A pharmacoeconomic model of divalproex vs lithium in the acute and prophylactic treatment of bipolar I disorder

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
Lithium vs divalproex for patients with acute mania in bipolar I disorders.

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost effectiveness analysis.

Study population
Male and female patients with bipolar I disorders who had been hospitalised for acute mania.

Setting
Hospital and secondary care (outpatients). The economic study was conducted in Cincinnati, Ohio, USA.

Dates to which data relate
Effectiveness data were taken from studies published in 1991, 1992, 1994 and 1995. Resource use data were obtained from study reports published in 1995.1994 prices were used.

Source of effectiveness data
Estimates of effectiveness data were derived from a review/synthesis of previously completed studies and expert opinion.

Modelling
A decision analysis model was used in estimating benefits/costs. The model was used in order to deal with the uncertainty in the treatment outcomes and to make up for the lack of studies directly comparing the strategies in question in terms of their clinical and economic impact. The model incorporated four main elements: the time course of onset (embodied in the costs of initial hospitalizations), initial response rate across different subtypes of bipolar disorder patients, side effects associated with each therapy, and relapse rates.

Outcomes assessed in the review
The initial response rate to therapy and rate of side effects were assessed in the literature review.

Study designs and other criteria for inclusion in the review
Study designs were not specified. Only studies published since 1980 in the English language were included in the review. In addition, unpublished data (from the University of Cincinnati Mania Project) were included.

Sources searched to identify primary studies
A literature search was conducted using Paperchase (Ben Israel Hospital, Boston, Ma, USA). In addition to papers retrieved using this search strategy, references cited in these papers were also examined, as were references from a textbook on bipolar disorder.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated. Summary statistics were used to extract data.

Number of primary studies included
Five primary studies were included.

Methods of combining primary studies
The probabilities of response to treatment (by sample sizes) using the two therapies were estimated from the weighted means reported in the studies. Pooling was not possible for incidence of side effects as only one rate was reported for both divalproex and lithium.

Investigation of differences between primary studies
Not stated.

Results of the review
The review determined the following base case values which were used in the decision analysis model. The initial response rates to therapy using lithium were 0.65, 0.40 and 0.41 for classic, mixed and rapid-cycling respectively. For divalproex these rates were 0.45, 0.71 and 0.55 respectively. The overall mean rates were 0.49 for lithium and 0.59 for divalproex. The percentage of patients reporting side effects derived from the literature were 1.7%, 0.85% and 2.4% for lithium, divalproex and using both drugs respectively.

Methods used to derive estimates of effectiveness
A consensus panel was used to derive effectiveness data. This panel consisted of five psychiatrists who were considered by the study authors to be experienced in treating and conducting clinical research in the field of bipolar I disorders. The panelists came from different regions of the United States. Each panellist was sent a postal questionnaire requesting information on resource use and procedures used in prophylactic treatment of individuals using lithium or divalproex. The panel members were also asked to provide relapse rates for each drug, the time to the initial relapse, the number of relapses, probability of hospitalisation following relapse, and the rate of reported side effects treated. The panellists were also interviewed by telephone after completing the questionnaire and mean rates were calculated for use in the decision analysis model.

Estimates of effectiveness and key assumptions
The mean relapse rate for all patients was estimated to be 0.56. The time to first relapse was estimated to be 4.2 months for those that relapsed, (classic 5.0 months, mixed 3.9 months and rapid 3.3 months). The mean number of relapses per patient who relapsed was estimated to be 1.7 (classic 1.3, mixed 1.8 and rapid 2.2). The probability of hospitalisation
given relapse was estimated to be 0.43 for all patients (classic 0.38, mixed 0.45 and rapid 0.49). The percentages of patients who reported side effects and had these treated were 1.1 for lithium, 0.55 for divalproex and 1.5 for patients who had used both drugs. The relapse rate and time to first relapse were based on those in a published study of 1 year of lithium prophylaxis adjusted with a multiplier to take account of the responses of the consensus panel. This multiplier was the rate for subtype in the published study / rate derived from panel for classic patients.

**Measure of benefits used in the economic analysis**
The number of patients freed from relapse (at 1 year), rate of recurrent mania, and side effects avoided.

