The cost-effectiveness of lamotrigine in the maintenance treatment of adults with 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
The study examined several maintenance treatments for adults with bipolar I disorder (BD-I). These were lamotrigine (LAM), lithium (LIT) and olanzapine (OLA). LAM was given at 200 mg/day, LIT at 900 mg/day and OLA at 12.5 mg/day. All treatments were given during the euthymic phase of BD-I for the prevention of episodes of mania and depression.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients deemed to have stabilised BD-I following a mixed/manic BD-I episode.

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

Dates to which data relate
The effectiveness data were derived from studies published between 2000 and 2006. No dates for resource use were explicitly reported. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A Markov model was constructed to simulate the clinical and economic outcomes associated with the four strategies under investigation (LAM, LIT, OLA and no maintenance) in a cohort of patients who entered the simulation once their illness had stabilised, and who were initially assigned to the euthymic state. The model considered three mutually exclusive states (euthymia, mania, and depression). Subsequently, patients either remained euthymic or transitioned either to the acute depression or mania health states. The model took treatment discontinuation into account by allowing patients to switch from the maintenance treatment arm into the no-maintenance arm. The time horizon of the model was 18 months, divided into 6 quarterly transition periods. A schematic representation of the model was given.
Outcomes assessed in the review
The outcomes estimated in the review were a set of transition probabilities and estimates of utility weights.

Study designs and other criteria for inclusion in the review
The primary studies appear to have been identified selectively rather than through a systematic review of the literature. However, two main trials that compared LAM with LIT and a new trial that compared OLA with placebo were considered. Thus, all clinical data came from randomised, double-blinded, placebo-controlled clinical trials. The utility weights were obtained from pivotal trials of LAM and other studies.

Sources searched to identify primary studies
Not relevant.

Criteria used to ensure the validity of primary studies
The randomised and blinded design of the clinical trials ensures a high internal validity of the primary studies.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Six primary studies provided the clinical data.

Methods of combining primary studies
No head-to-head trial was found for the comparison between OLA and LAM, which was subsequently based on indirect comparison. The authors provided clear information on the approach used to pool the primary data in this case. In particular, the risks ratios of modelled events for patients receiving OLA compared with the placebo group were estimated and then multiplied by the absolute placebo rates from the pivotal LAM trial. Differences in patient populations were thus taken into account.

Investigation of differences between primary studies
Not reported.

Results of the review
The probability of having a manic episode in a given quarter was 0.592 with no treatment, 0.111 with LIT, 0.215 with LAM and 0.116 with OLA.

The probability of having a depressive episode in a given quarter was 0.408 with no treatment, 0.143 with LIT, 0.071 with LAM and 0.168 with OLA.

The probability of remaining euthymic in a given quarter was 0 with no treatment, 0.561 with LIT, 0.655 with LAM and 0.617 with OLA.

The probability of an adverse event or a patient withdrawing consent in a given quarter was 0.185 with LIT, 0.059 with LAM and 0.099 with OLA.

The utility value was 0.8 for euthymic state, 0.7 for manic state and 0.4 for depressive mood state.
Measure of benefits used in the economic analysis
The three main outcome measures used in the analysis were the number of acute episodes, number of euthymic days and quality-adjusted life-years (QALYs). Other model outputs, such as the number of manic episodes, number of depressive episodes, days in manic state and days in depression state, were also reported. No discount rate was applied because of the short time horizon.

Direct costs
The analysis was carried out from the perspective of the third-party payer. It included the direct medical costs of drugs for maintenance treatment, drug and hospitalisation for the treatment of acute manic and depressive episodes, and resources of contacts with health care professionals for monitoring and pathology tests. The unit costs and the quantities of resources used were presented separately. The costs were mainly derived from typical US sources such as drug prices from the Red Book. Resource consumption and other costs came from a survey of psychiatrists and primary care providers from a large, vertically integrated health system in the Midwest. Discounting was not relevant since the costs were incurred during an 18-month time horizon. The price year was 2004.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
One- and two-way sensitivity analyses were carried out to assess the robustness of the base-case results to variations in clinical and economic inputs. Scenario and threshold analyses were also performed. Most of the clinical inputs were varied. The sources of the alternative values were unclear. An alternative analysis was also carried out by using an alternative source of clinical data on the effectiveness of LAM and by excluding OLA from the comparison. This alternative clinical trial included bipolar patients with a recent depressive episode rather than bipolar patients with a recent bipolar manic episode, as in the primary study.

Estimated benefits used in the economic analysis
In the cohort of 1,000 patients, the number of QALYs was 1,143 (0.762 per patient per year, PPPY) with LAM, 1,103 (0.735 PPPY) with LIT, 1,038 (0.692 PPPY) with no treatment and 1,109 (0.739 PPPY) with OLA.

In the cohort of 1,000 patients, the total number of manic episodes was 1,418 (0.95 PPPY) with LAM, 1,313 (0.88 PPPY) with LIT, 2,644 (1.76 PPPY) with no treatment and 1,030 (0.69 PPPY) with OLA.

In the cohort of 1,000 patients, the total number of depressive episodes was 598 (0.4 PPPY) with LAM, 1,140 (0.76 PPPY) with LIT, 1,822 (1.21 PPPY) with no treatment and 1,080 (0.72 PPPY) with OLA.

In the cohort of 1,000 patients, the total number of acute episodes was 2,016 (1.34 PPPY) with LAM, 2,453 (1.64 PPPY) with LIT, 4,466 (2.98 PPPY) with no treatment and 2,110 (1.41 PPPY) with OLA.

