Budgetary impact of treating acute bipolar mania in hospitalized patients with quetiapine: an economic analysis of clinical trials

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 examined quetiapine, an atypical antipsychotic for the treatment of bipolar mania. Different scenarios were considered on the basis of the proportion of patients using quetiapine with respect to other standard treatments. The analysis focused on a base-case scenario in which 45% of patients were on monotherapy lithium, 25% were on lithium plus risperidone, 25% were on lithium plus olanzapine, and only 5% were on lithium plus quetiapine combination therapy. Two alternative scenarios that involved an increasing use of quetiapine were considered: 40% lithium and quetiapine combination, 25% lithium monotherapy, 20% lithium plus risperidone, and 15% lithium plus olanzapine (alternative scenario 1); 100% quetiapine and lithium combination therapy (alternative scenario 2).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis

Study population
The study population comprised a hypothetical cohort of patients with bipolar I disorder, in an acute mania phase.

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

Dates to which data relate
The clinical data were derived from studies published between 1974 and 2005. Resource use was derived from 1999 data. The price year was 2004.

Modelling
A discrete event simulation model of individual patients was constructed to simulate the history of disease in the different scenarios under examination. The structure of the decision model was described and presented graphically. Individuals began the simulation in the hospital with an acute mania episode and could receive one of the treatment options under analysis. Simulations were then performed for each scenario using weighted random sampling from pre-specified distributions of demographics, disease history, mood and co-morbidities. The time horizon was 100 days. The model considered key aspects such as treatment response and compliance, side effects, suicide risk and death.

Study designs and other criteria for inclusion in the review
The clinical data used in the decision model were treatment effect (determined using the Young Mania Rating Scale, YMRS), rates of non-compliance, rates of extrapyramidal symptoms, other side effects, suicide attempts and mortality rates.

Sources searched to identify primary studies
Treatment effectiveness and most data on side effects were derived from randomised clinical trials (RCTs) on quetiapine. Since there is no direct evidence of differential efficacy with one atypical antipsychotic over another, it was assumed that the treatment effect varied on the basis of the number of medications in the regimen, but not on the specific drugs. Other data came from the published literature, details of which were reported only for a few studies.
Mortality was estimated from US Life Tables for 2000. Mortality in the population of individuals with bipolar disorders came from a Swedish article.

**Methods used to derive estimates of effectiveness**
The primary studies were identified selectively and not through a systematic review of the literature. However, the authors appear to have selected all the quetiapine mania trials in order to obtain treatment effect.

**Measure of benefits used in the economic analysis**
No summary benefit measure was used in the analysis. The key model output was the number of days to remission, which was not combined with the costs. Other model outputs were the percentage of patients responding to the different treatment options at days 21 and 84.

**Direct costs**
The analysis of the costs was carried out from the perspective of the health care payer. It included the costs associated with hospital stay, treatment medications, physician visits, laboratory tests, suicide and the treatment of adverse events. The unit costs and the quantities of resources used were not presented separately, although daily medication costs were reported. The estimation of costs and quantities associated with hospital services was based on an all-payer 1999 acute hospital discharge database from California, Maryland, Massachusetts and Washington. Physician costs and laboratory costs came from the relevant 2002 national Medicare fee schedules. Drug costs were based on Red Book acquisition costs using recommended daily dosages. Discounting was not relevant given the short time horizon of the analysis. The price year was 2004. The medical care component of the US Consumer Price Index was used to inflate previous costs to 2004 values.

**Statistical analysis of costs**
The costs were presented as mean values with 95% confidence intervals.

**Indirect Costs**
Productivity costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
A deterministic sensitivity analysis was undertaken to address the issue of uncertainty in model inputs. Specifically, time horizon, drug costs, hospitalisation costs, age of the patients, initial manic symptom status of the patients, type of reactions to adverse events, and hospital discharge criteria. The use of a discrete event simulation model incorporated the variability and uncertainty in the patient population by randomly sampling on a pre-specified distribution.

