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

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, S Palmer, A-M Bagnall, J Darba,
S Duffy, M Sculpher and R Riemsma

May 2004

Health Technology Assessment
NHS R&D HTA Programme

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
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
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.

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

Declared competing interests of authors: Stephen Palmer, Mark Sculpher and Josep Darba have personal, non-specific interests as they have received consultancy and/or research funding from the manufacturers of the drugs considered in this review. Stephen Palmer has undertaken consultancy for AstraZeneca and Eli Lilly on unrelated products. Mark Sculpher has undertaken consultancy for AstraZeneca on unrelated products. Josep Darba has undertaken consultancy for Sanofi-Synthelabo on unrelated products. Other members of the team undertaking HTA reviews within the Centre for Health Economics have received consultancy and/or research funding from the manufacturers of the drugs considered in this review, but these individuals were not involved in this report and have not worked on any of the drugs considered in this review. Rob Riemsma is also a member of the editorial board for *Health Technology Assessment*, although he was not involved in the editorial process for this report.

Published May 2004

This report should be referenced as follows:

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).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

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.

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.

T

Abstract

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

Objectives: To evaluate the clinical and cost-effectiveness of quetiapine, olanzapine and valproate semisodium in the treatment of mania associated with bipolar disorder.
Data sources: Electronic databases; industry submissions made to the National Institute for Clinical Excellence.
Review methods: 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 selected for inclusion. Data were extracted by one reviewer into a Microsoft Access database and checked for quality and accuracy by a second. The quality of the cost-effectiveness studies was assessed using a checklist updated from that developed by Drummond and colleagues. 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. χ^2 tests of heterogeneity were performed for the outcomes if pooling was indicated. A probabilistic model was developed to estimate costs from the perspective of the NHS, and health outcomes in terms of response rate, based on an improvement of at least 50% 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.
Results: Eighteen randomised trials met the inclusion criteria. Aspects of three of the quetiapine studies were commercial-in-confidence. The quality of the included trials was limited and overall, key methodological criteria were not met in most trials. Quetiapine, olanzapine and valproate semisodium appear superior to placebo in reducing manic symptoms, but may cause side-effects. There appears to be little difference between these treatments and lithium in terms of effectiveness, but quetiapine is associated with somnolence and weight gain, whereas lithium is associated with tremor. 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. There was little difference between these treatments and haloperidol in reducing mania, but haloperidol was associated with more extrapyramidal side-effects and negative implications for health-related quality of life. 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. 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.
The results from the base-case analysis demonstrate that choice of optimal strategy is dependent on the maximum that the health service is prepared to pay per additional responder. For a figure of less than £7179 per additional responder, haloperidol is the optimal decision; for a spend in excess of this, it would be olanzapine. 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: 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 between the three drugs in terms of effectiveness, and all were associated with adverse events. Several limitations of the cost-effectiveness analysis exist, which inevitably means that the results should be treated with some caution. 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 and their cost-effectiveness. Participant demographic, diagnostic characteristics, the treatment of mania in children, the use of adjunctive therapy and long-term safety issues in the elderly population, and acute and long-term treatment are also subjects for further study.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Abnormal Involuntary Movement Scale This has been used to assess tardive dyskinesia, a long-term, drug-induced movement disorder. It can be used to assess some short-term movement disorders such as tremor.

Agitated Behaviour Scale Developed to allow objective assessment of agitated behaviour in traumatic brain injury patients. A 14-item scale, with each item scored 1–4. Higher scores indicate greater agitation.

Akathisia A movement disorder characterised by subjective feelings of inner restlessness, mental unease or dysphoria.

Anticholinergic Drugs which act to suppress side-effects of the antipsychotic drugs related to acetylcholine.

Antiparkinsonian Drugs which act to suppress the movement disorder or 'parkinsonian' side-effects of antipsychotic drugs, such as poverty of movement and tremor (these symptoms can be similar to those seen in Parkinson's disease).

Atypical antipsychotic Drugs which aim to treat the psychotic symptoms of schizophrenia but which are thought to cause fewer movement disorder side-effects than typical antipsychotics. Atypical antipsychotics tend to be newer and therefore more expensive than typical antipsychotics. The only definition for 'atypicality' relates to catalepsy in rats.

Barnes Akathisia Scale The scale comprises items rating the observable, restless movements that characterise akathisia, a subjective awareness of restlessness, and any distress associated with the condition. These items are rated from 0 = normal to 3 = severe. In addition, there is an item for rating global severity (from 0 = absent to 5 = severe). A low score indicates low levels of akathisia.

Brief Psychiatric Rating Scale This is used to assess the severity of abnormal mental state. The original scale has 16 items, but a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from 0 to 6 or from 1 to 7. Scores can range from 0 to 126, with high scores indicating more severe symptoms.

Clinical Global Impression Scale This scale has been used to assess the overall condition of a mentally ill person – both severity of illness and clinical improvement – by comparing those conditions of investigated patients with those of other patients with the same diagnosis. An eight-point (0–7) scoring system has been used, with low scores indicating decreased severity and/or overall improvement.

