Treatment options in moderate and severe depression: decision analysis supporting a clinical guideline

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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 present study compared pharmacotherapy with and without psychological therapy for the treatment of moderate and severe depression. The antidepressant therapy protocol consisted of daily 40 mg fluoxetine and outpatient care. Added to this protocol was a cognitive-behavioural therapy (CBT) that comprised 16 sessions lasting for an average of 50 minutes each. Both therapies were conducted for 3 months and had a 12-month follow-up period. An additional scenario of intensive clinical management of antidepressant therapy, additional care over and above what would usually be provided in routine care by the National Health Service (NHS), was also evaluated. Fluoxetine was selected because of its low toxicity in overdose and because it was the most widely prescribed antidepressant in 2002 in England. The CBT was selected on the basis that it had a relative large, high-quality evidence base in comparison with other psychological therapies.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The target population for the model comprised patients suffering from moderate and severe depression, defined according to the Hamilton Rating Scale for Depression and the range of cut-off scores proposed by the American Psychiatric Association.

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

Dates to which data relate
The studies used for the effectiveness evidence dated from 1981 to 2005 and those for the cost data from 2000 and 2003. The price year was the financial year 2002/03.

Source of effectiveness data
The evidence was derived from a review or synthesis of studies.

Modelling
A decision analysis model was developed to compare both strategies with a 15-month time horizon (3-month initial treatment and 12-month follow-up) and no maintenance therapy.
Outcomes assessed in the review
The outcomes included were:

- the probability of the patients being treated successfully;
- the absolute risks of treatment non-completion, no remission during treatment, and relapse at the 12-month follow-up for the pharmacotherapy strategy; and
- the risk differences in treatment non-completion, no remission during treatment, and relapse at the 12-month follow-up for the combination therapy strategy.

Study designs and other criteria for inclusion in the review
A systematic review of the literature was performed to identify randomised controlled trials comparing psychological therapies with other treatments. The search was conducted from inception to January 2002 and was updated to August 2004. Data for CBT, behaviour therapy, short-term psychodynamic psychotherapy, interpersonal therapy, couples therapy, problem-solving therapy and non-directive counselling were reviewed.

Sources searched to identify primary studies
CINAHL, MEDLINE, EMBASE and PsycINFO databases were searched. In addition, the reference lists of identified studies were screened and known researchers in the field were contacted.

Criteria used to ensure the validity of primary studies
Trials were included if the randomisation method of treatment allocation was adequate and if a masked assessor undertook efficacy ratings.

Methods used to judge relevance and validity, and for extracting data
Two independent reviewers initially assessed the studies. To preserve the robustness of the estimated effect sizes, data were not extracted if more than 50% of the treatment group left treatment for any reason.

Number of primary studies included
From 5,292 retrieved citations, 29 studies were included in the clinical systematic review of CBT.

Methods of combining primary studies
The clinical evidence was synthesised using a meta-analysis.

Investigation of differences between primary studies
Data were pooled using a fixed-effect model unless significant heterogeneity was present that could not be explained by sensitivity analyses, in which case a random-effects model was used.

Results of the review
The results of outcomes assessed in the review were as follows:

- for the pharmacotherapy strategy, the absolute risk was 30% for treatment non-completion, 70% for no remission during treatment, and 55% for relapse at the 12-month follow-up; and
- for the combination therapy strategy, the risk difference was -6% in treatment non-completion, -18% in no remission during treatment, and -17% in relapse at the 12-month follow-up.
All of the parameters used in the decision model were listed in the study with their respective confidence intervals (CIs) and sources.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). The quality of life weights were obtained from a systematic review of the economic evidence of depression (National Collaborating Centre for Mental Health 2005, see ‘Other Publications of Related Interest’ below for bibliographic details). The authors also expressed their results as the incremental cost per successfully treated patient.

Direct costs
The direct cost categories of the initial treatment protocols included medication costs, staff costs, dispensing fees, and subsequent health care resource use. These were calculated using estimates based on the expert opinion of the Guideline Development Group, the literature and a systematic review of the economic evidence (National Collaborating Centre for Mental Health 2005). To calculate the treatment cost, UK-specific unit costs were obtained from the British National Formulary, the Personal Social Services Research Unit and the Prescription Pricing Authority. Cost data for the subsequent treatment of depression were taken from published research and covered hospitalisation, visits to the emergency department, outpatients and general practitioner, community psychiatric nurse and community mental health team visits, and medication costs. The original estimate was adjusted to 2002/03 prices using the Hospital and Community Health Services inflation index. Discounting was not carried out as the costs were incurred during less than 2 years. The price year was 2002/03.

Statistical analysis of costs
The costs were treated deterministically and no statistical tests were carried out.

Indirect Costs
No indirect costs were reported.

Currency
UK pounds sterling (£).

Sensitivity analysis
An extensive sensitivity analysis was carried out to explore the uncertainty around different input values and assumptions. A univariate sensitivity analysis was carried out for all parameters. Uncertainty around the various risk difference estimates, quality of life weights and the likely cost of subsequent depression treatment were analysed separately. The scenario of intensive clinical management of antidepressant therapy was also explored, as most of the trials from which the effectiveness estimates were derived used this protocol. In addition, a probabilistic analysis was conducted to assess the joint uncertainty between the different parameters and to estimate the 95% uncertainty interval around the cost-effectiveness ratios. Appropriate distributions were assigned for each parameter estimate. Monte Carlo simulation was used to recalculate estimates 10,000 times. Finally, cost-effectiveness acceptability curves were used to show the decision-makers’ maximum willingness-to-pay for an additional successfully treated patient or QALY.

