A pharmacoeconomic evaluation of escitalopram versus citalopram in the treatment of severe depression in the United Kingdom

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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
Escitalopram was compared with citalopram for the treatment of severe depression. The dose of escitalopram was 20 mg/day and that of citalopram 40 mg/day.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The target population for the model were patients suffering from severe depression, as defined by a Montgomery-Asberg Depression Rating Scale (MADRS) total score of at least 30.

Setting
The setting was primary and secondary care. The economic study was carried out in the UK.

Dates to which data relate
The studies providing effectiveness evidence dated from 1997 to 2005. For cost data, the studies were from 2000 and 2001. The price year was 2003.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on experts’ opinions.

Modelling
A decision tree with a 6-month time horizon was used with a univariate sensitivity analysis and Monte Carlo simulation to evaluate the effect of uncertainty. This study was an adaptation of the models described in three other studies (Borghi et al. 2000, Hemels et al. 2004 and Brown et al. 1999, see ‘Other Publications of Related Interest’ below for bibliographic details).

Outcomes assessed in the review
The outcomes included were:

remission (MADRS <= 12) rate,
remission without switching drug treatment,
continuation rate,
discontinuation rate,
response rate,
compliance, and
the overall probability of treatment-emergent adverse events (AEs), evaluated for both drugs.

**Study designs and other criteria for inclusion in the review**
A review of the literature was undertaken for cost-effectiveness decision models in severe depression. The criteria for the search were English-language modelling studies published from 1966 to 2004. The authors reported meta-analyses, studies of varying design, and published literature in the study. Although designs of the primary studies were generally not reported, data for remission, discontinuation and response rates at week 8 were derived from a meta-analysis and extrapolated to 6 months (Llorca et al. 2005, see 'Other Publications of Related Interest' below for bibliographic details).

**Sources searched to identify primary studies**
MEDLINE, EMBASE, and the Cochrane Library were searched. The keywords and search terms were "cost", "cost-effectiveness" and "depression".

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

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

**Number of primary studies included**
Five English-language modelling studies were identified, of which two were conducted in France, two in Austria and one in the UK. These models used similar decision trees (with identical time horizon of 6 months), which were representative of the treatment strategy and guidelines for severe depression in their respective settings.

**Methods of combining primary studies**
A narrative method was used to combine the primary studies.

**Investigation of differences between primary studies**
The authors appear to have investigated differences between the primary studies, but did not report the approach used.

**Results of the review**
The continuation rate after 8 weeks was 88.3% (83.5 - 93.1) for escitalopram and 86.3% (81.1 - 91.5) for citalopram.

The discontinuation rate after 8 weeks was 11.7% (6.9 - 16.5) for escitalopram and 13.7% (8.5 - 18.9) for citalopram.

The response rate after 8 weeks was 65.3% (58.1 - 72.5) for escitalopram and 47.6% (40.1 - 55.1) for citalopram.
The inadequate response/switch rate was 34.7% (27.5 - 41.9) for escitalopram and 52.4% (45.0 - 59.9) for citalopram.

The rate of compliance with the regimen was 63.4% (41.1 - 85.6) for both groups.

The remission rate at 6 months was 76.0% (69.5 - 82.5) for escitalopram and 71.0% (64.3 - 77.8) for citalopram.

The rate of compliance with switched treatment was 69.7% (67.3 - 72.1) for both groups.

The remission rate at 6 months after the treatment switch was 58.3% (52.0 - 64.5) for both groups.

The rate of suicide attempt was 3.0% (2.8 - 3.2) for both groups.

The incidence of AEs was 72.7% (69.4 - 76.0) for escitalopram and 76.5% (72.4 - 80.6) for citalopram.

All probabilities used in the decision model, with their respective sources, were listed in the study.

**Methods used to derive estimates of effectiveness**

This analysis was based on published data, authors' assumptions and expert opinion.

**Estimates of effectiveness and key assumptions**

This study was an adaptation of the models described in three other studies (Borghi et al. 2000, Hemels et al. 2004 and Brown et al. 1999). The authors stated that when published estimates were not available, they assumed a conservative estimate of the parameter based on the literature. For example, in the case of spontaneous remission rate for patients who discontinued at 8 weeks, and for those who switched treatment. A local Delphi panel was used in one of the main models (Borghi et al. 2000) on which this analysis was based, and its results were reported in the present study.

