Newer drugs for treatment of mania associated with bipolar affective disorder

# A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder

C Bridle,[1] S Palmer,[2] A-M Bagnall,[1] J Darba,[2] S Duffy,[1] M Sculpher[2] and R Riemsma[1*]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK

*Corresponding author

## *Executive summary*

*Health Technology Assessment* 2004; Vol. 8: No. 19

**Health Technology Assessment**
**NHS R&D HTA Programme**

# Executive summary

## Background

Bipolar disorder is a relatively common, recurrent and sometimes chronic disorder that leads to harmful effects for the individual's psychological, professional and social welfare. Treatment is dependent on the phase of the disorder being experienced, for example acute mania, depression or maintenance therapy to prevent future manic or depressive episodes. This review is concerned only with the acute treatment of mania.

## Objective

To evaluate the clinical and cost-effectiveness of quetiapine, olanzapine and valproate semisodium in the treatment of mania associated with bipolar disorder.

## Methods

### Search strategy

A wide range of electronic bibliographic and specialist databases were searched from inception to July 2002. In addition, the bibliographies of retrieved articles and submissions received from drug companies were examined.

### Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. Full manuscripts of potentially relevant studies were ordered and assessed for inclusion or exclusion. Disagreements were resolved through discussion. Randomised trials and economic evaluations that evaluated the effectiveness of quetiapine, olanzapine or valproate semisodium in the treatment of mania associated with bipolar disorder were eligible for inclusion.

### Data extraction strategy

Data were extracted into a Microsoft Access database by one reviewer and checked for accuracy by a second. Any disagreements were resolved by discussion.

### Quality assessment strategy

The quality of each clinical study was assessed by one reviewer and checked for accuracy by a second. Any disagreements were resolved by discussion.

The quality of the cost-effectiveness studies was assessed using a checklist updated from that developed by Drummond and colleagues.[24]

### Methods of analysis

Details of the extracted data and quality assessment for each individual study of clinical effectiveness were presented in structured tables and as a narrative description. Where sufficient data were available, treatment effects were presented in the form of relative risks (RR) or mean differences as appropriate. Relative risk and mean difference data were presented as Forest plots but only pooled where this made sense clinically and statistically. Studies were grouped by drug and, within each drug, by comparator used. $\chi^2$ tests of heterogeneity were performed for the outcomes if pooling was indicated.

## Results

### Number and quality of studies

Eighteen randomised trials met the inclusion criteria: five for quetiapine, six for olanzapine, five for valproate semisodium and two in which valproate semisodium and olanzapine were compared directly. Aspects of three of the quetiapine studies were commercial-in-confidence (CIC). The quality of the included trials was limited. Common limitations were lack of adequate randomisation procedures, failure to conceal allocation and lack of intention-to-treat analysis. In addition, the sample sizes were often small (<100 patients), accompanied by high rates of withdrawal and use of proxy rather than actual data, that is, last observation carried forward (LOCF) method. Overall, key methodological criteria were not met in most trials.

### Clinical effectiveness

Treatments versus placebo:

- Quetiapine appears superior to placebo in reducing manic symptoms, but is associated with side-effects such as somnolence, dry mouth and dizziness.

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- Olanzapine appears superior to placebo in reducing manic symptoms, but is also associated with side-effects such as somnolence, dry mouth and dizziness.
- Valproate semisodium appears superior to placebo in reducing manic symptoms, but may cause gastrointestinal side-effects.

Treatments versus lithium:
- There appears to be little difference between quetiapine and lithium in terms of effectiveness, but quetiapine is associated with somnolence and weight gain, whereas lithium is associated with tremor.
- There appears to be little difference between olanzapine and lithium in terms of clinical effectiveness and adverse events.
- There appears to be little difference between valproate semisodium and lithium in terms of clinical effectiveness and adverse events.

Treatments as adjunct to mood stabilisers:
- Quetiapine as adjunct therapy to mood stabilizers may be more effective than placebo in reducing mania and improving global health but it is associated with more dry mouth, somnolence, postural hypotension and asthenia.
- Olanzapine as adjunct therapy to mood stabilisers may be more effective than placebo in reducing mania and improving global health, but it is associated with more dry mouth, somnolence, weight gain, increased appetite, tremor and speech disorder.

Treatments versus haloperidol:
- There was little difference between quetiapine and haloperidol in reducing mania, but haloperidol was associated with more extrapyramidal side-effects, such as akathisia and tremor.
- There was little difference between olanzapine and haloperidol in terms of clinical effectiveness, but haloperidol was associated with more negative implications for health-related quality of life.
- Valproate semisodium was as effective as haloperidol in a small, short-term trial of patients with psychotic features, but haloperidol caused more extrapyramidal side-effects.

