Cost-effectiveness of mirtazapine relative to fluoxetine in the treatment of moderate and severe depression in France

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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 new antidepressant drug mirtazapine was compared with fluoxetine.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with moderate (17-Hamilton-Depression, HAM-D, score of 20 to 25) or severe depression (17-HAM-D score of at least 25) who were aged between 18 and 75 years.

Setting
The setting was primary and secondary care. The economic evaluation was conducted in France.

Dates to which data relate
The effectiveness data were derived from a single study published in 1998. Resource use was established retrospectively in 1999. The price year was 1995/96.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was not carried out on the patient sample in the study, but was estimated by an expert panel.

Study sample
The following data were reported in the parent clinical trial cited by the authors (see Other Publications of Related Interest).

A sample size of 60 patients per group would have an 80% power to detect a difference between the two groups that was 0.5 times the standard deviation of changes from baseline in the individual items of the VAMRS (Visual Analogue Mood Rating Scale), estimated to be 10 the 20% of the range of the scale at a significance level of 5%.

The patients were recruited from outpatient and inpatient psychiatric populations. Female and male patients who
fulfilled DSM-III-R criteria for a major depressive episode, had a total score of at least 21 on the 17-HAM-D, and a score of at least 2 on HAM-D item 1 at the start and end of the placebo washout period, were eligible. The patients were also required to be in a stable physical condition, and were not to be taking any medication that affected serotonin/noradrenalin neurotransmission.

The exclusion criteria were an episode duration of less than 2 weeks or more than a year, bipolar disorder, depressive disorder (unspecified), anxiety disorder, schizophrenia, adjustment disorder, schizotypal or borderline personality disorder, organic mental disorder, eating disorder. Also, epilepsy or seizure history or treatment, alcohol or substance abuse, postpartum depression, or investigator assessment of being at high suicidal risk. Prior nonresponders, patients recently receiving antidepressants or electroconvulsive therapy, pregnant or lactating women, and fast placebo responders, were also excluded.

Of the 151 patients screened for participation, 133 were randomised (66 to mirtazapine and 67 to fluoxetine). Randomisation was conducted using a centrally prepared list. Sixty and 63 patients were included in the intention to treat analysis.

**Study design**
This was a 6-week, multicentre, double-blind, randomised clinical trial. It was carried out in 8 centres in the UK, 7 in Belgium and 5 in the Netherlands, between August 1994 and March 1996. Twenty-seven per cent of mirtazapine-treated patients and 33% of fluoxetine-treated patients were subject to treatment drop-out and did not complete the 6-week trial. Further details were provided by Wheatley et al. (see Other Publications of Related Interest).

**Analysis of effectiveness**
The basis of the analysis was intention to treat. Although the parent trial reported several outcomes, the economic evaluation used adequate response. This was defined as a 50% decrease from the baseline score of the 17-HAM-D instrument. The groups were well matched at baseline.

**Effectiveness results**
In the parent trial, the authors reported that at all assessment points, more mirtazapine patients were classified as responders than those taking fluoxetine. The difference was statistically significant only at day 28, (p=0.006).

Fifty-two per cent of mirtazapine-treated patients and 42% of fluoxetine-treated patients completed the 6-week trial and showed at least a 50% reduction in the 17-HAM-D score.

There was no difference in side effects between the two study arms.

**Clinical conclusions**
In the parent trial, the authors reported that mirtazapine was as well tolerated as fluoxetine, and was significantly more effective after 3 and 4 weeks of therapy.

**Modelling**
Clinical trial data with 6 weeks' follow-up were combined with resource use data obtained from interviews with a French Delphi Panel and the published literature. This enabled a decision model to be constructed of the treatment of moderate and severe depression in France for 6 months. The decision analysis software DATA (version 3.0.8, Treeage, USA) was used.

**Methods used to derive estimates of effectiveness**
The resource use data were derived from a French Delphi Panel as well as authors' assumptions, backed up by published literature.
Estimates of effectiveness and key assumptions
The Delphi Panel estimated the initial outpatient treatment, frequency of visits, mean daily doses of benzodiazepines and their timing, and the treatment of non-compliant or intolerant patients. The panel also assumed that:

- the patients who responded at 6 weeks would continue with the medication for at least 6 months;
- the drugs would be switched if the patients discontinued treatment at 6 weeks; and
- the patients would be unable to work whilst depressed and on social security payments.

The authors made assumptions based on the literature. These related to the patient’s behaviour after the drug switch, 6-month compliance rates, success rates in compliant patients, and the remission rate and resource use in patients who discontinue therapy.

The model assumed that both drugs had similar effectiveness after the initial 6 weeks.

Measure of benefits used in the economic analysis
The measure of benefits was the proportion of successfully treated patients.

