Cost of depression: effect of adherence and treatment response
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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
Three strategies for the management of patients with depression were studied. These were a compliance-enhancing programme (CP), a therapeutic drug monitoring (TDM) intervention, and a control strategy. The CP (RHYTHMS) included educational material with information covering typical issues and recovery patterns associated with the successful treatment of depression. For TDM patients, plasma levels of sertraline and desmethyleraline were determined on two occasions during the treatment period and reported back to the general practitioners (GPs) for continued discussion with the patients. Control patients were treated in accordance with the GPs' clinical routine.

Type of intervention
Treatment.

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

Study population
The study population comprised adult patients with a diagnosis of depression. The main exclusion criterion was contraindication for and/or interactions with sertraline.

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

Dates to which data relate
The effectiveness and resource use data were gathered from June 1999 to February 2003. The costs were expressed using 2002/03 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 analysis.

Study sample
Power calculations, if performed, were not reported. Overall, limited information on the primary trial was given. Of the 114 GPs that were invited to participate in the study, 93 were involved and recruited an overall sample of 1,031 patients. Reasons for exclusion and patient selection criteria were not described. At baseline, the mean age was 48.4 (+/- 14.36) years in the whole group and the proportion of men was 28.1%. A total of 57.8% of patients had
experienced a previous depressive episode, while 40.7% had previously used antidepressant treatments.

**Study design**
This was a prospective, randomised, open-label clinical trial that was carried out in several primary care centres. The unit of randomisation was the GP (cluster randomisation). Thus, each GP included patients in only one treatment arm. The initial treatment phase was 24 weeks, but total follow-up was 2 years. The loss to follow-up was not reported.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on an intention to treat basis. The primary health measures were rate of adherence, rate of response and quality of life.

Criteria for treatment adherence performed at weeks 4, 12 and 24 weeks were:

- detectable serum levels of sertraline and/or desmethylsertraline;
- self-reported assurance that the patient had taken sertraline as prescribed; and
- scheduled visits performed within the stipulated time frames (4 +/- 1, 12 +/- 4, and 24 +/-2 weeks).

Response at 24 weeks was defined as a reduction of at least 50% on the Montgomery-Asberg Depression Rating Scale, a Clinical Global Impression Scale-Severity score of between 1 and 3, and a Clinical Global Impression Scale-Improvement score of 2 at the most.

Health-related quality of life data were estimated using the EuroQol questionnaire at week 24, year 1 and year 2. Quality-adjusted life-years were then calculated by combining longevity and quality of life in one single measure over the 2-year period.

The authors did not discuss the baseline comparability of the study groups.

**Effectiveness results**
Overall adherence to treatment during the first 24 weeks was 40.5%. No statistically significant difference between the groups was observed.

The overall response rate at 24 weeks was 66.6%. The response rate was 71.0% in the CP group, 68.1% in the TDM group and 60.5% in the control group.

The difference between the CP and the control groups was statistically significant, (p=0.014), while the difference between the TDM and the control groups was not statistically significant, (p=0.14).

The response rate was 82.5% for adherent patients and 55.8% for non-adherent patients, (p<0.001).

Health-related quality of life improved by 0.16 from baseline to year 2 in the whole group, (p<0.001), but no differences between groups were observed.

Improvements were more pronounced amongst adherent than non-adherent patients.

The difference in quality-adjusted life-years was 0.27, favouring the group of adherent patients. Similarly, responders showed statistically significant improvements in quality of life in comparison with non-responders, (p<0.0001).

**Clinical conclusions**
The effectiveness analysis showed that CP improved treatment response in comparison with the GP’s clinical routine. However, similar improvements in quality of life and treatment adherence were observed among the different
Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was carried out.

Direct costs
The analysis of the costs was carried out from a societal perspective. The direct medical costs included were for GP visits, specialist visits, nurse visits, psychotherapy visits, bed-day at hospital ward and at nursing home, medications and compliance-enhancing interventions. The unit costs were presented for most items but information on resource use was not extensively reported. Resource use was based on data derived directly from the clinical trial. The accuracy of patient-reported data was checked against GP records. The costs came from different sources, such as the Uppsala County Council, the Uppsala University Hospital, the National Insurance Board, Pharmaceutical Statistics and a published study. The costs were updated to 2002/03 values using the Consumer Price Index for Sweden. Discounting was not relevant since the costs were incurred during a 2-year period.

Statistical analysis of costs
The costs were compared amongst groups assuming a chi-squared distribution and using generalised estimation equations with Wald chi-squared tests. Missing cost data were imputed using a regression analysis.