In the cohort of 1,000 patients, the total number of days in euthymic state was 463,789 (309 PPPY) with LAM, 429,313 (286 PPPY) with LIT, 339,986 (227 PPPY) with no treatment and 441,485 (294 PPPY) with OLA.
Cost results
In the cohort of 1,000 patients, the total direct costs were $59,755,052 ($6,503 PPPY) with LAM, $58,709,608 ($5,806 PPPY) with LIT, $516,083,654 ($10,722 PPPY) with no treatment and $511,092,542 ($7,395 PPPY) with OLA.

Synthesis of costs and benefits
An incremental analysis was carried out to combine the costs and benefits of the alternative strategies.

All three maintenance treatment strategies dominated the no treatment option, which was the least effective (for all outcome measures) and most expensive.

LAM dominated OLA, regardless of the outcome measure (excluding the case of manic episodes).

Compared with lithium, the incremental cost with LAM was $2,400 per episode avoided, $30 per euthymic day gained and $26,000 per QALY gained.

Compared with lithium, the incremental cost with OLA was $200 per euthymic day gained, $7,000 per acute episode avoided and $374,500 per QALY gained.

The sensitivity analysis suggested that the cost-effectiveness ratios were sensitive to variations in the transitional risk probabilities. For example, a 10% increase in the LAM mania quarterly transitional probability produced a 66% increase (from $30.30 to $50.00) in the value of the incremental cost per euthymic day gained.

In terms of the cost-utility, the analysis showed a relatively sensitive (16%) improvement (reduction) in the cost per QALY for LAM from increasing (10%) the euthymic utility. This was in contrast to a relatively insensitive (1.5%) improvement arising from an increase (10%) in the utility of the mania state.

The threshold analysis revealed that the base-case results were robust to reasonable variations in the model inputs. The only relevant result was the dominance of LAM over LIT if the value of the mania risk transitional probability changed to a value of 0.172 from the base-case value of 0.215.

When an alternative source of clinical data was used, LAM was still cost-effective versus no maintenance, with an incremental cost of $20 per euthymic day, $1,300 per acute episode avoided, and $19,400 per QALY. Compared with LIT instead, the incremental cost per euthymic day gained with LAM was $1,043 and the incremental cost per QALY gained was $360,000.

Authors’ conclusions
Both lamotrigine (LAM) and lithium (LIT) were cost-effective maintenance treatments for adults with bipolar I disorder (BD-I) in the USA.

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparators examined in the study, which appear to have been appropriate. In effect, both conventional treatment and new drugs were considered. The dosages were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data used to populate the decision model were obtained from published studies. However, it was unclear whether these studies were identified selectively as the methods and conduct of a systematic review were not reported. The use of clinical trials represents a strong feature of the analysis. The authors used a robust approach to carry out an indirect comparison of the clinical trials from different studies. In terms of the comparability of the two primary clinical trials, the authors stated that, despite the indirect comparison, there were similarities in the study design and patient inclusion criteria. However, the sensitivity analysis showed that the results of the base-case analysis were quite sensitive to variations in the clinical inputs, in particular when efficacy data from an alternative trial
involving a population having recently experienced a manic/mixed (as opposed to a recently depressed episode) were used.

**Validity of estimate of measure of benefit**

QALYs were an appropriate benefit measure because they capture the impact of the interventions on quality of life, which is a relevant dimension of health for adults with BD-I. The instrument used to derive utility was reported, but there was little information on the sources of quality of life data. QALYs are comparable with the benefits of other health care interventions. Disease-specific measures were also reported. Discounting was not performed due to the short timeframe of the analysis.

**Validity of estimate of costs**

The analysis of the costs was consistent with the stated perspective of the study, thus only the direct medical costs were considered. The authors stated that the use of a broader perspective would have been interesting and would have presumably favoured all maintenance treatment strategies. The unit costs and the quantities of resources used were presented separately, which enhances the possibility of replicating the results of the analysis in other settings. Conventional sources for most costs were used. However, the opinions of a panel of experts were used to determine treatment patterns. Some of these assumptions were investigated in the sensitivity analysis. The price year was reported, which will simplify reflation exercises in other time periods.

**Other issues**

The authors stated that their findings were more favourable than those achieved in a recent appraisal by the National Institute for Health and Clinical Excellence in the UK, which recommended that OLA and valproate should both be prescribed to National Health Service patients. The issue of the generalisability of the study results to other settings was not addressed, but several sensitivity analyses were carried out; these enhance the external validity of the study. The authors discussed the possible explanations for the unfavourable results achieved when the effectiveness data were derived from an alternative bipolar trial population (patients with a recent mixed/manic episode) as opposed to the recently depressed population used in the modelled base case.

It was acknowledged that the main limitations of the analysis were related to simplifying assumptions made in the construction of the decision model. Further, the results of the analysis should be restricted to a population of BD-I patients similar to that included in the primary clinical trials used as the source of effectiveness data. Caution will therefore be required when extrapolating the results of the analysis to patients that were excluded from the trials, for example, rapid cyclers. Finally, the authors pointed out that the time horizon of the model was determined by the follow-up of the clinical trials, but the use of a longer perspective would have been interesting given the characteristics of the disease considered.

**Implications of the study**

The study results support the use of LAM as well as LIT as maintenance treatment for BD-I patients. The authors suggested that further research should be undertaken to provide more reliable data on utility weights required for the estimation of QALYs in patients with BD-I. Moreover, the comparative effectiveness of the maintenance treatments examined in the study should be evaluated in a head-to-head clinical trial.

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**Bibliographic details**

Other publications of related interest


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Subject indexing assigned by NLM

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