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

The outcome measure used in the economic analysis was patient treated successfully. This was defined as a patient in remission (i.e. MADRS score <= 12 at week 24).

**Direct costs**

The cost categories included were medications, general practitioner and psychiatrist visits, inpatient psychiatric hospitalisations, discontinuation of treatment, treatment-emergent AEs and attempted suicide. Estimates for the majority of the resources used and costs were derived from published literature (Borghi et al. 2000 and Netten et al. 2001, see ‘Other Publications of Related Interest’ below for bibliographic details).

The price year was 2003. All unit costs were updated using the British Consumer Price Index. The authors noted that there was no price difference between escitalopram 10 and 20 mg (branded and generic). The drug prices were obtained from the Drug Tariff in the Prescription Pricing Authority Web site. Discounting was not carried out since the costs were incurred during less than 2 years. The estimations of the quantities and the costs were derived by modelling.

**Statistical analysis of costs**

The costs were included as parameters in the model. No statistical analysis of the costs was reported.

**Indirect Costs**

For this cost category, the costs resulting from absenteeism from work (i.e. lost productivity) were included. The number of workdays lost due to severe depression was derived from published literature (Borghi et al. 2000 and Netten et al. 2001). The calculation of the societal cost of lost productivity due to severe depression was based on the human capital approach, based on mean market wages for the year 2003. Discounting was not carried out since the costs were incurred during less than 2 years.
Currency
UK pounds sterling (\(\)). The reported conversion rate was 1.00 = US\$0.62 in January 2003.

Sensitivity analysis
The robustness of the results was tested in univariate and multivariate sensitivity analyses. These were based on 95% confidence intervals (CIs) or feasible ranges for the specified variables, as reported in the literature, and assuming a triangular distribution. Univariate sensitivity analyses were carried out on the drug-specific probabilities and unit costs (variation +/- 15%) used in the model. In the case of dominance, a break-even analysis was performed, based on the unit cost of the dominated drug. All parameters, with their ranges tested, were reported.

Estimated benefits used in the economic analysis
The clinical outcomes were:

overall success, 53.7% (50.3 - 57.5) for escitalopram and 48.7% (45.8 - 51.7) for citalopram; and

first-line success without switch, 41.7% (37.5 - 46.3) for escitalopram and 30.8% (27.5 - 34.6) for citalopram.

Treating patients with escitalopram instead of citalopram rendered a higher overall remission rate (relative difference 10.3%) and first-line success rate (relative difference 35.4%).

Cost results
From the NHS perspective, the expected total cost per patient was 422 (range: 404 - 441) for escitalopram and 454 (range: 436 - 471) for citalopram.

From the societal perspective, considering indirect costs, the expected total cost per patient was 690 (range: 665 - 714) for escitalopram and 740 (range: 715 - 767) for citalopram.

Synthesis of costs and benefits
Mean cost-effectiveness ratios were calculated by dividing the expected cost of treatment by the outcome measure. Further, where dominance (i.e. in lower expected costs and improved efficacy) was lacking, an incremental cost-effectiveness ratio, expressed as the expected additional cost per successfully treated patient, was calculated. In case of the presence of a dominant strategy, the expected costs per successfully treated patient were calculated.

From the NHS perspective, the expected total cost per successfully treated patient was 786 (range: 702 - 876) for escitalopram and 932 (range: 843 - 1,028) for citalopram. The difference per successfully treated patient after 6 months of treatment was -146 (range: -141 - 152), accounting for a relative difference of 15.7% (range: 14.8 - 16.7).

From the societal perspective, the expected total cost per successfully treated patient was 1,283 (range: 1,157 - 1,419) for escitalopram and 1,521 (range: 1,383 - 1,675) for citalopram. The difference per successfully treated patient after 6 months of treatment was -238 (range: -226 - 256), accounting for a relative difference of 15.6% (range: 15.3 - 16.3).

The sensitivity analysis indicated that changes in drug-specific probabilities had no impact on the results. Within all ranges tested, including the same remission rate for citalopram at 6 months, escitalopram was more effective and was cost-saving in comparison with citalopram. In addition, the model did not appear to be sensitive to changes in the costs used. From the societal perspective, the model did not appear to be sensitive to changes in the cost per day of absence from work.

