Comparison of the cost-effectiveness of milnacipran (a SNRI) with TCAs and SSRIs: a modeling approach

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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 use of selective serotonin re-uptake inhibitors (SSRI), tricyclic antidepressants (TCA), and selective norepinephrine re-uptake inhibitors (SNRI) in the treatment of patients with major depressive episodes.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with major depressive episodes.

Setting
Community and primary care. The study was carried out in France.

Dates to which data relate
Effectiveness data were collected from studies published between 1973 and 1997. Resource use data were collected from a 1992 source. Cost data were collected from 1996-1997 sources. The price year was 1997.

Source of effectiveness data
Effectiveness data were derived from a review of the literature.

Modelling
A 6-month decision analytic model was used to determine the cost-effectiveness of the various treatment strategies.

Outcomes assessed in the review
The review assessed the following outcomes: efficacy, tolerability, response rate and usage of anti-depressant drugs.

Study designs and other criteria for inclusion in the review
Efficacy data were derived from three meta-analyses. The studies included in these meta-analyses were all randomised, double blind trials, with a parallel design and a 6 to 12 week follow-up period.
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
Summary statistics from individual studies.

Number of primary studies included
At least 23 studies were included.

Methods of combining primary studies
Narrative method.

Investigation of differences between primary studies
Not stated.

Results of the review
The results of the review were as follows:

Comparing milnacipran to placebo, a statistically significant difference was found in favour of milnacipran (14.4%, \( p<0.01 \)).

Comparing milnacipran with TCA imipramine, a slight difference was found in favour of imipramine, although this was not statistically significant.

Imipramine had a lower tolerability than milnacipran.

Comparing milnacipran with fluoxetine and fluvoxamine, a statistically significant difference was found in favour of milnacipran (13.9%, \( p<0.02 \)).

The tolerability of milnacipran was comparable to that of fluoxetine and fluvoxamine.

The authors assumed the current efficacy rates of low doses of all anti-depressants to be 50%.

The usage of anti-depressants at full dose was fixed at 90% for SSRIs.

The response rate at optimal daily dose was 67% with TCA, 63% with milnacipran, and 55% with SSRI.

The response rate was 50% with low dose anti-depressant drugs, and 40% with placebo therapy.

The response rate on second line treatment was equal to that on first line.

The probability of second line treatment failure care was 33%.

The probability of relapse while treatment is continued was 25%.

The probability that treatment is stopped before sixth months was 28%.
The probability of relapse while treatment is stopped was 50%.

**Methods used to derive estimates of effectiveness**
Estimates of effectiveness were also derived from experts' opinion (panel of psychiatrists).

**Estimates of effectiveness and key assumptions**
The efficacy of low dose anti-depressant drugs was fixed at 50%. The prevalence of the full dose use of TCAs was fixed at 50%. Usage of milnacipran at full dose would be the same as that of the SSRIs. Relapse estimates were assumed to be independent from effectiveness, and therefore were fixed as equal for the strategies.

**Measure of benefits used in the economic analysis**
The number of weeks that a patient was a responder was used as the measure of benefits.

**Direct costs**
Direct costs were not discounted given the short time frame of the study (less than 1 year). Quantities and costs were reported separately. Direct costs included costs of hospitalisation, anti-depressant medication, visits, and laboratory tests. The quantity/cost boundary adopted was that of the health service. The estimation of quantities and costs was based on actual data. TCAs and SSRIs were valued according to the mean price from a representative panel of the French market. Length of stay in hospital was evaluated according to national statistics collected by the Ministere des Affaires Sociales et de l'Integration. Current tariffs from the Nomenclature Generale des Actes Professionnels were used. The price year was 1997.

**Statistical analysis of costs**
Not reported.

**Indirect Costs**
Not included.

**Currency**

**Sensitivity analysis**
Threshold sensitivity analyses were performed on the following parameters: response rate with low dose anti-depressants, percentage of TCAs used at the recommended dosage, hospitalisation rate following second line treatment failure, hospitalisation cost, and SSRI response rate.

**Estimated benefits used in the economic analysis**
An efficacy was noted of 61.7% with milnacipran, 54.5% with SSRI, and 58.5% with TCA. The number of weeks with anti-depressant treatment response was 12.9 with milnacipran, 12.1 with SSRI, and 12.6 with TCA.

**Cost results**
Total costs were Ffr8,123.49 with milnacipran, Ffr9,084.55 with SSRI, and Ffr8,411.51 with TCA.

**Synthesis of costs and benefits**
Milnacipran is economically dominating both a representative panel of TCAs and SSRIs: milnacipran costs less and is slightly more effective. These results were sensitive to response rates.

Authors’ conclusions
The results suggest that milnacipran is a cost-effective alternative: the expected cost of treatment per depressive episode is lower than either a French representative panel of TCAs or SSRIs. The expected length of clinical remission is slightly higher than comparators. The robustness of these findings was supported by sensitivity analysis.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. You, as a user of this database, should verify whether these health technologies are relevant to your own setting.

Validity of estimate of measure of benefit
A relevant measure of benefits was used. Other measures of benefits such as the number of working days could also have been included. Suicides and suicide attempts were not taken into account. Although the authors do not provide specific evidence of a systematic review of the literature, their estimates are based on three meta-analyses of double blind randomised trials and are therefore likely to have good internal validity. However, limitations were that SSRI and TCA comparators included in the meta-analyses were not representative of current practice in France (being addressed by ongoing research), and there was a lack of primary data regarding the effectiveness (as opposed to efficacy, derived from the RCTs) of milnacipran. In the absence of data, assumptions had to be made based on the opinion of a panel of psychiatrists. Available information regarding the usage of anti-depressants in standard practice was poor or, at least, incomplete. These limitations were, however, taken into account in the sensitivity analyses and the conservative assumptions made in the model's parameters.

Validity of estimate of costs
Only direct costs were included. Indirect costs including productivity lost were not considered. The cost of concomitant drugs was not taken into account. Cost estimates were derived from local sources and are therefore unlikely to be generalisable to other countries. Cost data were based on tariffs and, hence, do not represent true opportunity costs.

Other issues
Adequate comparisons with other relevant studies were made. The generalisability of the results to other settings or countries was not discussed. The authors do not, however, appear to have presented their results selectively. The study enrolled patients with major depressive episodes and this was reflected in the authors’ conclusions.

Implications of the study
Future research should examine anti-depressant drugs that are representative of current practice at the dose generally used in practice.

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