Effectiveness and medical costs of divalproex versus lithium in the treatment of bipolar disorder: results of a naturalistic clinical 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 compared two medical regimens for the treatment of bipolar disorder. One was divalproex sodium (Depakote; Abbott Laboratories) at a dose of 15 to 20 mg/kg per day. The other was lithium (Eskalith; GlaxoSmithKline) at a dose of up to 1,800 mg/day during acute mania treatment and between 900 and 1,200 mg/day for maintenance therapy. It was reported that the patients continued to receive their usual psychiatric care and that during the patients' hospitalisation the drug dose was titrated in order to achieve better clinical outcomes. In addition, investigators were allowed to prescribe other medications as clinically necessary to treat bipolar disorder.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients (aged 18 years or over), with an American Psychiatric Association DSM-IV diagnosis of bipolar disorder, who had been hospitalised for treatment of an acute manic or mixed episode. All women included in the study who were at childbearing age had to be using effective birth control and not be lactating. Patients with clinically significant focal neurological abnormalities, seizure disorders and various diseases of the nervous system were excluded from the study. Also excluded were those who suffered from drug-induced or AIDS-induced mania, or an uncontrolled medical disorder (e.g. gastrointestinal, renal, hepatic, endocrine, cardiovascular, pulmonary, immunological or haematological disease). In addition, patients included in the study were not allowed to use anticoagulants.

Setting
The setting was community- and university-based psychiatric practices. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were collected between 1995 and 1997. Most of the cost data were received from official sources published in 1997. The price year was 1997.

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

Link between effectiveness and cost data

NHS Economic Evaluation Database (NHS EED)
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Although not explicitly reported, the costing appears to have been carried out prospectively on the same sample of patients as that used in the effectiveness study.

**Study sample**

It appears that power calculations have been conducted retrospectively. The authors reported that the sample sizes had a power of 87% to detect a difference in SF-36 mental component summary (MCS) scores. The standard deviation (SD) was assumed to be 12 and the difference was assumed to be 3 points. A p-value of 0.05 was assumed to be statistically significant.

Overall, 221 patients fulfilling inclusion and exclusion criteria were randomised within 72 hours of initial hospitalisation into the two treatment groups, at a 1:1 ratio, and entered the acute phase of the study (i.e. from randomisation to hospital discharge). There were 112 patients in the divalproex group and 109 in the lithium group. No patients were reported to have refused to participate in the study. One hundred and four (93%) patients from the divalproex group and 97 (89%) from the lithium group entered the maintenance phase of the study (i.e. period between hospital discharge and the 12-month follow up). Based on the criterion that patients included in the analysis had to receive at least one dose of the drug regimens under study and to have completed at least one follow-up assessment, 18 (16%) patients in the divalproex group and 11 (10%) in the lithium group were excluded from the study.

**Study design**

The analysis was based on a multi-centre, open-label, parallel-group, randomised clinical trial. Thirty-three community- and university-based psychiatric practices were involved. Details of the method of randomisation were not reported in the study and no blinding was carried out. The patients were followed up at 1, 3, 6, 9 and 12 months after discharge through telephone interviews. The authors reported that 79 (76%) patients in the divalproex group and 85 (88%) in the lithium group were successfully followed up for more than 10 months, but no reasons for losses to follow-up were reported.

**Analysis of effectiveness**

The analysis was conducted on an intention to treat basis. The patient groups were comparable at baseline in demographic, clinical characteristics and quality of life outcomes. The primary outcomes used in the analysis were:

- the mean time without DSM-IV level manic and depressive symptoms;
- the SF-36 MCS and physical component summary (PCS) scores;
- adverse events; and
- the number of patients who stayed on or discontinued drug mood stabilising therapy at 12 months.

Symptoms of mania and depression were assessed using the Mania Rating Scale and the Depressive Syndrome Scale. The mania and depression components of the World Health Organization Composite International Diagnostic Interview modified for telephone surveys were included in the patient interviews. The Medical Outcomes Study 36-item short-form Health Survey was used to measure SF-36 MCS and PCS scores. The 17-item Mental Health Index was also included in the survey.

Two standard questions on disability days were also included in the interviews. Patients were asked how many days over the previous month their usual activities had been restricted for more than one half-day, and how many days they had spent more than half of the day in bed because of illness.

**Effectiveness results**

The mean number of months without DSM-IV mania and depression was 5.3 (SD=4.6) for the divalproex group and 5.4 (SD=4.4) for the lithium group, (p=0.814).
There were no statistically significant differences between the treatment groups based on the MCS, the PCS, or measures of disability days (the latter results were not shown).

Less than half of the study patients (39% of the divalproex group and 40% of the lithium group) remained on drug treatment for 12 months.

Divalproex-treated patients were less likely to discontinue study medications for lack of efficacy or adverse effects than lithium-treated patients (12% versus 23%; p=0.035). Of those patients who discontinued treatment, 5% in the divalproex group and 8% in the lithium group discontinued because of inadequate efficacy of the treatment while 7% and 14%, respectively, discontinued because of adverse effects.

