Economic, clinical, and quality-of-life outcomes associated with olanzapine treatment in mania: results from a randomized controlled 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 use of olanzapine (5 - 20 mg) for patients diagnosed with mania.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised male and female patients diagnosed with bipolar disorder, manic or mixed, who met the inclusion criteria following a 2 to 4 day screening phase. The mean age of the patients enrolled was 40.2 years (standard deviation, SD=11.6) for the olanzapine group and 38.7 (SD=10.3) for the placebo group.

Setting
The setting was an institution. The economic study was carried out in a hospital in Cincinnati, USA.

Dates to which data relate
The dates to which the effectiveness and resource use data related, were not stated. The price year was 1995.

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

Link between effectiveness and cost data
The costing was carried out prospectively for the 49-week open label period, and retrospectively for the prior 12 months, using the same sample of patients as that used in the effectiveness study. It was implied that the resource use data were collected similarly.

Study sample
There was no mention of whether power calculations were used to determine the sample size. The patients were randomly allocated into the two groups, but there were no details of how the randomisation was conducted. A total of 171 patients were initially enrolled in the study, of which 139 patients entered the randomisation phase. Seventy received olanzapine (5 - 20 mg) and 69 placebo. From these 139 patients, 113 entered the 49-week open label extension. During the open label extension, 36 (32%) used lithium (786 mg/kg) and 37 (33%) were given fluoxetine (13.5 mg/kg) as adjunctive treatment. Forty-six patients (41%) received neither lithium nor fluoxetine. The reasons for
exclusions or drop-outs were not reported.

Study design
A prospective randomised controlled trial was used for the treatment phase (the method of randomisation was not stated) and the patients were required to remain in hospital for one week. The patients were then randomised to two different treatment arms for the 3-week acute phase. A before-and-after study was carried out for the final 49-week open label extension phase, during which all patients were treated with olanzapine. The study was carried out in a single centre.

Analysis of effectiveness
It was not explicitly stated, and it was difficult to ascertain from the context of the paper, whether the basis of the analysis of the study was intention to treat or treatment completers only. The primary outcomes used in the analysis were clinical and health-related quality of life. Efficacy was measured using the Y-MRS and SF 36. There were no statistically significant differences between the two treatment groups in terms of their age, gender and ethnic origin. The two treatment groups were also comparable at baseline in terms of the scores on the eight dimensions of the SF 36. However, it should be noted that the economic analysis only used the open label phase. Thus, only those results will be reported here. All other results were presented in detail in the paper.

Effectiveness results
The statistically significant mean changes in SF-36 score over the 49 weeks of olanzapine treatment were:

- for bodily pain, 10.1 (SD=24.8), (p<0.01);
- for vitality, -9.3 (SD=25.8), (p<0.01);
- for general health, 5.9 (SD=20.0), (p<0.01);
- for role-emotional, 14.6 (SD=60.0), (p=0.03); and
- for social functioning, 11.6 (SD=35.8), (p<0.01).

The baseline for this analysis was the end of the acute phase.

The mean Y-MRS total score at baseline (end of acute phase) was 19.3 (SD=14.3). At the end of the open label phase, the mean total Y-MRS score was 7.5 (SD=13.5). This corresponded to a statistically significant mean change of 11.8 units, (p<0.01).

Clinical conclusions
The authors concluded that in the 3-week acute phase, patients on olanzapine had a greater mean improvement than those in the placebo group and that, from the quality of life outcomes standpoint, olanzapine patients experienced a statistically significant difference in physical functioning. At the end of the open label extension, the mean Y-MRS total score was statistically significantly different from that at the beginning of the period.

Measure of benefits used in the economic analysis
The authors did not derive a summary measure of benefit. The study has therefore been classified as a cost-consequences analysis.