Indirect Costs
The indirect costs (i.e. productivity losses associated with depression) were included, which was appropriate given the societal perspective. The traditional human capital approach was used to assess the value of sick leave. Average earnings plus payroll taxes were used as a proxy for productivity. The unit costs were presented but the quantities of resources used were not. As in the analysis of the direct costs, discounting was not relevant and the costs were expressed as 2002/03 values.

Currency
Swedish kroner (SEK) and Euros (EUR). The exchange rates for 2002 were SEK 1 = EUR 0.11 = 0.10 US dollars ($).

Sensitivity analysis
Sensitivity analyses were not carried out.

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

Cost results
The average costs (during 2 years) per patient in the whole group were SEK 363,000 (EUR 38,953). Indirect costs accounted for 87% of the total costs (SEK 315,000 or EUR 33,802). The cost of the intervention (CP) represented 0.1% of the total costs.

The average cost per patient was SEK 383,000 (EUR 38,953) in the CP group, SEK 355,000 (EUR 38,094) in the TDM group and SEK 350,000 (EUR 37,558). Differences amongst the groups were not statistically significant.

Adherent patients had slightly higher average total costs than non-adherent patients (SEK 371,000 or EUR 39,811 versus SEK 358,000 or EUR 38,416), but the difference was not significant. The average total cost per patient for responders was SEK 299,000 (EUR 32,085), which was substantially lower than the average of SEK 491,000 (EUR
52,688) for non-responders, (p<0.0001).

**Synthesis of costs and benefits**
A synthesis of the costs and benefits was not relevant as a cost-consequences analysis was carried out.

**Authors’ conclusions**
Adherence to treatment represents a key aspect of treatment for major depression. Patients who responded to treatment had considerably lower costs and higher quality of life than those who did not respond to therapy. However, the study demonstrated that the two interventions examined in the study (a compliance-enhancing programme and therapeutic drug monitoring) were more effective than no treatment, but did not improve patient adherence.

**CRD COMMENTARY - Selection of comparators**
The authors did not provide an explicit justification for the choice of the comparators, which were the relevant comparators in the primary clinical trial. 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. Limited information on the approach used to select the sample of participating patients was reported, and it was not stated whether some patients refused to participate or were excluded for any reason from the initial study sample. Statistical analyses were carried out to test the significance of differences between the groups. The length of follow-up was appropriate. The use of intention to treat enhanced the internal validity of the analysis. It was unclear whether the study groups were comparable at baseline. The evidence came from several GPs, which makes the study sample representative of the patient population. Further, the authors stated that the naturalistic design of the study represented a strength of the analysis. These issues should be considered when assessing the internal validity of the analysis.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the ‘Validity of estimate of measure of effectiveness’ field (above).

**Validity of estimate of costs**
The choice of a societal perspective for the analysis was appropriate. As such, all the relevant categories of costs appear to have been included. The indirect costs were estimated using a validated approach. Unit costs were given for most items but little information on resource consumption was provided. This could limit the possibility of replicating the analysis in other settings. Statistical analyses of the costs were carried out to deal with missing data and the non-normal distribution of costs. The sources of the data were reported. Resource use referred to a large sample of patients. However, the authors noted that the sample size might not have been adequate to detect statistically significant differences in the costs. The cost estimates were specific to the study setting and the impact of using alternative cost estimates was not investigated in the sensitivity analysis. The price year (i.e. the financial year) was reported, which will facilitate reflation exercises in other time periods.

**Other issues**
The authors did not make extensive comparisons of their findings with those from other studies, although it was noted that the cost estimates were comparable to those observed in other economic analyses. The issue of the generalisability of the study results to other settings was not explicitly addressed and sensitivity analyses were not performed. Therefore, the external validity of the study appears to have been low. The study referred to depressed patients and this was reflected in the authors’ conclusions.
Implications of the study
The study results suggest that measures that improve response to treatment have a substantial impact on the total costs of care in patients suffering from major depression.

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Other publications of related interest
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MeSH
Antidepressive Agents /blood /economics /therapeutic use; Demography; Depressive Disorder, Major /drug therapy /economics /therapy; Drug Monitoring /economics /statistics & numerical data; Female; Follow-Up Studies; Health Care Costs; Humans; Male; Mental Health Services /economics; Middle Aged; Patient Compliance /statistics & numerical data; Primary Health Care /methods; Quality of Life /psychology; Sertraline /blood /economics /therapeutic use; Social Environment; Surveys and Questionnaires

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