Estimated benefits used in the economic analysis
Over the 15-month analysis period, the average gain in QALYs from combination therapy was 0.11 per patient with severe depression and 0.04 per patient with moderate depression.

The QALYs per person with severe depression were 0.52 for the pharmacotherapy treatment and 0.63 for the combination therapy.
The QALYs per person with moderate depression were 0.84 for the pharmacotherapy treatment and 0.89 for the combination therapy.

The probability of successful treatment was 0.14 for pharmacotherapy, and 0.29 for the combination therapy (a benefit of 0.16 for the combination therapy).

Cost results
The total health care cost per person was 660 for the pharmacotherapy treatment and 1,297 for the combination therapy. This represented a total difference of 637 over 15 months.

Synthesis of costs and benefits
The cost-effectiveness of combination therapy was calculated to be 4,056 per additional successfully treated patient. This resulted in a cost per QALY gained of 5,777 for severe depression and 14,540 for moderate depression.

The univariate sensitivity analysis showed that the results were robust to the investigated input parameters and assumptions. The cost-effectiveness estimates were most sensitive to the difference in the risk of no remission at the end of treatment between the two treatment strategies.

The probabilistic analysis showed that the 95% CI around the cost per additional successfully treated patient was between 1,400 and 18,300. When taking the patients' quality of life into consideration, there was a 97% probability that combination therapy would be more cost-effective than antidepressant therapy alone for severe depression (95% CI: 1,900 to 33,800 per QALY) and an 88% probability for moderate depression (95% CI: 4,800 to 79,400 per QALY) at a 30,000 decision-makers' maximum willingness-to-pay per QALY in the UK. In contrast to severe depression, however, the probability of cost-effectiveness for moderate depression was greatly affected by the maximum willingness-to-pay value. At values lower than 30,000 per QALY, the uncertainty around the cost-effectiveness of combination therapy greatly increased for patients with moderate depression.

Authors' conclusions
When considering the number of successfully treated patients for both moderate and severe depression, an additional benefit of combination therapy over pharmacotherapy alone was observed. However, when the patients' quality of life was also included, the analysis showed that there were greater gains for patients with severe depression versus those with moderate depression. The authors concluded that combination therapy is likely to be a cost-effective first-line secondary care treatment for severe depression, but that it was much more uncertain from the currently available evidence whether its use is cost-effective for moderate depression.

CRD COMMENTARY - Selection of comparators
The authors provided a justification for the comparators. Specifically, there had been little research on the comparative cost-effectiveness of antidepressant therapy and combination therapy, and their selection was recommended by the Guideline Development Group. You should judge whether these strategies are relevant in your own setting, or whether other comparators from other drug classes and psychological treatments could also have been relevant.

Validity of estimate of measure of effectiveness
The authors performed a good-quality systematic review of the literature. This helped ensure that all data available were used in the model. The estimates of effectiveness were combined using a meta-analysis and were derived credibly from the primary studies. The authors used data from published sources. The estimates were investigated by sensitivity analyses using ranges from the literature, and the authors provided specific details of the types of analyses used.

Validity of estimate of measure of benefit
The authors used QALYs, derived from modelling, as the primary measure of benefits. This measure of benefit enables
cross health technology comparisons. The methods used to derive utility scores were reported elsewhere and the source reference was reported. Sensitivity analyses of utilities scores were conducted and the range values were reported.

**Validity of estimate of costs**
The authors reported that the study had been conducted from an NHS perspective and appropriate costs for that perspective were included. The direct costs were reported in sufficient detail, with resource use quantities and costs presented separately along with their references and sensitivity ranges. The sources of the unit costs were reported. A statistical analysis of the costs was not undertaken. Sensitivity analyses of cost variables were conducted to assess the robustness of the estimates used. The costs were not discounted as they were incurred during less than 2 years. The estimations of the quantities and the costs were derived using modelling. The fact that the price year and revaluation of costs were reported will aid any future reflation exercise.

**Other issues**
The authors made appropriate comparisons of their findings with those of other studies, and their conclusions reflected the scope of the analysis. They explicitly addressed the generalisability of the results, stating that the findings were likely to be generalisable across high-income countries. Several limitations were also reported. First, the probability of overestimating a successful outcome for both treatment options based on trial data. Second, the use of studies dating from the 1980s (though more recent studies suggested they were applicable). Third, the scarcity of QALY estimates for depression. Fourth, the relatively short time horizon justified by the lack of direct clinical evidence. Fifth, the possibility that individual CBT might be less resource intense in the future. Finally, the omission of productivity costs, which might have improved the cost-effectiveness of combination therapy from a societal perspective.

**Implications of the study**
Although the initial treatment cost of combination therapy is substantially higher, these costs are partially offset by savings accruing from lower treatment costs in the subsequent year. Targeting combination therapy at severe forms of depression could be a more efficient way of using limited resources. The choice of combination therapy as a first-line treatment for either moderate or severe depression might be affected in countries with different thresholds for society's maximum willingness-to-pay for an additional health benefit.

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**Other publications of related interest**
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