Direct costs
No discounting was undertaken since the study was conducted over one year. The cost boundary adopted was that of the third-party payer. Although it was not explicitly stated (there were no details on the quantities), it appears as though the
quantities and the costs were analysed separately. The direct costs measured were the inpatient, outpatient and olanzapine costs. The costs were estimated from actual data. The direct cost data came from several sources, including the Health Care Financing Administration, the Monroe Livingston Mental health programme and the National Association of Psychiatric Health systems. All the direct costs were adjusted to reflect 1995 prices. Only 76 of the 113 patients in the open label phase provided the resource use data for both the open label phase and the comparator (the 52 weeks prior to enrolment in the study).

**Statistical analysis of costs**
Student's t-test and analysis of variance were used to make group comparisons on the total scores. The authors reported the mean costs along with SDs.

**Indirect Costs**
An indirect costing was not undertaken since the study was conducted from the perspective of a third-party payer.

**Currency**
US dollars ($)

**Sensitivity analysis**
A sensitivity analysis was not undertaken.

**Estimated benefits used in the economic analysis**
No summary measure of benefit was derived. The study has therefore been classified as a cost-consequences analysis.

**Cost results**
The total cost per month was $649 (SD=399) for olanzapine open label treatment, and $1,533 (SD=2,262) for treatment received for the 52 weeks prior to the study.

Both the inpatient and out patient costs were statistically significantly different, (p<0.01).

Therefore, the total costs of the two treatment periods were statistically significantly different, (p<0.01).

**Synthesis of costs and benefits**
No synthesis of the costs and benefits was undertaken.

**Authors' conclusions**
There were direct cost-savings of almost $900 per month, largely driven by inpatient cost reductions over the open label extension. In terms of quality of life measures, statistically significant improvements from the baseline were seen in five of the eight dimensions. The statistically significant decrease in the vitality score may have indicated a mood stabilising effect associated with olanzapine treatment. The authors also concluded that the study demonstrated that olanzapine had a significant impact in the treatment of mania. Their results suggested that olanzapine might be a cost-effective option for the treatment of acute mania episodes, as well as in the maintenance of response over an extended period of time.

**CRD COMMENTARY - Selection of comparators**
The reason for the choice of the comparators (placebo or no olanzapine) was not explicitly stated. You should decide whether the comparators represent current practice in your setting.
Validity of estimate of measure of effectiveness
The economic study used a within-group comparison, which has the potential for introducing bias and confounding issues. The study sample appears to have been representative of the study population. Although the patients in the acute phase of the study were shown to be comparable at analysis, no details of the 76 patients used for the economic analysis were reported. The open label extension period used fluoxetine and lithium as adjunct treatments, which may have had some effect on the effectiveness results. The authors did not perform any analysis to take into account the effect of using these drugs. The authors also did not elucidate how the drop-outs were handled in the later analysis. There were 139 patients in the initial study and only 113 entered the open label extension phase. Also, only 76 were used in the economic analysis. The authors did, however, explain that the study was initially intended to examine the clinical effectiveness of olanzapine and that the economic analysis was carried out as a secondary analysis. Hence, the lack of rigour in the methodology of the economic analysis.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences analysis.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis, although the drug costs for the 12 months prior to the study were omitted from the analysis. The authors indicated that the omission of these costs was unlikely to have affected the conclusions. No details were provided, but it appears that the costs and the quantities have been measured separately. No statistical analyses of the quantities and prices were performed. Discounting was unnecessary since all the costs were incurred during one year. Charges were used as proxy to the prices. The price year was 1995.

Other issues
The authors made appropriate comparisons of their effectiveness results with findings from other studies, but they did not address the issue of generalisability to other settings. The authors do not appear to have presented their results selectively and they highlighted several limitations of their study. First, although the comparator was placebo for the acute phase, the authors did not know what other medications the patients might have been taking. Second, the study mandated hospitalisations for all patients and that study deigns should be considered when interpreting the results, as the study was designed primarily to assess the clinical outcomes associated with olanzapine treatment. Third, some patients received lithium and fluoxetine, and finally, the sample size was small. The authors clearly indicated that the results should therefore be interpreted with caution.

Implications of the study
The authors highlighted the fact that this study demonstrated that olanzapine has potential for treating mania, but further research is required to assess the outcomes of the different treatment options (for mania) in order to obtain conclusive results. Future studies need larger sample sizes.

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