-line, followed by IR (immediate release)-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 (extended release)-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, which should be borne in mind when interpreting the model results.

Recommendations

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 behavioral 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.

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 type of comparison. Data for MPH were analyzed 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, Clinical Global Impression, 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. For parallel studies, change scores were reported where given, otherwise means and SDs were presented for end of trial data. Mean differences with 95% confidence intervals were calculated for each study. For adverse events, self-ratings or parent reports were used. Percentages of participants reporting adverse events were used to calculate numbers of events in each treatment arm. All clinical effectiveness data and economic evaluations 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, using a mixed treatment comparison model to estimate the differential mean response rates. Monte Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

Further research/reviews required

- Trials of MPH, DEX, and ATX that prioritize assessment of tolerability and safety
- Longer-term followup of individuals participating in trials
- Research on whether somatic complaints are related to drug treatment or to the disorder itself.

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