Treatments versus other comparators:
- Intramuscular olanzapine and lorazepam were equally effective and safe in one very short (24 hour) trial.
- Valproate semisodium and carbamazepine were equally effective and safe in one small trial in children.

Head-to-head comparison:
- Olanzapine may be more effective than valproate semisodium in reducing mania, but was associated with more dry mouth, increased appetite, oedema, somnolence, speech disorder, Parkinson-like symptoms and weight gain. Valproate semisodium was associated with more nausea than olanzapine.

## Cost-effectiveness

Two studies identified in the systematic review met the criteria for inclusion in the cost-effectiveness review. In addition to these two studies, supplementary economic evidence was submitted by two of the stakeholders (Sanofi-Synthelabo and Eli Lilly). The review of the economic evidence from the literature and stakeholder submissions highlighted a number of significant limitations in existing studies assessing the cost-effectiveness of alternative drugs for the acute manic episode in bipolar disorder.

These limitations meant that it was not possible to make a reliable comparison of the relative cost-effectiveness of the alternative drugs on the basis of existing evaluations in the context of the NHS. To overcome these limitations and to assist the decision-making process in the context of the NHS, a new model was developed. The model is used to provide an estimate of the cost-effectiveness of the alternative drugs when used as part of treatment for the acute manic episode only.

A probabilistic model was developed to estimate costs from the perspective of the NHS, and health outcomes in terms of response rate, based on a ≥ 50% improvement in a patient's baseline manic symptoms derived from an interview-based mania assessment scale. The model evaluated the cost-effectiveness of the alternative drugs when used as part of treatment for the acute manic episode only. For the base-case analysis, a 3-week time horizon was used to reflect the most commonly reported length of follow-up for which the effectiveness data are reported in the clinical trials. Sensitivity analysis was undertaken to determine the robustness of the base-case results to alternative assumptions concerning the additional costs of treating patients beyond the initial 3-week period.

The results from the base-case analysis demonstrate that the choice of optimal strategy is dependent on the maximum that the health service is prepared to pay per additional responder. If the decision-maker is prepared to ►

pay <£7179 per additional responder, then haloperidol is the optimal decision. If the decision-maker is prepared to pay >£7179 per additional responder, then olanzapine is the optimal decision. The relative ordering of strategies based on their mean costs and outcomes is robust to the uncertainty in the cost assumptions used in the base-case model. Under the most favourable scenario in relation to the costs of responders and non-responders beyond the 3-week period considered in the base-case analysis, the incremental cost-effectiveness ratio of olanzapine is reduced to £1236.

## Conclusions

### Clinical effectiveness

In comparison with placebo, quetiapine, olanzapine and valproate semisodium appear superior in reducing manic symptoms, but all drugs are associated with adverse events.

In comparison with lithium, no significant differences were found for olanzapine, quetiapine and valproate semisodium in terms of effectiveness. All drugs were associated with adverse events.

### Cost-effectiveness

Several limitations of the cost-effectiveness analysis exist, which inevitably means that the results should be treated with some caution. These include: (i) the possible bias introduced by using indirect evidence; (ii) the limited timeframe of the analysis and the exclusion of the costs and quality of life impact of adverse events; (iii) the exclusion of olanzapine and quetiapine combination therapies from the base-case models; (iv) the lack of data concerning the effectiveness of the drugs when used in second- and third-line treatments; and (iv) the lack of suitable data on quality of life.

The available evidence derives from trials that are too small, methodologically flawed and rely on proxy data, that is, the use of the LOCF method for large proportions of patients. These limitations need to be carefully considered when interpreting the effectiveness evidence, and conclusions drawn from these data need to be treated with great caution.

## Recommendations for further research

There remains a need for well-conducted, randomised, double-blind head-to-head comparisons of drugs used in the treatment of mania associated with bipolar disorder. Participant demographic and diagnostic characteristics need to be clearly differentiated and investigated separately in future research. The treatment of mania in children is particularly poorly investigated, yet effective intervention may be especially important in early onset bipolar disorder. The use of adjunctive therapy and long-term safety issues in the elderly population should also be investigated. Perhaps most importantly, separate acute and long-term treatment investigations are needed. The efficacy of long-term prophylaxis of mania, and bipolar disorder more generally, with these drugs, cannot be inferred from short-term trials.

The current evidence concerning the cost-effectiveness of alternative drugs for bipolar disorder is extremely limited from a NHS perspective. These estimates would be most appropriately derived by ensuring that future trials are designed to assess both effectiveness and cost-effectiveness considerations. The cost-effectiveness estimates would be most appropriate if they were based on a direct 'head-to-head' analysis of all relevant prophylactic treatments, rather than on a partial comparison with placebo only.

## Publication

Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. *Health Technol Assess* 2004;**8**(19).



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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 01/60/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278



Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.