Cost–utility analysis Estimates of the additional cost per quality-adjusted life-year (QALY) saved or gained.

Extrapyramidal syndrome/symptoms A type of movement disorder which can be a side-effect of antipsychotic drugs.

Extrapyramidal Symptom Rating Scale This consists of a questionnaire relating to parkinsonian symptoms (nine items), a physician's examination for parkinsonism and dyskinetic movements (eight items), and a clinical global impression of tardive dyskinesia. High scores indicate severe levels of movement disorder.

Global Assessment of Functioning Scale A graduated continuum (varying between 0 and 100) from psychological or psychiatric sickness to health.

continued

Glossary *continued*

Global Assessment Scale Used to evaluate the overall functioning of a person during a specified period in terms of psychological well-being or sickness. Time period assessed is generally 1 week prior to evaluation. The scale covers the entire range of severity and can be used in any situation or study where an overall evaluation of the severity of the illness or degree of health is needed.

Hamilton Depression Rating Scale A scale generally used in psychopharmaceutical studies with depressed patients. Various versions exist with different numbers of items. Its objective is the quantification of the results of a semi-structured interview. This scale gives more importance to somatic and behavioural symptoms than to psychological manifestations of depression. Low values indicate less depression.

Heterogeneity Differences between studies in terms of drugs or interventions used (either the drugs being investigated or the drugs with which they are being compared, or dose), participants, study setting or outcomes measured. Where significant heterogeneity is present, studies should not be statistically combined in a meta-analysis.

Intention-to-treat analysis The practice of reporting results for all trial participants who entered the study, rather than just those who remained at the end. Failure to use an intention-to-treat analysis means that the trial findings may not be representative of all the people who entered the study.

Mania Rating Scale An 11-item scale, measuring symptoms of mania. Scores increase with symptom severity.

Montgomery Asberg Depression Rating Scale Developed using a 65-item comprehensive psychopathology scale to identify the 17 most commonly occurring symptoms in primary depressive illness. Ratings on 10 items, with higher score indicating poor outcome. Maximum score is 30.

Positive and Negative Syndrome Scale This schizophrenia scale has 30 items, each of which can be defined on a seven-point scoring system varying from 1 = absent to 7 = extreme. This scale can be divided into three subscales for measuring the severity of general psychopathology, positive symptoms (PANSS-P) and negative symptoms (PANSS-N). A low score indicates lesser severity.

Positive symptoms Symptoms of schizophrenia such as hallucinations and delusions.

Publication bias The tendency for studies which show a positive effect to be published more readily than those which show no effect for a particular intervention.

Quality-adjusted life-years An index of survival that is weighted or adjusted by the patient's quality of life during the survival period.

Quality of Life Enjoyment and Satisfaction Questionnaire A self-administered questionnaire to assess the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. It has 93 items.

Relative risk A measure of the likelihood of a certain event occurring in a group of people taking one intervention versus another. A relative risk >1 means that the group is more at risk for the particular event and a relative risk of <1 means that the group is less at risk.

The Schedule for Affective Disorders and Schizophrenia – Change Version The SADS scale was developed with the primary aim of differentiating between schizophrenia and mood disorders. The scale makes use of collateral information and past history. The SADS-C scale is adapted to measure change over time. It rates symptoms at their highest level of severity over the previous week. Used serially, it provides a detailed record of the individual's progress.

Simpson – Angus Scale This 10-item scale, with a scoring system of 0–4 for each item, measures drug-induced parkinsonism, a short-term drug-induced movement disorder. A low score indicates low levels of parkinsonism.

Tardive dyskinesia Abnormal, repetitive and involuntary movements around the mouth, face and extremities.

continued

Glossary *continued*

Typical antipsychotics Drugs which aim to treat the psychotic symptoms of schizophrenia and which generally act on dopamine receptors in the brain. The typical antipsychotics are thought to cause more movement disorder side-effects than the atypical antipsychotics. They tend to be older and less expensive than the atypical antipsychotics.

Young Mania Rating Scale An 11-item instrument used to assess the severity of mania, designed to be administered by a trained clinician in a 15–30-minute interview. Scoring for the items is on a five-point scale with varying descriptors for each. Four items are given twice the weight of the remaining seven to compensate for poor cooperation from severely ill patients. A high score indicates a high level of manic symptoms.