**Estimated benefits used in the economic analysis**
The expected number of days to remission was 55 (+/- 0.22) in the base-case scenario, 53 (+/- 0.16) with 40% quetiapine (scenario 1) and 51 (+/- 0.21) with 100% quetiapine (scenario 2).

The percentages of patients responding at days 21 and 84 were, respectively, 43 (+/- 0.39) and 74 (+/- 0.33) in the base-case scenario, 47 (+/- 0.30) and 77 (+/- 0.23) with 40% quetiapine (scenario 1), and 54 (+/- 0.29) and 80 (+/- 0.33) with 100% quetiapine (scenario 2). Thus, increasing the proportion of patients on quetiapine led to better rates of response and remissions.

**Cost results**
The expected total costs were $6,912 (+/- 21) in the base-case analysis, $6,277 (+/- 19) with 40% quetiapine (scenario 1) and $5,525 (+/- 20) with 100% quetiapine (scenario 2).

The reduction in costs was mainly due to a reduction in hospital length of stay with quetiapine.

Overall, the sensitivity analysis confirmed the robustness of the base-case analysis, suggesting that increasing quetiapine
use improved both clinical and economic outcomes. The use of quetiapine also reduced the number of lost workdays, but the impact of this on the total cost was not calculated.

**Synthesis of costs and benefits**
The costs and benefits were not combined as a cost-consequences analysis was performed.

**Authors’ conclusions**
The authors concluded that increased use of quetiapine for the treatment of patients with acute bipolar mania was both economically and clinically convenient from the perspective of the third-party payer in the USA.

**CRD COMMENTARY - Selection of comparators**
The authors provided a justification for the choice of scenarios considered in the analysis. The base-case scenario reflected current practice in the 1999 Florida Medicaid population. The alternative scenarios were selected in order to reflect the effect of increasing the use of the lithium and quetiapine combination. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The clinical data were derived from published sources which appear to have been identified selectively, as the authors did not state whether a review of the literature was undertaken to identify primary studies. A typical source of data (life tables) was used for all-cause mortality. A justification was provided for the other sources chosen. The selection of pivotal RCTs of quetiapine appears appropriate. However, little information on the other sources of data was reported. Treatment effect was simulated over time by means of a quadratic function of YMRS that took account of age, number of treatments and baseline score. This represents a strength of the analysis.

**Validity of estimate of measure of benefit**
No summary benefit measure was used. The model outputs used in the analysis were specific to the disease considered in the study and will be difficult to compare with the benefits of other health care interventions.

**Validity of estimate of costs**
The analysis of the costs was consistent with the authors' stated perspective. Accordingly, the sources of data reflected the perspective of the third-party payer. Similarly, the accounting system used to derive costs reflected the cost/resource boundary of the analysis. The costs were presented as macro-categories and a detailed breakdown of the cost items was not provided. Thus, caution should be exercised if extrapolating the cost analysis to other settings. Some statistical analyses of the costs were performed and the impact of variations in key cost items was investigated in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods.

**Other issues**
The authors reported the results from a few studies on treatments for bipolar disorder. However, direct comparisons with other findings were not made. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the use of sensitivity analysis partly addresses this issue. The authors noted some limitations of the analysis. These were mainly related to the assumptions made in the pivotal clinical trials, where patients were hospitalised during manic episodes, while in the real-world setting most psychiatrists treat patients on an outpatient basis. Furthermore, the short-term nature of the RCTs prevents reliable extrapolation to a long timeframe. A cost-consequences analysis was performed as the study focused primarily on the economic impact of the different treatments. Consequently, the analysis of clinical aspects of therapies was marginal.

**Implications of the study**
The study results support an increase in the use of quetiapine for the treatment of bipolar disorder. The authors suggest that future studies should examine whether compliance rates observed in schizophrenia are a reliable approximation of these data in patients with bipolar mania.

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