A probabilistic cost-effectiveness analysis of escitalopram, generic citalopram and venlafaxine as a first-line treatment of major depressive disorder in the UK

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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
Three therapies for the treatment of major depressive disorder (MDD) were examined. These were escitalopram (ESC; 10 - 20 mg daily), citalopram (CIT; 20 - 40 mg daily) and venlafaxine-XR (VEN; 75 - 150 mg daily).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of adult patients (older than 18 years) with MDD. MDD was defined as baseline scores in the range of 18 to 40 inclusive on the Montgomery-Asberg Depression Rating Scale (MADRS).

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

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2004. Some resource use data were estimated from studies published in 1993 and 2003. The price year for the costs was 2003.

Source of effectiveness data
The effectiveness evidence came from a synthesis of completed studies and experts' opinions.

Modelling
A pre-existing cost-effectiveness model was adapted to reflect the treatment of patients with MDD in the UK. In the primary care model, patients receiving one of the three study antidepressants could move to remission, fail due to lack of efficacy, or fail due to adverse events. In the case of failure due to lack of efficacy, the patients were allowed to receive a titration of the initially prescribed antidepressant or to be switched to another antidepressant. Patients who did not respond to their treatment (including those that had a switch or titration) were referred to secondary care. In the secondary care model, patients could again switch to another antidepressant, or receive augmentation of the therapy, titration or hospitalisation. The time horizon was 24 weeks for the primary care model and 12 weeks for the secondary care model. A graphical representation of the whole model was provided.
Outcomes assessed in the review
The outcomes estimated from the literature were:

the remission rates (defined as a MADRS total score $\leq 12$ after 8 weeks of treatment);
the relapse rates;
the rates of adverse events;
the rates of switch, titration, premature stop, relapse, relapse after discontinuation, suicide attempt, death due to suicide attempt, and remission after switch in the primary care model; and
the rates of relapse, premature discontinuation, and relapse after discontinuation in the secondary care model.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature had been undertaken to identify the primary estimates used in the decision model. Limited information on the design of the primary studies was provided. However, the clinical evidence came mainly from a meta-analysis of 4 studies involving a total of 1,472 patients and from head-to-head clinical trials.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
Eight primary studies provided clinical data.

Methods of combining primary studies
In the meta-analysis, the data were combined using a random-effects model with studies weighted by sample size and by between-study variance.

Investigation of differences between primary studies
Not stated.

Results of the review
In the comparison between ESC and CIT, the remission rates were 52.8% (95% confidence interval, CI: 47.3 - 58.3) with ESC and 43.5% (95% CI: 38.2 - 48.8) with CIT.

In the comparison between ESC and VEN, the remission rates were 69.9% (95% CI: 62.4 - 77.3) with ESC and 69.7% (95% CI: 62.1 - 77.3) with VEN.

The remission rate after titration was 36.2% (95% CI: 24.9 - 49.2) with ESC and 23.8% (95% CI: 14.9 - 35.8) with CIT.
The relapse rate was 12.5% (95% CI: 8.3 - 16.7) with each of the three treatments and 27.5% (95% CI: 18.3 - 36.8) with no treatment.

In the comparison between ESC and CIT, the rates of adverse events were 2.6% (95% CI: 1 - 6.7) with ESC and 3.8% (95% CI: 1.7 - 8.1) with CIT.

In the comparison between ESC and VEN, the rates of adverse events were 8.0% (95% CI: 4.2 - 13.1) with ESC and 11.0% (95% CI: 7 - 17.5) with VEN.

In the primary care model, for all drugs:
the rates of switch were 36.1%,
the rates of titration were 63.9%,
the rates of premature stop were 31.3%,
the rates of relapse were 12.5%,
the rates of relapse after discontinuation were 27.5%,
the rates of suicide attempt were 3.1%,
the rates of death due to a suicide attempt were 0.31%, and
the rates of remission after switch were 43.4%.

In the secondary care model, for all drugs:
the rates of relapse were 12.5%,
the rates of premature discontinuation were 31.3%, and
the rates of relapse after discontinuation were 27.5%.

Methods used to derive estimates of effectiveness
The authors made some assumptions to derive the clinical estimates. In addition, a panel of eight psychiatrists was contacted to validate the decision model and to provide treatment pattern data for the secondary care model.

Estimates of effectiveness and key assumptions
The remission rate after titration was 36.2% (95% CI: 24.9 - 49.2) with VEN (assumed equal to that for ESC because of a lack of data).

The rates of titration were 50%, the rates of switch 10.7% and the rates of augmentation 28.6%. The rates of hospitalisation were 10.7% and the rates of community services 78%. The rates of response were 50% after switch, 60% after titration, and 60% after increase.

Measure of benefits used in the economic analysis
The summary benefit measure used was the overall success rate. This was estimated using the decision model. Other model outputs, such as the rate of first-line success (without switch), rate of titration, switch rate and secondary care rate, were also reported.

Direct costs
The analysis of the direct costs was carried out from the perspective of the NHS. The health services in the economic evaluation were drugs, general practitioner visits, and psychiatrist visits. The unit costs were presented separately from the quantities of resources used. Resource use was estimated from published data and experts' opinions. The costs came from drug tariffs, PSSRU, and published studies. The total costs were calculated using a modelling approach. Discounting was not relevant due to the short timeframe of the model. The price year was 2003. The costs from years other than 2003 were transformed to 2003 using the UK Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs (i.e. productivity losses) were included in the cost analysis undertaken from a societal perspective. The indirect costs were calculated using the human capital approach. The unit costs were presented separately from the quantities of resources used. The cost of absence from work was derived from typical UK sources. Resource use was based on the literature. Discounting was not relevant and was not performed. The price year was 2003.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the impact of changes in the unit costs and probabilities on the estimated costs and benefits of the three interventions examined in the study. Best- and worst-case scenarios for resource use were also considered. A Monte Carlo simulation was performed with 10,000 iterations, varying the estimates between the upper and lower limits of the 95% CI. Ranges of values were based on published estimates.