Direct costs
Discounting was unnecessary as the time horizon of the model was 6 months. The categories of costs for the social security perspective were antidepressant drugs, psychiatric consultations, concomitant medication, management of drop-outs, and social security payments made to patients while off work. The costs of side effects were excluded since the trial results had shown that the adverse effects were similar. Resource used was estimated through an expert panel, while the costs were derived using modelling. Unit cost data and detailed resource use data were not provided. The costing strategy was published elsewhere (Wheatley et al., see Other Publications of Related Interest).

Statistical analysis of costs
The costs were analysed deterministically.

Indirect Costs
Discounting was unnecessary as the time horizon of the model was 6 months. The indirect costs were estimated as described elsewhere (see Other Publications of Related Interest).

Currency
French francs (Ffr).

Sensitivity analysis
One-way sensitivity analyses assessed the impact on the results of varying the assumptions.

Estimated benefits used in the economic analysis
Six months’ treatment with mirtazapine was associated with an increase in the proportion of successfully treated patients from 15.6 to 19.1% (absolute incremental benefit 3.5%; relative increase 22%).

Cost results
From the social security perspective, the total costs per patient for 6 months were Ffr 22,798.75 for mirtazapine and Ffr...
22,681.61 for fluoxetine.

The incremental cost per patient was Ffr 117 for mirtazapine.

The expected indirect costs were Ffr 98,883 for mirtazapine and Ffr 99,310 for fluoxetine (incremental cost of fluoxetine Ffr 427 per patient).

**Synthesis of costs and benefits**
The cost of each additional patient successfully treated with mirtazapine, instead of fluoxetine, was Ffr 3,343 at 6 months. Also, the expected cost for each patient successfully treated was Ffr 119,494 with mirtazapine versus Ffr 145,408 with fluoxetine.

In the sensitivity analysis, changing the proportion of patients achieving a 50% reduction in 17-HAM-D from its baseline value of 52% to 54.5% (without changing the baseline fluoxetine values) resulted in mirtazapine being dominant.

Changing the proportion of patients who were unable to work had a negligible effect on the comparative results.

An increase of almost double the mirtazapine acquisition cost did not alter its cost-effectiveness.

Social security payments for time off work accounted for 86% of the expected direct costs.

Antidepressant acquisition costs accounted for 1 to 3% of the direct costs.

**Authors’ conclusions**
The study showed that, despite differences in the acquisition costs, compared with fluoxetine, mirtazapine is potentially a cost-effective antidepressant in the treatment of moderate to severe depression in France.

**CRD COMMENTARY - Selection of comparators**
The authors stated that fluoxetine was the most common antidepressant in the French setting, thus making it an appropriate comparator. The authors did not state why they chose to exclude other older antidepressants still in use at the time of the study, such as tricyclic drugs, which may have altered their results. However, they did state in the discussion (and cited a study in support of this contention) that mirtazapine is a cost-effective alternative in comparison with tricyclic antidepressants. You should judge if this omission is reasonable in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data came from a 6-week, double-blind, randomised, multicentre trial, which was not described in detail in this paper. As is usually the case, although depression needs chronic treatment, the trial follow-up was only for 6 weeks. The extrapolation to 6 months was carried out using a decision model that used expert judgement and assumptions based on the literature.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The use of the cost per additional successfully treated patient, although intuitive, makes it difficult to compare the authors’ results with other psychiatric conditions, and impossible to compare them with other non-psychiatric health problems. However, it does enable comparisons to be made with other depression-specific economic evaluations.

**Validity of estimate of costs**
This analysis focused on patients with moderate to severe depression. The authors gave no justification for why they excluded hospitalisation costs due to depression or suicide attempts. Their inclusion would probably have resulted in
little change in the incremental results. The unit costs were not reported separately from resource use. The quantities were estimated through an expert panel since trial data were unavailable, and a partial sensitivity analysis was undertaken. The sources of the unit costs were not given, although a reference to the costing methodology was provided.

**Other issues**
The authors compared their results with other studies. The issue of generalisability to other settings was partially discussed, and the sensitivity analyses enhanced the generalisability of the results. The authors reported some limitations of the study. First, the results were based on a decision model that extrapolated 6-week trial results to a 6-month horizon. The model should be updated when new data become available. Second, the Social Security Fund and indirect costs were overestimated because of the assumption that no patient was able to work. However, the authors stated that, although a proportion could be able to work, their productivity would be diminished and they would therefore still generate indirect costs through lost productivity.

**Implications of the study**
In a setting with payment to patients during their time off work, this cost category is the main cost driver. Any therapy that enables the patients to return to work more quickly will significantly reduce direct costs to the Social Security Fund. Mirtazapine increased the proportion of successfully treated patients with a small additional cost over 6 months. It also demonstrated that it could be potentially cost-effective, compared with fluoxetine, in the treatment of moderate and severe depression in France. The authors stated that these data should be updated when local and longer term data become available to update the model.

**Source of funding**
None stated.

**Bibliographic details**

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
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