Cost-effectiveness and cost-utility of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine: randomised controlled trial

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 study examined three treatments for adult patients with depression. The treatments were selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and lofepramine (LOF).

The dosage of TCAs varied with age. For patients aged between 18 and 65 years, the daily dose 50 mg, rising in 25-mg weekly steps to a maximum of 150 mg. For patients older than 65 years, the daily dose was 25 mg, rising in 25-mg weekly steps to a maximum of 120 mg.

The dosage of SSRIs varied with drug. The daily dose of fluoxetine was 20 mg throughout. For paroxetine, the daily dose was 20 mg, increasing to 30 mg after 3 weeks and to a maximum of 40 mg after 6 weeks. For sertraline, the daily dose was 50 mg, increasing after 3 weeks to 100 mg and after 6 weeks to a maximum of 150 mg.

The daily dose of LOF was 70 mg, rising in weekly 70-mg increments in divided doses to a maximum of 210 mg.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised adults diagnosed with depression. Patients accepting antidepressant treatment were also eligible, including those with co-morbid physical or mental illness and those aged over 65 years. Those already taking antidepressants, younger than 18 years old, pregnant, breastfeeding, terminally ill, confused, with insufficient English language skills, or temporarily resident in the UK were excluded. Patients who were prescribed antidepressants for indications other than depression (e.g. chronic pain) were also excluded.

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

Dates to which data relate
The effectiveness and resource use data were gathered from October 1999 to April 2002. The costs were expressed using 2001/02 prices.

Source of effectiveness data
The effectiveness evidence was derived from a single study.
Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were not performed for clinical outcomes. Patients were referred by their general practitioner (GP) and were visited by study researchers for enrolment. Of the 388 patients initially contacted, 61 were excluded (2 did not meet the inclusion criteria and 59 refused to participate). Thus, 327 patients were randomised, 113 to the TCA group, 109 to the SSRI group, and 105 to the LOF group. Of these 327 participants, 239 (73%) received a primary diagnosis of a depressive disorder, 40 (12%) of anxiety disorder and 48 (15%) no identifiable psychiatric diagnosis. The number of female participants was 76 in the TCA group, 71 in the SSRI group, and 72 in the LOF group. The numbers of patients in the age class 17 - 59 years were 94 (TCA), 92 (SSRI) and 99 (LOF), respectively.

Study design
This was a prospective, randomised, open-label, clinical trial that was carried out at several centres in the UK. Randomisation was performed by telephone and was stratified by referring GP. At recruitment, patients were informed that, if they or their doctor preferred, an alternative treatment could be prescribed from a different class to that allocated at random. Of the 327 participants, 92 patients were finally prescribed a different class of antidepressant. Doctors prescribed using UK recommended dosages and continued treatment for 6 months after remission of the depressive episode, or for at least 12 months if the patient had experienced two or more depressive episodes within the past 5 years. Therefore, the length of follow-up was 12 months. Full data on the outcome measures were available for 254 patients at 3 months (78%), 203 (62%) at 6 months, 188 (58%) at 9 months and 171 (52%) at 12 months, with no significant difference in completeness between the groups. The authors stated that blinding was not performed as it was impossible to mask researchers to group allocation.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. All outcome measures were self-completed. The primary clinical measure was the number of weeks free from depression, defined as a score of below 8 on the Hospital Anxiety and Depression Scale - Depression sub-scale (HADS-D). Other clinical outcomes were measures of psychiatric symptoms, such as the Clinical Interview Schedule - Revised (CIS-R), a measure of general health status (the 36-item Medical Outcomes Study Short Form, SF-36), and quality of life (EuroQol EQ-5D questionnaire). Linear interpolation of missing values was performed. Differences in the number of weeks free from depression were adjusted by baseline HADS-D scores. A multilevel generalised model was used to adjust for differences in baseline EQ-5D scores. The baseline comparability of the study groups was not explicitly discussed, but it is likely that there were no differences in the patients' characteristics given the randomisation process.

