Cost effectiveness of guanfacine extended-release versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder: application of a matching-adjusted indirect comparison
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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.

CRD summary
The study objective was to assess the cost-effectiveness of guanfacine extended-release (GXR) versus atomoxetine for the treatment of ADHD (attention-deficit/hyperactivity disorder) in children and adolescents. The authors concluded that GXR was cost-effective compared to atomoxetine. The study methods seemed appropriate and were reported clearly and transparently. The authors’ conclusions appear to be appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The study objective was to assess the cost-effectiveness of guanfacine extended-release (GXR) versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents.

Interventions
Two interventions were compared in the cost-effectiveness analysis: guanfacine extended release (GXR) and atomoxetine. The effectiveness analysis also considered three dosage strategies for GXR: 0.09 to 0.12mg/kg/day; 0.075 to 0.09mg/kg/day; and 0.046 to 0.075mg/kg/day. One atomoxetine dosage strategy was considered: 1.2mg/kg/day.

Location/setting
USA/outpatient

Methods
Analytical approach:
A Markov model was used to assess the costs and effects associated with each intervention over a one-year period (four-week drug titration period and 48-week maintenance period). Efficacy data were derived from a published matching-adjusted indirect comparison (MAIC) that incorporated two GXR and one atomoxetine double-blind randomised placebo-controlled trials. The authors stated that the perspective was that of a USA third-party payer.

Effectiveness data:
Effectiveness was measured in terms of the proportion of responders (defined as patients with ≥25% reduction from baseline in the ADHD rating scale fourth edition total score). A systematic review of the literature was used to identify relevant trials. One trial with summary results data was included for atomoxetine versus placebo and two trials with individual patient data were included for GXR versus placebo. Comparative efficacy results were derived from a MAIC in which efficacy outcomes were compared between balanced trial populations as the GXR trial populations were slightly broader than that of the atomoxetine trial. This is a type of observational study controlling for patient characteristics. The atomoxetine trial included in the MAIC did not report response rate as an endpoint so a prediction model based on a meta-regression analysis was developed using other published atomoxetine trials to translate the change in ADHD rating scale total score into response rate. A constant discontinuation rate was estimated for each treatment based on a two-year rate observed in long-term GXR and atomoxetine open-label trials.

Monetary benefit and utility valuations:
Utility values associated with response, non-response and adverse events were applied in the model. Utility valuations
were derived for the response and non-response health states using a published study that estimated utilities in a group of patients with ADHD in the UK using the EQ-5D instrument. Adverse events that affected more than 5% of patients who received either drug were obtained from the package inserts. Disutility associated with each adverse event was obtained from the literature.

Measure of benefit:
The benefit was measured in quality-adjusted life-years (QALYs) and in terms of the proportion of responders.

Cost data:
Only direct costs (drug costs and direct medical costs) were considered in the model. Unit drug costs were obtained from USA wholesale acquisition costs. The unit cost of atomoxetine was estimated as a weighted average of wholesale acquisition costs for all dosing forms, weighted by the market share of each dosing form. The number of pills consumed per day was assumed to be one for both drugs. Medical costs associated with non-response were obtained from a published study. All costs were inflated to 2011 US dollars ($) using the medical care component of the Consumer Price Index.

Analysis of uncertainty:
Univariate sensitivity analysis varied all model parameters between given ranges to assess the effect of single parameter uncertainty on the results. The results were reported in tabular form.

Results
The base-case total cost was $1,482 for GXR and $1,408 for atomoxetine. GXR was associated with an incremental cost of $74 per patient for 0.007 additional QALYs and 86 more responders per 1,000 treated patients compared to atomoxetine. The associated incremental cost-effectiveness ratio (ICER) was $10,637 per QALY gained and $853 per responder for GXR. The results were analysed assuming a willingness-to-pay threshold of $50,000 per QALY.

Univariate sensitivity analyses showed that the model results were robust to changes in model parameters; all analyses yielded ICERs with a value less than $50,000 per QALY. Results were most sensitive to changes in the unit costs of GXR and atomoxetine. The scenario with the highest ICER ($48,340) was when the unit cost of GXR was 25% more than its base-case.

Authors' conclusions
The authors concluded that GXR was cost-effective compared with atomoxetine.

CRD commentary
Interventions:
The choice of interventions was justified: the authors stated that GXR and atomoxetine were the only non-stimulants approved by the US Food and Drug Administration for once-daily use for treatment of children and adolescents with ADHD in USA. The different dosage strategies considered were reported clearly and justified.

Effectiveness/benefits:
The response rates, utility values and any relevant sources were all reported clearly. Use of an indirect-comparison to estimate efficacy outcomes was justified by the author's statement that there was a lack of head-to-head trials for the two interventions. The authors reported that a systematic review was conducted to identify studies for this comparison analysis. The selection criterion for this review was reported clearly but there were no details of databases searched and the review methodology. Detailed information was reported on the three included trials. The authors did not justify their choice of papers for the prediction model and sources used to derive utility values.

Costs:
All costs were clearly reported and relevant to the perspective and location. Sources used to derive costs were justified and reported clearly. The authors stated that the assumption that one pill was consumed per day was conservative for atomoxetine (FDA-approved atomoxetine dosing regimens included once- and twice-daily administration for atomoxetine). Costs were inflated appropriately.

Analysis and results:
The model structure and assumptions were reported clearly and a model diagram was supplied. There was no reported justification for adopting a one-year time horizon: if treatment and outcomes could be expected to occur beyond this horizon a one-year horizon may have underestimated treatment benefits. The MAIC methods used to derive model efficacy inputs were described clearly. The authors highlighted several issues with the MAIC analysis. In particular, since MAIC is not based on a randomisation of treatment groups, unobserved confounding factors between trials could bias the results; it appeared that the authors adopted a rigorous approach to minimise this possibility.

The impact of parameter uncertainty on the results may not have been fully addressed in the sensitivity analysis. A multivariate and probabilistic sensitivity analysis may have better assessed the overall impact of uncertainty. Ranges used within the deterministic sensitivity analysis were not justified and some ranges varied between arbitrary upper and lower bounds. Although the results appeared robust to individual parameter values, unaccounted for uncertainty may have occurred.

The authors stated that because the results were based on a few selected trials and may not be generalisable to the entire ADHD population. Regarding The authors stated that indirect costs were a major component of ADHD costs and future studies should include these.

Concluding remarks:
The study methods seemed appropriate and were reported clearly and transparently. The conclusions reached by the authors appear to be appropriate.

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