A cost-effectiveness model of escitalopram, citalopram, and venlafaxine as first-line treatment for major depressive disorder in Belgium

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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
The health technologies compared were escitalopram (10 - 20 mg/day), citalopram (20 - 40 mg/day) and venlafaxine (75 - 150 mg/day) as first-line treatment for major depressive disorder (MDD). MDD was defined as baseline scores on the Montgomery-Asberg Depression Rating Scale 13-1s of 18 to 40 inclusive.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with MDD.

Setting
The setting was primary and secondary care. The economic study was performed for Belgium.

Dates to which data relate
All data for the analysis came from a review of the literature, a survey and a panel of experts. The authors used data from studies published from 1995 to 2004 for their model. The dates to which the survey and expert panel consultation referred were not stated. Monetary values were reported in year 2003 prices.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies, and opinion (survey and expert panel).

Modelling
The model used in this study was adapted from another study (Hemels et al. 2004, see ‘Other Publications of Related Interest’ below for bibliographic details). The study presented a 2-path decision model that approximated current standards of care (i.e. general clinical practice for the treatment of MDD) to predict outcomes and estimate the costs associated with first-line treatments. One pathway was a primary care path on which all patients started treatment. The other pathway was a secondary, or specialist, care path on which patients who demonstrated an insufficient response to a second-line therapy were referred. Escitalopram (10 - 20 mg/day) was compared with citalopram (20 - 40 mg/day) and venlafaxine (75 - 150 mg/day). Two parallel cost-effectiveness analyses, comparing escitalopram with citalopram and escitalopram with venlafaxine, were carried out.
Outcomes assessed in the review
The outcomes assessed in the review were the remission rates, remission rate after titration, relapse rate and adverse events. Non drug-specific inputs were:

for primary care, premature discontinuation, remission rate after switch, relapse rate after switch, relapse rate after discontinuation, titration after failures, suicide attempt and death due to suicide attempt; and

for secondary care, switch after referral, titration after referral, augmentation after referral, response after titration, relapse, premature discontinuation and relapse rate after discontinuation.

Study designs and other criteria for inclusion in the review
Most of the effectiveness outcomes were derived from RCTs.

Sources searched to identify primary studies
For non drug-specific inputs, the authors searched MEDLINE, EMBASE and the Cochrane Library for the years 1966 to 2004 for publications in the English language. The search terms were "depression", "MDD", "naturalistic", "management" and "Belgium". No details of other searches were reported.

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
The search for non drug-specific inputs revealed no detailed studies of pharmacotherapy in naturalistic settings in Belgium. Details of other searches were not reported.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
Drug-specific outcomes.

The remission rates for escitalopram versus citalopram were 52.8% (95% confidence interval, CI: 47.3 - 58.3) versus 43.5% (95% CI: 38.2 - 48.8), and for escitalopram versus venlafaxine, 69.9% (95% CI: 62.4 - 77.3) versus 69.7% (95% CI: 62.1 - 77.3).

The remission rate after titration was 36.2% (95% CI: 24.9 - 49.2) with escitalopram, 23.8% (95% CI: 14.9 - 35.8) with citalopram and 36.2% (95% CI: 24.9 - 49.2) with venlafaxine.

The relapse rate with escitalopram, citalopram, venlafaxine was 12.5% (95% CI: 8.3 - 16.7).

Adverse events for escitalopram versus citalopram were 2.6% (95% CI: 1.0 - 6.7) versus 3.8% (95% CI: 1.7 - 8.1), and
for escitalopram versus venlafaxine, 8.0% (95% CI: 4.2 - 13.1) versus 11.0% (95% CI: 7.0 - 17.5).

**Methods used to derive estimates of effectiveness**
A randomly selected group of psychiatrists and general practitioners (GPs), identified through professional listings, were surveyed by mail. Approximately two thirds of the sample were GPs and one third was psychiatrists. Thirty-one psychiatrists and 109 GPs participated in the survey. Moreover, the authors stated that assumptions within the model were checked with a panel of experts to be sure that they reflected current practice in the study setting.

