The cost-effectiveness of mirtazapine versus paroxetine in treating people with depression in primary care
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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 mirtazapine, a noradrenergic and specific serotonergic antidepressant, versus paroxetine, a selective serotonin reuptake inhibitor, for the treatment of patients with depression in primary care. The doses examined were 30 to 45 mg/day mirtazapine and 20 to 30 mg/day paroxetine.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with depression who were treated in general practice. Males and females fulfilling DSM-IV criteria for a major depressive disorder, with a baseline score of greater than 18 on the 17-item Hamilton Rating Scale for Depression (17-HAMD), met the inclusion criteria.

Setting
The setting was primary care. The economic study was conducted in Scotland, UK.

Dates to which data relate
The effectiveness evidence and health care resources were obtained from a clinical study published in 2003 (see Other Publications of Related Interest). Prices relating 2001/2002 were used.

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

Link between effectiveness and cost data
The costing was conducted prospectively on the same patient sample used in the effectiveness analysis. A sub-group of patients participating in the effectiveness study was selected for the economic analysis, and the effectiveness data used in the economic analysis referred to this sub-group of patients.

Study sample
Patients were recruited from general practices in the greater Glasgow area of Scotland. Power calculations had been undertaken to determine an appropriate sample size for the detection of differences in the clinical efficacy measures. In total, 197 patients were randomised to either mirtazapine (n=99) or paroxetine (n=98). Fourteen were excluded from
the analysis. Of these, 4 mirtazapine and 5 paroxetine patients were lost to follow-up, 1 mirtazapine and 4 paroxetine patients dropped out early, and 2 paroxetine patients did not participate any further. In addition, one of the mirtazapine group refused to participate in the study, while in the paroxetine group, one discontinued because of lack of efficacy, another was hospitalised as a result of a concomitant disease, and another did not fulfil the selection criteria.

The remaining 177 patients (93 in the mirtazapine group and 84 in the paroxetine group) formed the sub-group used in the economic analysis. The effectiveness data used in the economic evaluation referred to this sub-group of patients. The mean age of the patients was 40 years (range: 17 - 74) and 74% were females. There was no evidence of whether the initial study sample and the sub-group used in the economic analysis were appropriate for the clinical study question. Further details on the parent clinical study can be found in another publication (see Other Publications of Related Interest).

**Study design**

The study was a double-blind, randomised controlled trial. Randomisation was performed according to centrally prepared randomisation lists. No further details on the methods of randomisation or blinding were provided. The study was conducted in general practices in the greater Glasgow area of Scotland, UK. The duration of follow-up was 24 weeks. Assessments were performed at baseline and at weeks 1, 2, 4, 6, 8, 12, 16 and 24, or on premature withdrawal. Twenty patients were excluded from the analysis: 6 from the mirtazapine group and 14 from the paroxetine group. This was due to loss to follow up, drop outs, discontinuation of treatment effectiveness, one hospitalisation and one non-fulfilment of the study criteria.

**Analysis of effectiveness**

The effectiveness analysis was based on patients for whom data were available. The primary health outcome was the change from baseline on the 17-HAMD. The primary measure was also expressed as the number of patients classed as HAMD responders (i.e. patients with a 50% decrease in the 17-HAMD score from baseline to the assessment point). A secondary outcome also used in the economic study was the improvement in quality of life, as assessed using the Quality of Life in Depression Scale (QLDS). The patient groups were comparable in the majority of demographic characteristics. There were no significant differences in baseline characteristics between the sub-group included in the economic analysis and those patients excluded. It was not reported whether any adjustments for confounding factors were made.

**Effectiveness results**

The group, mean 17-HAMD scores decreased from baseline at all assessment points in both treatment groups.

At all assessments, with the exception of week 8, the magnitude of reduction was greater for the mirtazapine group. It reached statistical significance over paroxetine at weeks 1, 2 and 4.

The number of HAMD responders at the 24-week end point was 59 (63%) in the mirtazapine group and 47 (56%) in the paroxetine group, (p=0.31).

The change in QLDS score from baseline to the 24-week end point was 13 in the mirtazapine group and 9 in the paroxetine group, (p=0.021).

**Clinical conclusions**

Both antidepressants were efficacious for 24 weeks of treatment in depressed primary care patients. Compared with paroxetine, mirtazapine was associated with greater improvements in quality of life.

**Measure of benefits used in the economic analysis**

Two measures of benefit were used in the economic analysis. These were the number of HAMD responders (i.e. patients with a 50% decrease in the 17-HAMD score) and the change in QLDS score (from baseline), at the 24-week
end point. These were derived directly from the effectiveness results.

**Direct costs**
The direct costs consisted of health service costs and the costs of social services. The health service costs were those associated with treatment and concomitant medication, contact with specialists (e.g., general practitioners, community psychiatric nurses, physiotherapists and other health care professionals), hospital outpatient services, and acute and long-term inpatient care. The costs of social services were associated with counselling or social worker services, and police custody. The costs and the quantities were reported separately. Resources use was derived from actual data collected alongside the effectiveness study. The unit costs were derived from the British National Formulary (medication), the National Health Service Schedule of Reference costs (outpatient attendances), and published literature (contact with health and community professionals, and inpatient services). All unit costs were based on 2001/2002 estimates. Discounting was not necessary, as the costs were incurred within 24 weeks, and was not carried out.

**Statistical analysis of costs**
The costs were treated stochastically. All the results were reported as mean values +/- the standard deviation (SD), with 95% confidence intervals (CIs) where applicable. Differences in the mean costs between treatment groups were calculated. The mean costs were compared using Student’s t-test. The robustness of these results was confirmed using parametric bootstrapping techniques to account for any non-normality in their distribution.