**Estimated benefits used in the economic analysis**
In the comparison between ESC and CIT, the overall success rate was 63.5% (95% CI: 61.5 - 65.4) with ESC and 58.2% (95% CI: 56.3 - 60.3) with CIT. ESC was also associated with higher first-line success (51.2% versus 41.0%), a lower titration rate (27.6% versus 32.6%), a lower switch rate (35.7% versus 47.0%) and a lower secondary care rate (23.0% versus 29.4%).

In the comparison between ESC and VEN, the overall success rate was 68.9% (95% CI: 66.7 - 70.9) with ESC and 68.5% (95% CI: 66.2 - 70.6) with VEN. ESC and VEN were also associated with very similar first-line success, titration, switch and secondary care rates.

**Cost results**
In the comparison between ESC and CIT, the expected total costs per patient were £465 (95% CI: 436 - 493) for ESC and £544 (95% CI: 514 - 573) for CIT from the NHS perspective, and £2,307 (95% CI: 2,179 - 2,439) and £2,636 (95% CI: 2,502 - 2,772), respectively, from the societal perspective.

In the comparison between ESC and VEN, the expected total costs per patient were £376 (95% CI: 342 - 410) for ESC and £415 (95% CI: 382 - 449) for CIT from the NHS perspective, and £1,817 (95% CI: 1,655 - 1,982) and £1,842 (95% CI: 1,677 - 2,008), respectively, from the societal perspective.

**Synthesis of costs and benefits**
The costs and benefits were combined by calculating the average cost-effectiveness ratio.

In the comparison between ESC and CIT, the cost per successfully treated patient was £732 (95% CI: 665 - 807) for ESC
and 933 (95% CI: 850 - 1,023) for CIT from the NHS perspective, and 3,635 (95% CI: 3,338 - 3,963) and 4,519 (95% CI: 4,147 - 4,924), respectively, from the societal perspective.

In the comparison between ESC and VEN, the cost per successfully treated patient was 546 (95% CI: 481 - 618) for ESC and 607 (95% CI: 542 - 677) for CIT from the NHS perspective, and 2,640 (95% CI: 2,363 - 2,669) and 2,693 (95% CI: 2,376 - 3,031), respectively, from the societal perspective.

Incremental cost-effectiveness ratios were not calculated because ESC always dominated both CIT and VEN, which were more expensive and less effective.

The univariate sensitivity analysis showed that the base-case results were robust to variations in both costs and probabilities in the comparison between ESC and CIT. However, the results of the comparison between ESC and VEN were sensitive to the probability values used in the model, thus the two drugs were considered comparable in primary care.

Changes in resource use confirmed the results of the base-case analysis, although wide variations in the total costs were observed.

The Monte Carlo simulation showed that ESC was dominant in more than 99% of the cases for both perspectives in the comparison with CIT. The multivariate sensitivity analysis suggested that, in the comparison with VEN, ESC was dominant in 60.6% of cases from the NHS perspective and in 54.2% of cases from the societal perspective.

The break-even analysis demonstrated that, from both perspectives, ESC remained the dominant treatment option even at an acquisition cost of 0 for generic CIT.

Authors' conclusions
Within the setting of primary care in the UK, escitalopram (ESC) was a cost-effective treatment for major depressive disorder (MDD) in comparison with CIT and was quite similar to venlafaxine (VEN).

CRD COMMENTARY - Selection of comparators
The authors provided a justification for the choice of the comparators. In particular, the new SSRI was compared with both CIT, which was the most available generic drug for patients with MDD, and VEN, which was an alternative SSRI with an increasing market share. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were estimated from published studies, supplemented with experts' opinions when published evidence was not available. It was unclear whether a systematic review of the literature had been undertaken to identify the primary studies. Much of the evidence came from a meta-analysis and UK-specific data. The meta-analysis was based on head-to-head clinical trials and this should enhance the internal validity of the study. However, limited information on the other primary studies was reported. Sensitivity analyses were extensively performed on key estimates, in order to address the uncertainty around some clinical parameters.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. It is not easily compared with the benefits of other health care interventions. The impact of the intervention on quality of life was not investigated, although this might have been an important dimension of health for patients with MDD.

Validity of estimate of costs
The cost analysis was consistent with the two perspectives adopted in the study. The source of the data was appropriate as typical sources were used to derive the costs. Resource consumption reflected UK treatment patterns. Information on the unit costs and quantities of resources used was extensive, which enhances the possibility of replicating the analysis.
in other settings. No statistical analyses of the costs were carried out. The cost estimates were specific to the study setting but were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors reported the results of other economic evaluations of treatments for MDD. Different estimates of costs had been published, but reasons for such differences could not be investigated due to the limited information on the other cost analyses. The authors noted that a simultaneous comparison of the three treatments could not be performed because head-to-head trials had not been published. Thus, two parallel analyses were carried out in the current study. However, the authors noted that an indirect comparison would not have changed the conclusions of the analysis.

Implications of the study
The study results supported the use of ESC for the treatment of MDD within the context of primary care in the UK. The authors suggested that long-term analyses should be carried out to corroborate the results of the current study.

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