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 Sculpher2 and R Riemsma1*

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
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 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.
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 allow.
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 £1296.

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

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public and private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:
– fax (with credit card or official purchase order)
– post (with credit card or official purchase order or cheque)
– phone during office hours (credit card only).

Additionally the HTA website allows you either to pay securely by credit card or to print out your order and then post or fax it.

Contact details are as follows:
HTA Despatch Email: orders@hta.ac.uk
c/o Direct Mail Works Ltd Tel: 02392 492 000
4 Oakwood Business Centre Fax: 02392 478 555
Downley, HAVANT PO9 2NP, UK Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in pounds sterling, made payable to Direct Mail Works Ltd and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?
Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. HTA on CD is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.
NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’ that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

HTA Programme Director: Professor Tom Walley
Series Editors: Professor John Gabbay, Dr Chris Hyde, Dr Ruairidh Milne, Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Caroline Ciupek

© Queen's Printer and Controller of HMSO 2004

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to NCCHTA, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

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.