**Indirect Costs**
The indirect costs consisted of patient productivity losses. The days off work and reasons for absence were recorded for patients in part-time and full-time employment. An estimate of lost productivity due to sickness-related absence from work was derived from these data, using the human capital approach. Wages were assumed as a proxy measure of lost production. The 2001 national average wage rates taken from published literature were used. Days off work per patient were provided. Discounting was not undertaken as it was not necessary.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
One-way sensitivity analyses were conducted to examine the responsiveness of cost results to changes in specific cost estimates. The scenarios examined were the reduction in cost of primary care general practitioner consultations (following an assumed 50% reduction in consultation time), the unit cost of a hospital inpatient stay for both an acute stay and a long stay, and the cost of paroxetine if a generic treatment price was assumed. The choice of variables and ranges examined was not justified.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The mean, total NHS cost per patient was 1,408 (SD=1,777) in the mirtazapine group and 1,528 (SD=2,022) in the paroxetine group. The difference was -120 (95% CI: -750 - +377; p=0.51).

The mean, total societal cost per patient was 1,850 (SD=2,314) in the mirtazapine group and 2,225 (SD=3,662) in the paroxetine group. The difference was -375 (95% CI: -1,125 - +385; p=0.32).

The costs were incurred over 24 weeks (the duration of the study). The cost of treating adverse events was included in the overall cost of treating patients with depression.
**Synthesis of costs and benefits**

The costs and benefits were not combined in the form of incremental cost-effectiveness ratios because there were no significant differences in the costs. In addition, there were no significant differences in the benefits between the two groups when the number of HMAD responders was the outcome considered. However, improvement in quality of life was shown to be significantly higher with mirtazapine than with paroxetine, (p=0.021). These results were robust under all scenarios examined in the sensitivity analysis.

The results were also presented in the form of cost-effectiveness acceptability curves. In this case, each additional point improvement in 17-HAMD score was given a monetary value, and the probability of the cost-effectiveness of mirtazapine versus paroxetine was estimated. If society were willing to pay nothing for a point improvement in depressive syndromes, there was an 80% probability that mirtazapine would be more cost-effective than paroxetine. If the willingness-to-pay increased to 1,000, this probability rose to 89%. At values of willingness-to-pay up to 20,000, the probability of cost-effectiveness of mirtazapine was still greater than 80% (83%).

**Authors’ conclusions**

The results of the study suggested that, compared with paroxetine, mirtazapine might be a cost-effective treatment choice for depression in a primary care setting.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparators was implicitly justified, as both represented novel antidepressant agents that were established in primary practice. You should consider whether any of these agents represents widely used practice in your own setting.

**Validity of estimate of measure of effectiveness**

The basis of the analysis was a double-blind, randomised controlled trial, which is considered the "gold" standard method for the evaluation of effectiveness. The study sample was likely to have been representative of the study population. However, the effectiveness analysis used in the economic evaluation considered a convenient sub-group of patients that completed the 24 weeks of the study period (i.e. no patients who were lost to follow-up, dropped out early, or discontinued were included in this subgroup). Therefore, the analysis was subject to potential selection bias. Nevertheless, it was reported that patients excluded from the sub-group did not differ from the patients included in terms of baseline characteristics. It was stated that the two patient groups were, with minor exceptions, comparable in terms of demographic characteristics. The sub-group used in the economic analysis consisted of treatment completers only. No further statistical analyses, to account for potential biases and confounding factors, were undertaken.

**Validity of estimate of measure of benefit**

The estimation of benefit was obtained directly from the effectiveness study. Two measures of benefit were used in the economic analysis. In one case (HAMD response rate), the therapeutic equivalence of the treatment alternatives was demonstrated. These measures are disease-specific, so the results from this economic analysis are not comparable with those of analyses on other diseases.

**Validity of estimate of costs**

It was stated that the study adopted both NHS and societal perspectives. Most of the categories of cost relevant to these perspectives were included in the analysis. However, neither the direct costs to the patient, nor the family or carer costs, were included. The authors recognised this to be a limitation of the analysis. Intangible costs, such as the psychological effects of caring for people with depressive illness, were also excluded from the analysis. The costs and the quantities were analysed separately and the date to which the prices related was reported. This enhances the transferability of the results and improves the generalisability. The authors considered another limitation of their study was the fact that the costs of treatment medication were based on the exposure rate to medication, rather than stochastic data. A statistical analysis of the costs was provided. However, it was acknowledged that the demonstrated lack of statistical difference in
costs might have arisen from an insufficient sample size, as no power calculations were undertaken specifically for the economic analysis. A sensitivity analysis of some cost estimates, including mainly unit costs, was performed. Discounting was not necessary, as all the costs were incurred during 24 weeks, and was not carried out.

**Other issues**
The authors mainly compared their clinical findings with those of other studies. The issue of generalisability to other settings was addressed. The focus on intermediate outcomes, rather than the long-term outcomes of mortality and morbidity, was implicitly considered to be a further limitation of the study. The results of the study were reported in full and the authors' conclusions reflected the scope of the analysis.

**Implications of the study**
The authors suggested that the treatment of depression with mirtazapine might be a cost-effective alternative to paroxetine when prescribing in primary care. However, when considering improvements in quality of life following the administration of these two agents, it can be inferred that mirtazapine should be considered the treatment of choice.

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**Other publications of related interest**

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