Effectiveness results
The proportions of patients who were prescribed a different class of drug differed significantly between allocated classes: 42% for TCAs, 27% for LOF and 16% for SSRIs, (p=0.001).

No statistically significant differences between the groups were observed in any outcome measure. For example, the numbers of depression-free weeks over 12 months were 25.3 (95% confidence interval, CI: 21.3 to 29.0) for TCAs, 28.3 (95% CI: 24.3 to 32.2) for SSRIs and 24.6 (95% CI: 20.6 to 28.9) for LOF, (p=0.327).

Clinical conclusions
The effectiveness analysis showed that the three treatments were equally effective.

Measure of benefits used in the economic analysis
The summary benefit measures were the number of disease-free weeks and quality-adjusted life-years (QALYs). The number of disease-free weeks was obtained directly from the effectiveness analysis. The QALYs were estimated by
applying a tariff of health state values, based on a representative UK sample, to the utility scores from the EQ-5D. Discounting was not relevant as the benefits were estimated during a short timeframe.

**Direct costs**
The analysis of the costs was carried out from the perspective of the health system. It included the costs of medications, visits to GPs at surgery, contacts with GP by telephone, home visits by GPs, contacts with practice nurse at surgery, home visits by district nurse, contacts with community psychiatric nurses, visits to counsellor, attendance at day centre, attendance at non-psychiatric hospital clinic, contacts with psychiatrist, visits to accident and emergency department, psychiatric inpatient stay, and inpatient stays. The quantities of resources used were reported, but the unit costs were not. The unit costs were derived from several published sources, including cost studies and typical NHS sources. Resource use was estimated directly from the clinical records of patients included in the effectiveness study. The costs were expressed using 2001/02 values. Discounting was not relevant as the costs were incurred during a short timeframe.

**Statistical analysis of costs**
The costs were presented as mean and median values. Power calculations were performed. These showed that 260 evaluable patients per group at follow-up would have been required to demonstrate equivalence of the total costs (within 5% of the expected mean log cost).

**Indirect costs**
The indirect costs were not included in the economic evaluation.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
In a sensitivity analysis, only those patients who actually received an initial prescription from the randomised class were included. Further, an alternative definition of “depression-free” was employed (using a cut-off HADS-D score of below 11). The issue of uncertainty was handled by bootstrapping the costs and benefits with 5,000 replications and by generating cost-effectiveness acceptability curves.

**Estimated benefits used in the economic analysis**
The numbers of depression-free weeks over 12 months (based on repeated-measures analysis of variance) were 35.5 for the TCA group, 36.6 for the SSRI group and 34.8 for the LOF group. The differences were not statistically significant.

The average numbers of QALYs, adjusted for baseline EQ-5D, were 0.55 (95% CI: 0.48 to 0.61) for the TCA group, 0.59 (95% CI: 0.52 to 0.64) for the SSRI group and 0.55 (95% CI: 0.49 to 0.61) for the LOF group.

**Cost results**
The expected mean 1-year costs per patient were 762 (+/- 1,136) (median 359; 95% CI: 553 to 1,059) in the TCA group, 875 (+/-1,566) (median 503; 95% CI: 675 to 1,355) in the SSRI group and 867 (+/-1,907) (median 384; 95% CI: 634 to 1,521) in the LOF group.

Costs in all prescriptions and in antidepressant prescriptions only were significantly different between the groups (with higher figures in the SSRI group), but differences in the total costs did not reach statistical significance. (p=0.09).

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility ratios were calculated in order to combine the costs and benefits of the
alternative strategies.

The incremental cost per depression-free week gained was 32 with SSRI over TCA, 59 with SSRI over LOF, and 183 with TCA over LOF. The cost-effectiveness acceptability curve showed statistically non significant differences in benefits and costs.