**Direct costs**
Some quantities were reported separately from the prices. The costs of 1 year of treatment using either lithium or divalproex were estimated. Specifically, these costs included initial hospitalisation (room, services, fees, drugs), administering prophylactic treatment (physician fees, laboratory, side effects and concomitant medications), drug acquisition and treatment of relapse. The boundary adopted was that of the hospital. Quantities of resources used were determined by the consensus panel. Unit prices for physicians fees and laboratory tests were derived from the Physicians Fee and Coding Guide. The costs of inpatient treatment were derived from the California Office of Statewide Health Planning and Development database for 1992. Hospital length of stay was derived from the University of Cincinnati Mania project. The ‘Red Book’ (1994) of wholesale drug prices was used to determine the costs of medications. Prices from 1992 were inflated to 1994 prices using the Hospital and Related services component of the US Consumer Price Index for all Urban Consumers. The final costs were calculated using a model.

**Currency**
US dollars ($)

**Sensitivity analysis**
One way sensitivity analysis was conducted to examine uncertainty in the variability of data. The parameters examined were length of stay in initial hospitalisation, response rate to initial therapy, relapse rate, number of relapses, probability of rehospitalisation following relapse, costs of treating side effects and prophylactic treatment, Medicare prices and prevalence of bipolar disorder subtypes.

**Estimated benefits used in the economic analysis**
From a hypothetical cohort of 10,000 patients with bipolar disorders, hospitalised for acute mania, the expected number of patients freed from relapse with divalproex, relative to lithium, turned out to be 440. (CRD Reviewer’s calculations) 0.85% additional patients in the lithium group experienced side effects compared with the divalproex group. When it was necessary to use both therapies the percentage of patients experiencing side effects increased by a further 0.7%.

**Cost results**
The 1 year costs of treating classic, mixed and rapid cycling patients initially with lithium were estimated to be $31,426, $50,856 and $49,078 respectively. For divalproex these costs were $33,139, $43,672 and $42,792.

**Synthesis of costs and benefits**
The 1 year costs per patient treated with lithium, who successfully responded to the therapy and who had no relapses were $20,348, $26,714 and $24,708 for the classic, mixed mania and rapid cycling subgroups respectively. Similarly the yearly costs per patient for those receiving successful divalproex therapy were $19,721, $22,575 and $16,268 respectively. Length of stay was the only parameter which had an effect on the costs of therapy in the sensitivity analysis. A 30% increase in the length of stay associated with divalproex or a 37% decrease in the length of stay associated with lithium would lead to the costs of treatment being equal for both drugs.
Authors’ conclusions
The authors concluded that the use of divalproex therapy in preference to lithium therapy for the acute and prophylactic treatment of bipolar I disorders could lead to savings per patient of more than the mean annual total medical care expenditure in the US.

CRD COMMENTARY - Selection of comparators
The comparators chosen were the only drug therapies licenced in the US for treating bipolar disorder, i.e. lithium and divalproex.

Validity of estimate of measure of benefit
Since the data sources used in the model were not comprehensive and given the limitations of the model used in the study, the estimate of measure of benefit is not likely to be valid.

Validity of estimate of costs
Since the quantities of resource use were derived from opinion, the validity of the results is doubtful. Adequate details of cost estimation were given. The sensitivity analysis was carried out by varying some parameters in only one direction, according to evidence from the literature. However the literature search was limited.

Other issues
The conclusions reached by the authors were not justified given the uncertainty in the data, in particular with respect to the data on length of hospital stay. The authors reported the generalisability of their study results outside the US as "unknown". No previous study was known which compared the strategies in question in terms of their clinical and economic effects. It is worth stressing that the results reported in the synthesis were related to the subgroup of "successful" patients (those with initial response and no relapse after 1 year). As the authors noted, the costs for this group were much lower than the mean for all patients. Therefore, corresponding cost-effectiveness ratios are not valid for the entire population for which the study was originally designed.

Implications of the study
Well designed controlled trials with prospectively collected data on resource use should be conducted in order to determine the clinical efficacy of the two treatment options, as well as to obtain accurate information on quantities of resources used by the two therapies.

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