Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: 
health-related quality of life and medical cost outcomes

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 use of divalproex sodium and olanzapine to treat acute mania associated with bipolar disorder. Treatment with divalproex was initiated at 20 mg/kg per day, while treatment with olanzapine commenced at 10 mg/day. The doses of both drugs could be increased if symptoms persisted. The maximum daily dose was 20 mg/kg plus 1,000 mg/day for divalproex and 20 mg/day for olanzapine.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with bipolar disorder who experience episodes of acute mania. Patients were eligible for inclusion in the trial if they had a DSM-IV diagnosis of bipolar disorder Type I and scored at least 25 on the Mania Rating Scale (MRS). They also had to be aged between 18 and 65 years, and be hospitalised for an acute manic episode. In addition, female patients of childbearing age were required to be using effective contraception. The exclusion criteria included pregnancy or intention to become pregnant, schizoaffective disorder, unstable medical condition, and alcohol or substance dependence. Other exclusion criteria were a history of intolerance or treatment failure after treatment with divalproex or olanzapine, depot psychoactive medications, or mood disorder secondary to the medical condition.

Setting
The setting was secondary care. The economic study was conducted in the USA.

Dates to which data relate
No dates were reported in the paper.

Source of effectiveness data
The effectiveness data were derived from a single study (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was undertaken prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were not performed before the trial commenced. Post hoc estimates of statistical power to detect significant differences in the outcome measures were 20%. Eligible patients were screened within 3 days of randomisation. Randomisation to divalproex or olanzapine occurred at a ratio of 1:1. In total, 120 patients participated in the trial, 63 received divalproex and 57 received olanzapine. However, only patients with at least one follow-up assessment were included in the economic study. Therefore, the sample size for the economic study was reduced to 52 patients, of which 27 received divalproex and 25 olanzapine.

Study design
The study was a 12-week, randomised, double-blind, double-dummy, parallel-group clinical trial, which was conducted at 21 sites in the USA. Of the entire sample, 78 patients were followed up for more than 21 days. Sixty-three of these 78 patients completed the baseline HRQL interviews.

Analysis of effectiveness
The analyses of the clinical outcomes were based on the initial random assignment, intention to treat principles, and last observation carried forward. However, the economic analysis was based only on those who had at least one follow-up assessment. The primary health outcomes were the MRS from the SADS Change Version and the Hamilton Rating Scale for Depression (HAM-D). Differences between the treatments were evaluated using an analysis of covariance (ANCOVA) with treatment group and baseline score as covariates.

Effectiveness results
No statistically significant differences were found in MRS scores between the two groups at baseline and 3 weeks, or over the 12-week study period, (p>0.05).

Similarly, the HAM-D scores were not statistically significantly different between the two groups at any follow-up period, (p>0.05).

Adverse events occurred with a higher incidence in the olanzapine group than in the divalproex group. These included somnolence (47% versus 29%), weight gain (25% versus 10%), rhinitis (14% versus 3%), oedema (14% versus 0%), and slurred speech (7% versus 0%), (p<0.05 for all comparisons). No adverse events occurred more frequently in the divalproex group.

Clinical conclusions
There were no statistically significant differences in the MRS or HAM-D scores between the divalproex- and olanzapine-treated groups.

Measure of benefits used in the economic analysis
HRQL was measured using:

the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q);

a global measure of quality of life, which rated current health on a scale from 0 (death) to 100 (complete health); and

questions on disability days, that is, the number of days on which usual activities had been restricted and the number of days when the patient was confined to bed due to illness.

These instruments and questions were administered during telephone interviews.

Direct costs
Discounting was not relevant since the costs were incurred during less than one year. The quantities and the costs were not analysed separately. The costs were considered from the perspective of the health care system. Therefore, only
direct medical costs were included in the study. The total direct costs were disaggregated into those incurred while the patient was in hospital and those arising from treatment on an outpatient basis. The costs were estimated using actual data from a number of sources. Although no dates for the cost data were explicitly reported, it would appear that the sources were accessed in 1999.