The incremental cost per QALY gained was 5,686 with SSRI over LOF and 2,692 with SSRI over TCA, while TCA was dominant in comparison with LOF.

The sensitivity analysis showed that, if an additional depression-free week was valued at less than 20, LOF would be likely to be the most cost-effective and SSRIs the least cost-effective. However, if an additional depression-free week was valued at above 50, SSRIs would be likely to be the most cost-effective and TCAs the least cost-effective, although the differences were small. For the cost-utility analysis, for values placed on an additional QALY of more than 5,000, the cost-utility of SSRIs was likely to be greatest, with little difference between the other two groups. In particular, for a willingness-to-pay for a QALY of between 20,000 and 30,000 there was a 60% probability that SSRIs would be the most cost-effective strategy, as against approximately 20% for the other two strategies.

Authors' conclusions
The analysis showed a lack of statistically significant differences in costs and benefits among the three treatments considered for patients with depression in primary care. Rough estimates of cost-effectiveness suggested that selective serotonin reuptake inhibitors (SSRIs) might be the most cost-effective strategy.

CRD COMMENTARY - Selection of comparators
The authors did not explicitly justify their choice of the comparators, although the comparators appear to have represented widely used treatments for depression. The analysis was based on typical UK primary care antidepressant treatments. The dosages were accurately reported in an appendix. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a clinical trial, which was appropriate for the study question. The method of randomisation was described and should have reduced the impact of selection bias. Extensive information on the approach used to select the sample of participating patients was reported, and patient refusals and exclusions were described for different assessment points. It was unclear whether the study groups were well balanced at baseline, not only in demographics but also in terms of clinical aspects. However, the authors applied appropriate statistical models to adjust for potential baseline differences between the groups. The trial was open-label, thus assessment bias might have affected the results of the study. Further, the sample size was not justified, which might explain the lack of statistically significant differences between the groups in all outcome measures. The length of follow-up appears to have been appropriate. The analysis of the clinical study was conducted on an intention to treat basis and although an alternative sample of patients was also considered, the results for this group were not clearly reported. The evidence came from several centres, which increases the representativeness of the patient population.

Validity of estimate of measure of benefit
Two benefit measures were used in the analysis. The first measure was disease-specific and is common only to other interventions for patients with depression. Therefore, it would be difficult to compare it with the benefits of interventions for other diseases. However, the use of QALYs as a benefit measure in the framework of the cost-utility analysis improves the comparability with the benefits of other interventions. Details on the calculation of the QALYs were provided.

Validity of estimate of costs
The analysis of the costs was consistent with the stated perspective. The authors stated that the impact of using a wider
perspective (i.e. societal) was unclear. A detailed breakdown of the cost items was provided. Extensive information on the quantities of resources used was reported, although the unit costs were not presented. However, information on resource consumption could be transferred to other settings. The costs were derived from several sources, although there was little information on these sources. Statistical analyses were carried out to deal with the skewed distribution of the costs and with the issue of uncertainty in some estimates. The price year was reported, thus facilitating reflation exercises in other time periods. Power calculations were carried out for the analysis of the costs, but the sample of patients included in the study was smaller than that required to show cost-neutrality.

Other issues
The authors stated that their results were similar to those reported in previous economic evaluations of antidepressants. The issue of the generalisability of the study results was not explicitly addressed and few sensitivity analyses were carried out. The use of bootstrapped estimates for the costs and benefits highlighted the uncertainty surrounding differences in these estimates. The authors pointed out both strengths and drawbacks of their analysis. One of the most relevant strengths was the naturalistic design of the effectiveness analysis. The use of dosages reflected usual practice. Further, patients' or physicians' preferences for treatment were accounted for in the study. The most important limitation of the analysis was the failure to recruit the desired number of patients. The robustness of the comparison was also limited by the loss to follow-up.

Implications of the study
The study results support the National Institute for Clinical Excellence guidelines on depression which recommend SSRIs as first-choice antidepressants in primary care.

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