**Estimates of effectiveness and key assumptions**
The rates obtained through the survey were:

for the primary care model, titration after failure (76%); and

for secondary care, switch after referral (3.9%), titration after referral (75.3%) and augmentation after referral (20.8%).

**Measure of benefits used in the economic analysis**
The measures used were the number of treated patients and the number of successfully treated patients.

**Direct costs**
The direct costs to the health service were evaluated. For each branch of the decision tree, the numbers of drug resource units, GP and psychiatrist visits, attempted suicides, deaths due to suicide, and hospitalisations were estimated. The quantities and the costs were reported separately, and their estimated was based on actual data or derived using modelling (secondary care). The quantities and cost data were obtained from a review of the literature, as well as an ad hoc survey. No details on the dates to which resource use referred were reported. The price year was 2003. Discounting was not relevant as the time horizon of the model was 6 months.

**Statistical analysis of costs**
The costs were treated stochastically. CIs were reported.

**Indirect Costs**
The authors calculated the indirect costs attributed solely to lost productivity (expressed as absenteeism from work). This cost was calculated using the friction method, and was derived from an article published by Hutubessy 1999 (see 'Other Publications of Related Interest' below for bibliographic details). It was converted from US dollars ($) to year-2003 Euros after adjustment using the Belgian Consumer Price Index (in 2003, Euro 1.0 = $1.1 and $1.0 = Euro 0.9). The quantities and the costs were reported separately, and their estimation was based on actual data or derived using modelling. The quantities and cost data were obtained from a review of the literature. No details on the dates to which resource use referred were reported. The price year was 2003. Discounting was not relevant as the time horizon of the secondary care model was 3 months.

**Currency**
Euros (Euro).

**Sensitivity analysis**
The authors performed extensive univariate and multivariate sensitivity analyses using the 95% CI (or feasible ranges derived from the literature) as well as a scenarios analysis. The univariate sensitivity analyses varied the following parameters:
probabilities (i.e. remission rate, remission rate after titration, discontinuation rate due to adverse events, relapse rate, premature discontinuation rate, relapse rate after premature discontinuation, and titration rate);

unit costs (i.e. cost per GP visit, cost per psychiatrist visit, hospitalisation, suicide and attempted suicide, indirect and direct costs associated with secondary care, and cost per workday lost); and

worst-case and best-case scenarios of the number of GP and psychiatrist visits and days absent from work.

Finally, a probabilistic multivariate Monte Carlo sensitivity analysis (10,000 iterations) was carried out on all drug-specific probabilities. The results were presented for escitalopram in incremental cost-effectiveness scatter plots, compared with citalopram or venlafaxine as a reference.

Estimated benefits used in the economic analysis
For escitalopram versus citalopram, the overall success rate at 6 months was higher for escitalopram (62.3%, 95% CI: 60.1 - 64.5) than for citalopram (57.2%, 95% CI: 55.0 - 59.4).

For escitalopram versus venlafaxine, the overall rate of treatment success at 6 months was similar for escitalopram (67.0%, 95% CI: 64.7 - 69.4) and venlafaxine (66.6%, 95% CI: 64.2 - 69.0). No incremental benefits were reported.

Cost results
The authors reported the total average expected costs per patient treated for each strategy.

Escitalopram versus citalopram.
At 6 months, from the insurance system perspective, patients treated with escitalopram accounted for lower total expected direct costs than citalopram, despite a slightly higher drug cost for escitalopram. The total expected costs were Euro 390 (95% CI: 372 - 409) versus Euro 411 (95% CI: 391 - 431).

From the societal perspective, the indirect expected costs represented about 60% of the total costs for both treatments. The total expected costs were Euro 1,162 (95% CI: 1,106 - 1,221) for escitalopram and Euro 1,276 (95% CI: 1,216 - 1,336) for citalopram.

Escitalopram versus venlafaxine. From the insurance system perspective, the total expected direct costs per patient were lower for escitalopram compared with venlafaxine (Euro 333, 95% CI: 313 - 354 versus Euro 350, 95% CI: 330 - 370), with drug costs being the key driver for cost-savings.

From the societal perspective, the expected total costs were Euro 1,002 (95% CI: 938 - 1,070) for escitalopram and Euro 1,036 (95% CI: 971 - 1,102) for venlafaxine.