**Statistical analysis of costs**
A statistical analysis of the costs was carried out using Wilcoxon rank-sum tests.

**Indirect Costs**
No indirect costs were included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
There were no statistically significant differences between baseline and 6 or 12 weeks in the Q-LES-Q domains or global measure of quality of life, (p>0.1 for these comparisons). Likewise, there were no statistically significant differences between the groups in the mean number of restricted activity days, (p=0.78), or bed disability days, (p=0.38).

**Cost results**
The total outpatient costs (mean +/- standard deviation) were $541 (+/- 327) in the divalproex group and $1,080 (+/- 638) in the olanzapine group, (p=0.004).

The emergency room costs were $60 (+/- 157) in the divalproex group and $23 (+/- 87) in the olanzapine group, (p=0.4).

The physician costs were $73 (+/- 101) in the divalproex group and $79 (+/- 144) in the olanzapine group, (p=0.84).

Other professional costs were $28 (+/- 52) in the divalproex group and $18 (+/- 31) in the olanzapine group, (p=0.74).

The study drug costs were $358 (+/- 279) in the divalproex group and $924 (+/- 622) in the olanzapine group, (p=0.002).

Other drug costs were $22 (+/- 31) in the divalproex group and $16 (+/- 34) in the olanzapine group, (p=0.20).

The inpatient costs were $13,162 (+/- 8,693) in the divalproex group and $14,442 (+/- 16,594) in the olanzapine group, (p=0.73).

The total medical costs were $13,703 (+/- 8,708) in the divalproex group and $15,180 (+/- 16,780) in the olanzapine group, (p=0.88).

**Synthesis of costs and benefits**
Not applicable.
Authors' conclusions
Given the comparable clinical and health-related quality of life (HRQL) outcomes between the two groups, the significant savings in outpatient costs for divalproex is meaningful for the clinical management of bipolar disorder and for the mental health system.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. The authors compared divalproex, an established treatment for acute mania, with a more recently approved alternative, olanzapine. You should decide if this is appropriate for your setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from a cohort study, which was part of a larger randomised controlled trial. The inclusion criteria for the economic analysis specified that the patients had to have at least one follow-up assessment. While this may have introduced some sampling selection biases, the authors found that there were no statistically significant differences in baseline variables between the entire sample and the sub-sample included in the economic study. As patients in the sample were hospitalised, the authors acknowledged that the study sample might not have been representative of the entire population of all patients (i.e. including those who were not hospitalised) who suffer from acute mania. Appropriate statistical analyses were undertaken (e.g. ANCOVA) to account for potential biases.

Validity of estimate of measure of benefit
The instruments used to derive the health benefits were appropriate. Since the analysis of clinical and HRQL outcomes indicated that the two treatments were equivalent, the economic analysis concentrated on the costs.

Validity of estimate of costs
The economic perspective adopted was that of the health care system and, therefore, the analysis was limited to the direct medical costs. It appears that all the relevant costs have been included in the analysis. However, it was unclear whether the costs of treating adverse events were included. The unit costs and the resources were not reported separately and the price year was not reported. Therefore, reflation exercises would not be possible. No statistical analysis of the quantities was performed. In addition, a sensitivity analysis was not undertaken. The authors acknowledged that the costs estimated in the trial might overstate those incurred in practice, owing to the inclusion of regular visits from health professionals in the trial protocol.

Other issues
The authors made no direct comparison between their results and those of other studies, although they did refer to other relevant studies. The authors recognised a number of limitations with their study. First, the selection of the sample for the economic study. Second, the lack of generalisability of the results to patients who were not hospitalised. Third, the collection of follow-up data using telephone interviews. The authors also acknowledged that the results were derived from a small sample over a relatively short follow-up period. The duration of the follow-up period is important given the need for long-term maintenance therapy for patients with bipolar disorder. The authors do not appear to have presented the study results selectively and their conclusions reflected the scope of the analysis.

Implications of the study
The authors recommended that the economic findings in this paper should be confirmed in larger prospective, naturalistic studies with a longer follow-up period.

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Other publications of related interest

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