In the group continuing treatment, the mean PCS scores were no different but there was a trend for improved MCS scores at 6, 9 and 12 months. The mean MCS score was 43.7 with mood stabiliser and 40.7 without mood stabiliser at 6 months, (p=0.194), 44.9 with mood stabiliser and 40.7 without at 9 months, (p=0.057), and 44.0 with and 41.9 without at 12 months, (p=0.280).

Patients who stayed on mood stabiliser therapy experienced less days of restricted activity compared with those who discontinued drug therapy. The difference was statistically significant (mean values 12.8 +/- 2.4 and 23.6 +/- 4.8; p=0.048).

**Clinical conclusions**
The authors concluded that the two treatment options were very similar as far as clinical and quality of life outcomes were concerned.

**Measure of benefits used in the economic analysis**
The authors did not use a summary measure of benefit in the economic analysis. As therapeutic equivalence was demonstrated in the effectiveness analysis the study could be characterised as a cost-minimisation analysis.

**Direct costs**
The health care costs included in the analysis were for hospitalisation, inpatient physician care, emergency room visit, outpatient visit to psychiatrist and physician, outpatient visit to clinical investigator, outpatient visit to non-physician health care provider, home health service visit, and drugs. The costs and the quantities were not analysed separately and the authors only reported summary costs. The quantities of resource use were derived directly from the effectiveness study, while the costs were derived from official published sources. Charges were used as a surrogate for costs. Discounting was not relevant since the costs were incurred during a short time (less than 2 years). All costs were appropriately adjusted for inflation based on the medical component of the Consumer Price Index, and were reported for the price year 1997.

**Statistical analysis of costs**
The authors used the Wilcoxon rank sum test to compare the medical costs between the two groups. A patient-year approach was used to estimate missing resource use values (the mean for all available measurements was carried forward for drop-outs).

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).
Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
The mean, total medical costs were $28,911 (standard error, SE=3,599) in the divalproex group and $30,666 (SE=7,364) in the lithium group, but the difference was not statistically significant, (p=0.693).

The mean total medical costs for the group discontinuing therapy were three-fold higher than those for the group remaining on therapy, (p=0.023). The differences in total costs were primarily due to greater hospital costs ($29,770 versus $6,300; p=0.022) and slightly greater outpatient treatment costs ($3,410 versus $2,366; p=0.273) in the group that discontinued therapy.

Synthesis of costs and benefits
Not applicable, as the study could be characterised as a cost-minimisation analysis.

Authors’ conclusions
Compared with lithium, divalproex maintenance treatment for bipolar disorder resulted in analogous medical costs, clinical and quality of life outcomes. Patients who remained on mood stabiliser therapy had substantially lower total medical costs and better health outcomes than those who discontinued therapy.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was sufficiently justified with reference to their efficacy. You should decide if these represent widely used health technologies in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a parallel-group pragmatic randomised trial, which was appropriate given the study question. The study sample was representative of the study population, and the patient groups were shown to be comparable at analysis. None of the participants in the study was blinded, which might introduce biases. In addition, details of the method of randomisation were not reported, which makes it difficult to comment on the internal validity of the study. The length of the study and loss to follow-up were reported, suggesting that the internal validity of the study was good. The analysis of effectiveness was handled credibly, as the outcomes were analysed on an intention to treat basis and an appropriate statistical analysis was undertaken to take potential biases and confounding factors into account.

Validity of estimate of measure of benefit
As the analysis demonstrated that both treatments were equally effective, only the costs were analysed. A cost-minimisation analysis was conducted.

Validity of estimate of costs
The perspective adopted in the economic analysis was not explicitly reported, but it was not societal since the indirect costs were not included. The costs and the quantities were not analysed separately, which limits the reproducibility of the analysis to other settings. All the quantities of resources used were derived from the effectiveness study and an appropriate statistical analysis was performed. The cost data were derived from published sources but the robustness of the estimates used was not tested in a sensitivity analysis. Hospital charges were used to proxy prices for health care; such charges do not reflect true opportunity costs (due to profit margin) and, in the absence of a cost-to-charge ratio,
may limit the generalisability of the results beyond the authors’ clinical setting. Discounting was not applied, which was appropriate given the short-time horizon of the cost analysis. The price year was reported, thus aiding future reflation exercises.

Other issues
The authors compared their findings with those from other studies and generally found them to be in agreement. They directly addressed the issue of generalisability of the results to other settings by referring to the fact that the study was restricted to patients who had experienced acute mania and necessitated hospitalisation. Therefore, the results of the study can be generalised only to severely ill patients with bipolar disorders. The authors do not appear to have presented their results selectively. The study enrolled patients with bipolar disorder who had an acute mania or mixed episode and this was reflected in the authors’ conclusions.

The authors reported a number of limitations to their study. For example, lithium therapy is not prescribed for rapid cyclers and, as the percentage of these patients in the study was less than 12%, it might have affected the study findings. The serum drug levels were not systematically controlled for during the study and were evaluated based on the clinical experience of the psychiatrists. The authors reported that the sample size did not have adequate statistical power to detect small differences in total medical costs between the two treatment groups.

Implications of the study
The authors did not make any explicit recommendations for changes in policy or practice, nor did they indicate areas for further research. However, their discussion highlighted some areas where more information is needed.

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Other publications of related interest

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MeSH
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AccessionNumber