Synthesis of costs and benefits
Escitalopram versus citalopram.
From the societal perspective, per successfully treated patient at 6 months, escitalopram therapy represented a Euro 365 (19.6%) cost-saving compared with citalopram.

From the insurance system perspective, patients treated with escitalopram accounted for lower total expected costs than citalopram (Euro 626, 95% CI: 577 - 681 versus Euro 719, 95% CI: 658 - 784).

Escitalopram versus venlafaxine.
From the societal perspective, the total expected costs per successfully treated patient were reduced by Euro 34 after 6 months in favour of escitalopram. This difference mainly arose from lower drug costs and lower costs due to absenteeism from work in patients treated with escitalopram.
From the insurance system perspective, the total expected costs per successfully treated patient at 6 months were lower for escitalopram than for venlafaxine (Euro 497, 95% CI: 451 - 547 versus Euro 525 95% CI: 478 - 576).

Authors’ conclusions
The treatment of major depressive disorder (MDD) with escitalopram appeared to be a cost-effective alternative to citalopram and venlafaxine, and led to better clinical outcomes and cost-savings in comparison with citalopram in the model used. The success rates were similar between venlafaxine and escitalopram, but higher total costs were observed with venlafaxine.

CRD COMMENTARY - Selection of comparators
The authors stated that the selection of the comparators was based on "all available competitors". The selected comparators were also the only drugs investigated in head-to-head comparisons of RCTs. You should decide if the technologies analysed represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors carried out a review of the literature. They reported the databases searched, but little else. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The authors used drug-specific data from a meta-analysis of RCTs available in the literature, thus it was not possible to comment on the strengths of these estimations. Non drug-specific data were obtained from a survey and published literature. For the latter, the authors appear to have used the data from the studies selectively. The authors seem to have conducted an extensive sensitivity analysis for the driver parameters within the model. Estimates were investigated using one- and multi-way sensitivity analyses, as well as scenario analysis and probabilistic sensitivity analysis (on all drug-specific probabilities). The authors used 95% CIs as ranges where available.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of benefits. They presented their results in terms of the number of treated patients and number of successfully treated patients. Other measures of health benefits, such as quality-adjusted life-years, would have been better as they could potentially reflect the quantity and quality of life individuals. Moreover, the time horizon for the study was 6 months for the primary care model and 3 months for the secondary care model. These periods seem to be short when trying to reflect the full benefits associated with health interventions in areas like depression.

Validity of estimate of costs
The analysis was performed from the perspectives of the insurance system and society. It seems that all the relevant cost categories for each perspective have been considered. Moreover, all relevant costs for each category seem to have been included in the analysis. The costs and the quantities were reported separately, which makes future replications of the model easier. The quantities were varied in the sensitivity analysis, using ranges obtained from the survey of psychiatrists and GPs. A sensitivity analysis of costs was conducted for each perspective adopted. The price year was reported, which will aid any future reflation exercise. Discounting was not performed as the time horizon was less than one year.

Other issues
The authors compared their findings with those from other studies that, in general, showed the results of their study to be consistent with other evaluations of the cost-effectiveness of escitalopram. The authors addressed the issue of generalisability when they stated that the results of economic evaluations like the ones performed for antidepressants were even less transferable than those of clinical trials. The authors do not appear to have presented their results selectively and their results would seem to reflect the scope of the analysis.

The authors reported some limitations of their analysis. First, some assumptions might have been based on weak data.
For example, the hospitalisation rate could have been inflated because it was assumed that all patients in secondary care were hospitalised when they experienced no response to therapy either after a switch, adding an agent, or a titration plus a switch. In clinical practice, however, hospitalisation may not take place that frequently. Second, there was an absence of data from clinical trials directly comparing escitalopram, citalopram and venlafaxine.

Implications of the study
The authors showed the importance of considering various aspects of patient management and health state, rather than simply considering drug costs, when determining which drugs should be used in the treatment of depression. On the basis of a decision model, the analysis suggested that escitalopram is cost-saving in comparison with citalopram and venlafaxine in the treatment of MDD in Belgium.

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