Economic evaluation of duloxetine versus serotonin selective reuptake inhibitors and venlafaxine XR in treating major depressive disorder in Scotland
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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
This study examined the cost-utility of duloxetine, compared with selective serotonin re-uptake inhibitors (SSRIs), venlafaxine extended release, and mirtazapine, for the treatment of major depressive disorder in primary and secondary care. The authors concluded that duloxetine was very likely to be cost-effective, in either setting. The methods and results were clearly reported, but insufficient details were provided on the key data sources, making it difficult to determine if the authors’ conclusions were appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
This study examined the cost-utility of duloxetine, compared with selective serotonin re-uptake inhibitors (SSRIs), venlafaxine extended release, and mirtazapine, for the treatment of major depressive disorder in primary and secondary care.

Interventions
In the primary care setting, duloxetine (serotonin-norepinephrine re-uptake inhibitor; SNRI) was compared with SSRIs as a group, venlafaxine extended release, and mirtazapine for the treatment of moderate-to-severe depression, defined by a Hamilton Rating Scale for Depression (HRSD-17) score of 19 or more. In the secondary care setting, duloxetine was compared with venlafaxine extended release, and mirtazapine for the treatment of more severe depression, defined by a HRSD-17 score of over 25; it was assumed that patients had already received several SSRI treatments.

Location/setting
UK/primary and secondary care.

Methods
Analytical approach:
A Markov model with an eight-week cycle length and time horizon of 48 weeks was used to capture the course of treatment and relapses up to a year. The authors reported that a Scottish NHS perspective was adopted in the base case and a societal perspective was assessed in a sensitivity analysis.

Effectiveness data:
The effectiveness of treatments, in primary care, came from a pooled analysis of two head-to-head randomised controlled trials (RCTs) of venlafaxine and a meta-analysis of six placebo-controlled RCTs (data on file at Eli Lilly), as well as a meta-analysis for mirtazapine. The estimates for secondary care were from the two head-to-head trials of duloxetine and venlafaxine; authors’ assumptions were needed for mirtazapine due to a lack of data. Drop-outs were expected to be higher in clinical practice, so the drop-out rates from the RCTs were increased by 13% for primary care and 30% for secondary care, based on expert opinion. The proportion of patients resuming treatment after discontinuation was based on expert opinion. Switching between active comparator treatments was allowed, due to no response in two consecutive cycles, a response but no remission and not maintained, or relapse from remission; these data were from UK prescription records.

Monetary benefit and utility valuations:
The utility estimates were weighted by UK tariffs, using European Quality of life (EQ-5D) scores from a RCT of about 300 participants, conducted by Eli Lilly (data on file).

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs).

Cost data:
The direct medical costs included those of drugs, general practitioner (GP) and psychiatrist visits, hospitalisations, and emergency department visits. The resource use was from expert panels that included a pharmacist, psychiatrists, and GPs. The unit costs were from published UK sources. The indirect costs (productivity losses) were estimated, using the human capital approach, with the number of hours worked from a published European study, and average gross wages from UK published sources. The costs were reported in UK pounds sterling (£).

Analysis of uncertainty:
One-way sensitivity analyses on the model parameters and probabilistic sensitivity analyses were performed. Three different scenarios were analysed. For example, using the efficacy of duloxetine from only head-to-head trials. The distributions applied to the parameters were reported. A Monte Carlo simulation was conducted, with 5,000 repetitions, and the results were presented in cost-effectiveness acceptability curves.

Results
In the primary care setting, the total costs were £543 for duloxetine, £585 for venlafaxine, £516 for mirtazapine, and £486 for SSRIs. The incremental QALYs gained with duloxetine were 0.002 compared with venlafaxine, 0.012 compared with mirtazapine, and 0.009 compared with SSRIs. Duloxetine had an incremental cost-effectiveness ratio (ICER) of £2,353 per QALY compared with mirtazapine, and £6,304 per QALY compared with SSRIs. It dominated venlafaxine extended release as it was more effective and less costly.

In the secondary care setting, the total costs were £1,622 for duloxetine, £1,667 for venlafaxine, and £1,640 for mirtazapine. The incremental analysis found that duloxetine dominated both venlafaxine and mirtazapine.

The ICERs in the primary care setting were most influenced by changes in the probabilities of remission, response, and relapse with duloxetine. For instance, an increase in the relapse rate for duloxetine from 13% to 21% increased the ICER over SSRIs to around £50,000 per QALY. The results were less sensitive to changes in these parameters in the secondary care setting.

The probabilistic sensitivity analysis showed that duloxetine was the most favourable treatment option. The inclusion of the indirect costs did not alter the results for either primary or secondary care scenarios.

Authors' conclusions
The authors concluded that duloxetine had similar efficacy, but was cheaper than venlafaxine and had different side-effects. It was very likely to be cost-effective for the treatment of major depressive disorder in both primary and secondary care settings in Scotland.

CRD commentary
Interventions:
The interventions were described and appear to have been relevant for the health problem. Not all of the available treatments were compared, even as switching options. For example, tricyclic antidepressants were not considered and titration of the doses was not considered. SSRIs were not considered in secondary care, as they were assumed to have failed. These comparators may have been all the relevant ones for other settings.

Effectiveness/benefits:
The effectiveness estimates were pooled from meta-analyses of RCTs and two head-to-head trials, which should have provided high-quality evidence, but the details of the trials and analyses were not fully reported. The authors did not report a systematic literature search, making it difficult to determine if all the relevant best-available evidence was used. Several key parameters, such as duloxetine efficacy and the utilities, were from data on file, provided by the
manufacturer of duloxetine (Eli Lilly) and details, such as the methods, design, population, and inclusion criteria, were not reported. This limits the transparency of the analysis and makes it difficult to determine the internal validity of the data. The methods used to extrapolate the short-term RCT efficacy (12 weeks of follow-up) to the long term (48 weeks) were not provided, which restricts the replication of the results for other settings. QALYs were an appropriate measure of benefit.

Costs:
The costs of treating adverse events were not reported and were probably not considered. The unit costs were from the NHS in England and Wales, and should be similar to Scottish costs (as stated by the authors). The identification and measurement of the resource use was by expert opinion, and the method used to select the expert panel was not reported. This raises some questions about the reliability of the cost data. The resource use and costs were not reported separately, but supplementary data were available in an online appendix and these should allow the analysis to be transferred to other settings. The price year was not stated, but seems to have been 2007, based on the data in the appendix. The costs were not discounted, as the analysis was for 48 weeks.

Analysis and results:
The model and assumptions were described and a diagram was given. The results were sensitive to some of the key parameters that were from data on file and insufficient details were given. This limits the transparency of the analysis. A comprehensive approach was used to evaluate the parameter uncertainty, including one-way and probabilistic sensitivity analyses and the results appear to have been robust. The authors provided a discussion of the main study limitations, including that the patients were not permitted to switch to tricyclic antidepressants and the resource use was from expert panels.

Concluding remarks:
The methods and results were clearly reported, but insufficient details were provided on the key data sources, which had a significant impact on the results. This makes it difficult to determine if the authors’ conclusions were appropriate.

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