Long-term outcomes of initial antidepressant drug choice in a "real world" randomized 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
Fluoxetine as the initial treatment for depression.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study consisted of patients suffering with major depression, dysthymic disorder, or minor depression without dysthymia. Exclusion criteria were: use of antidepressants within the previous 90 days, current alcohol abuse, current psychotic symptoms, history of mania, recent use of lithium or antipsychotic medication, current pregnancy, or current use of medications that might contraindicate the use of any study drug.

Setting
Primary care clinics of a staff-model health maintenance organisation. The economic analysis was carried out in Seattle, USA.

Dates to which data relate
Effectiveness and resource use data were collected over a 24-month period (no dates were specified). No price years were stated.

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

Link between effectiveness and cost data
Retrospective costing was undertaken on the effectiveness study sample.

Study sample
All patients referred for antidepressant drug therapy were selected for study inclusion if the patient and clinician would accept randomised drug assignment. 536 patients were enrolled. 72% were female. The median age was 41 years (range: 18 - 90 years). 7% of patients were aged 65 or over. 66.8% of subjects were suffering from current major depression (DSM-III-R), 6.7% had dysthymic disorder, and 26.5% had minor depression without dysthymia. No power calculations were reported in the determination of the study sample size.
Study design
This was a randomised, controlled trial (using computer-generated random numbers). Patients were stratified according to the presence of current major depression determined by a structured interview. The follow-up was 24 months. 87% of study subjects completed assessment at 6 months, falling to 71.5% at 24 months. Those missing one or more assessment did not differ significantly in initial treatment assignment, sex distribution, mean age, medical co-morbidity, or mean baseline score on the Hamilton Depression Rating Scale (HDRS) or Hopkins Symptom Checklist (SCL) depression sub-scales. 75.3% of patients were still enrolled in the treatment plan at 24 months. Those disenrolling had a significantly lower mean age (37.4 years versus 44.2 years; t=5.27; p<0.001) and a significantly higher mean baseline score on the SCL depression sub-scale (2.18 versus 2.00; t=2.23; p=0.03). 75% of patients reported previous depressive episodes.

Analysis of effectiveness
The analysis of the clinical study was undertaken on an intention to treat basis. Primary health outcomes were assessed using the HDRS, anxiety and depression sub-scales of the SCL, Medical Outcomes (SF-36) Health Survey, and questions concerning the use of out-of-plan medical and mental health services. The patients in the three groups had comparable baseline characteristics.

Effectiveness results
The effectiveness results were as follows:

There was a significant decrease in the probability of continuing use of the original medication over time (X²=48.4; p<0.001).

Pairwise comparisons found that with the fluoxetine group the likelihood of continuing use of the original medication was significantly lower in patients assigned to receive either desipramine (odds ratio=0.32, Z=5.06; p<0.001) or imipramine (odds ratio=0.47, Z=3.65; p<0.001).

More than 60% of medication switching or discontinuation occurred within the first 6 months of treatment.

HDRS data from months 6 to 24 showed a significant effect of time (F1=44.79; p<0.001).

Over the period of the study, mean SE HDRS score (adjusted for sex, age, baseline HDRS score, previous depression treatment history) was 8.10 for fluoxetine, 7.81 for desipramine, and 8.43 for the imipramine group.

SCL depression sub-scale scores showed a sharp decline in the first 6 months, followed by a gradual decrease.

Adjusted mean SE SCL scores for the period were 0.59 (fluoxetine), 0.54 (desipramine), and 0.63 (imipramine).

No confidence intervals were stated.

Repeated measures analysis found significant effects of time and randomisation group. SE scores (over the 18-month period) were 47.32 (fluoxetine), 49.13 (desipramine), and 46.76 (imipramine).

Clinical conclusions
Initial selection of fluoxetine or a tricyclic antidepressant drug should lead to similar clinical and functional outcomes.

Modelling
Repeated dichotomous measures were analysed using generalised estimating equation (GEE) models with a logistic link via SAS PROC GENMOD (SAS Inc, Cary, NC). Repeated continuous measures were analysed using mixed-model analysis of covariance via SAS PROC MIXED (SAS Inc).
Measure of benefits used in the economic analysis
As the effectiveness study showed similar effectiveness for the three treatments, the economic analysis was reduced to a cost-minimisation analysis.

Direct costs
Direct costs, from the perspective of a health care provider, included inpatient, outpatient, clinical contacts, lab tests and medication/prescription costs (obtained from the Group Health Cooperative's utilisation and cost accounting system). No price year was stated.

Statistical analysis of costs
Costs were reported as means +/- standard deviation using untransformed data. Some significance tests required appropriate transformations: log transformations for categories, which approximated a log-normal distribution (e.g. Total costs) and rank transformation for categories with a large proportion of nonusers (e.g. inpatient costs).

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was performed.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
Total intervention costs were not specifically recorded in the paper and were only presented in a chart. However, mean costs for antidepressant drug prescriptions were approximately $250 higher for the fluoxetine group than for either of the other two treatment regimens. The fluoxetine group had higher inpatient costs than the imipramine group ($1,582 versus $1,400), the comparison of rank transformed costs indicated significantly lower costs in the fluoxetine group, (p=0.02).

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
Initial selection of fluoxetine or a tricyclic antidepressant drug should lead to similar clinical outcomes, functional outcomes, and overall costs. The large minority of tricyclic-treated patients who switch to using more expensive medications blunts differences in antidepressant prescription costs. Restrictions on first-line use of fluoxetine in primary care will probably not reduce overall treatment costs.

CRD COMMENTARY - Selection of comparators
The selection of desipramine, and imipramine as comparators in the treatment of depression was justified in terms of current practice.

Validity of estimate of measure of benefit
The study was of a randomised design, which was appropriate for the study question, and the patient groups were shown
to be comparable at analysis. However it is not clear how the sample size was calculated, nor were any details about the patient groups reported in the paper. It was not clear whether the study sample reflected the study population, although adjustments were made at each stage of follow-up to allow for those switching or not completing their assigned treatment regimen.

Validity of estimate of costs
All categories of costs relevant to the study perspective were included in the analysis. Individual costs and quantities were not reported. Costs were not reported within a particular price year although they were clearly sourced and represented actual costs (and not charges).

Other issues
A sensitivity analysis would have been appropriate to test the study conclusions/assumptions. The authors made appropriate comparisons with other studies. Some comments regarding the generalisability of the results were also made.

Implications of the study
Further analysis is required to substantiate the long-term benefits of using either of the three reported treatments for depression. With an increased emphasis around reducing the numbers of inappropriate inpatient referrals within the UK and reduced inpatient beds within hospitals, adequate treatment regimens must be developed alongside services to divert such activity away from hospitals and back into the community, whilst effectively improving patient outcomes.

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