The multivariate sensitivity analyses demonstrated that escitalopram was, in more than 99.8% of cases, dominant from both perspectives at all ranges of probabilities tested. Incremental cost-effectiveness scatter plots of the probabilistic sensitivity analyses of escitalopram versus citalopram from both perspectives were presented. Data were drawn within the 95% CIs or feasible ranges of the input parameters, and 10,000 iterations were performed.
The break-even analysis demonstrated that, even if generic citalopram had an acquisition cost of 0.00, escitalopram would remain the dominant strategy from the societal perspective and would remain a cost-effective strategy from the NHS perspective.

Authors' conclusions
This analysis suggested that escitalopram was a cost-saving alternative to citalopram for the treatment of severe depression in the UK. From both the UK National Health Service (NHS) and societal perspectives, the relative cost-savings per treated patient and per successfully treated patient were 7% and 16%, respectively. Multivariate sensitivity analyses demonstrated that in more than 99% of cases, escitalopram was dominant at all ranges of probabilities tested, indicating the robustness of the results.

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparators. The cost-effectiveness of antidepressant therapy for severe depression has been little studied, and a recently published meta-analysis on the efficacy of escitalopram in patients with severe depression demonstrated significantly higher response rates and a greater mean change from baseline in the MADRS total score, compared with citalopram-treated patients, as early as week 1. You should judge whether these drugs are relevant in your own setting, or whether other comparators from other drug classes could have been relevant as well.

Validity of estimate of measure of effectiveness
The authors used data from published sources. The main sources of effectiveness evidence were two modelling studies (Borghi et al. 2000, and Hemels et al. 2004). Incomplete detail on the primary sources was given. According to the authors, these studies were two of only five cost-effectiveness studies in this area. Despite this opinion, it was unclear whether a systematic review of the literature was undertaken. The effectiveness estimates were combined and were derived credibly from the selected studies and from the authors’ assumptions. The authors reported the methods used to derive the estimates of effectiveness, and justified their choice of assumptions with reference to the medical literature. These estimates were investigated in sensitivity analyses, using feasible ranges.

Validity of estimate of measure of benefit
The number of successfully treated patients was used as a proxy for the measure of health benefit. This choice of estimate was justified, following a recommendation from the literature. The measure chosen is context specific and can only be compared with other severe depression studies, and not other economic evaluations. In addition, a 6-month time horizon could be somewhat short for a chronic illness such as depression.

Validity of estimate of costs
The authors reported that the costs were estimated from two perspectives, the NHS and society. Therefore, the indirect costs were appropriately included. Although some costs could have been omitted from the analysis, these were unlikely to have affected the authors' conclusions since they were common to both therapies.

To estimate the total direct costs, the authors used published literature from different sources and years and adjusted them accordingly. The resource use quantities were taken from published sources but were not reported in detail, a fact that may limit extrapolation exercises to other settings. The prices were taken from published sources. The authors reported the price year, which will enhance any future inflation exercises. Appropriate sensitivity analyses of the costs were conducted. Discounting was, appropriately, not applied as the study horizon was no longer than 6 months.

Other issues
The authors made appropriate comparisons of their findings with those of other studies. The results of their study were consistent with those of other cost-effectiveness analyses. The issue of generalisability to other settings was addressed.
Considering the limitations inherent to any decision model, the authors reported that incorporating real-life factors (e.g. discontinuation of treatment, AEs and switch of treatment), in addition to the clinical data reported in randomised clinical trials, the model tried to simulate real-world cost-effectiveness as closely as possible. In addition, the authors applied the human capital method to value production losses due to depression for the societal perspective. This approach might have overestimated the costs, because it assumed that potential production was equal to the indirect costs. For the probabilistic sensitivity analysis, the authors assumed triangular distributions of all probabilities, which may not be realistic, although the influence of the analysis would probably not be substantial.

Implications of the study
The relative cost-savings per treated patient and per successfully treated patient for escitalopram versus citalopram, for both the NHS and the societal perspectives, might indicate that possible advantages exist at the population level. An analysis including other commonly used drugs for depression might give a broader picture.

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