List of abbreviations

ABS	Agitated Behaviour Scale
ACES	Agitated Calmness Evaluation Scale
ADRS	Affective Disorder Rating Scale
AIMS	Abnormal Involuntary Movement Scale
BAS	Barnes Akathisia Scale
BNF	British National Formulary
BPRS	Brief Psychiatric Rating Scale
BPRS-A	Brief Psychiatric Rating Scale, Augmented
CDRS	Children's Depression Rating Scale
CEAC	cost-effectiveness acceptability curve
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression
CGI-BP	Clinical Global Impression – Bipolar
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
CIC	commercial-in-confidence
DSM	*Diagnostic and Statistical Manual*
EPS	extrapyramidal side-effects
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
GI	gastrointestinal
HAM-D	Hamilton Depression Rating Scale
HRQoL	health-related quality of life
i.m.	intramuscular
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
LOCF	last observation carried forward
MADRS	Montgomery Asberg Depression Rating Scale
MAS	Mania Assessment Scale
MCMC	Markov Chain Monte Carlo
MD	mean difference
MITT	modified intention-to-treat
MRS	Mania Rating Scale
NICE	National Institute for Clinical Excellence
OR	odds ratio
PANSS	Positive and Negative Symptom Scale
PANSS-EC	Positive and Negative Symptom Scale – Excited Component
QALY	quality-adjusted life-year

continued

List of abbreviations *continued*

QoL	quality of life
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
RCT	randomised controlled trial
RR	relative risk/risk ratio
SADS	Schedule for Affective Disorders and Schizophrenia
SADS-C	Schedule for Affective Disorders and Schizophrenia – Change version
SAS	Simpson–Angus Scale
SD	standard deviation
SE	standard error
SF-36	Short Form with 36 Items
WMD	weighted mean difference
YMRS	Young Mania Rating Scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

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. χ^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.

- 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 $\geq 50\%$ 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.

Chapter 1
Background

Introduction

Bipolar affective disorder is a recurrent condition where episodes of elevation of mood and increased energy and activity (mania and hypomania) and a lowering of mood and decreased energy and activity (depression) occur in the same person, sometimes at the same time.[1] Bipolar disorder has a lifetime prevalence of ~1% and is among the top 30 causes of world-wide disability.[2] Recurrent episodes lead to harmful effects for the individual's psychological, professional and social welfare, and can lead to suicide in as many as 15% of sufferers.[3]

The appropriate management strategy for bipolar disorder is dependent on the phase of the disorder being experienced, that is, acute mania, depression or maintenance therapy to prevent future manic or depressive episodes. This review evaluates the clinical and cost-effectiveness of the licensed atypical and anticonvulsant agents only in acute treatment of mania associated with bipolar disorder.

Description and diagnosis

There are two main types of mood disorder: major depressive (unipolar) and manic-depressive (bipolar).[4] Bipolar disorder can be further divided into bipolar I and bipolar II. Mania is associated with bipolar I whereas bipolar II is characterised by hypomania, which is a less severe form of mania not requiring hospitalisation.

Mania is not synonymous with euphoria, but is a syndrome that can occur in a variety of disorders and involves aberrations in mood, behaviour and thinking. Other clinical manifestations often include hyperactivity, pressure of speech, flight of ideas, inflated self-esteem, decreased need for sleep and distractibility. Symptoms of mania may vary in their severity and the consequences for the individual in terms of their social or occupational functioning.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), mania is characterised by at least 1 week of profound mood disturbance, where the mood disturbance is sufficient to cause danger to the patient or others, and where the disturbance is not the result of substance abuse or another medical condition. In addition, for a diagnosis of mania, the patient must exhibit three or more of the following: grandiosity, diminished need for sleep, racing thoughts or flight of ideas, clear evidence of distractibility, increased level of goal-focused activity at home, at work or sexually and risk-taking behaviours.[1]

The diagnosis of bipolar disorder must be carefully differentiated from substance-related disorders, antisocial behaviour and personality disorders, and also schizophrenia and unipolar depression. In children and adolescents, differentiation from attention-deficit hyperactivity disorder and conduct disorder must also be considered.

Epidemiology and aetiology

Bipolar disorder affects ~1% of the adult population, with estimates from community samples ranging between 0.4 and 1.6%.[5,6] Bipolar I disorder affects men and women fairly equally, although hypomanic episodes (bipolar II) have a higher incidence among women.[7] Onset of mania associated with bipolar affective disorder is most common in late adolescence or early adulthood, although first occurrence in other decades, such as childhood, has been documented.[8] The first episode in males is more likely to be a manic episode, whereas the first episode in females is more likely to be depressive.[9] There are no known significant differences among racial groups in the prevalence of bipolar disorder.

Several factors are associated with the frequency and distribution of bipolar disorder. Rates may be higher among unmarried, separated or divorced people, among homeless persons and among upper socio-economic groups.[10] Seasonal effects on incidence have also been reported, with the most common being a spring–summer excess of elation.[11]

The aetiology of bipolar affective disorder is unknown, although evidence suggests the

importance of genetic factors. Mania has greater heritability rates than any other major psychiatric disorder.[5] The concordance rate for monozygotic twins is ~70% and the risk for mood disorders among first-degree relatives is ~20%.[12] Despite greater heritability, the mode of inheritance is unknown and there is little evidence for a single major locus. It seems most likely that the disorder is heterogeneous with many interacting genes of intermediate or small effect.[13] Similarly, the precipitating role played by environmental stressors, particularly in the early stages of the illness, also remains unclear.

Course and outcome

If left untreated, patients with bipolar disorder may have >10 lifetime episodes of mania and depression, with the duration of episodes and inter-episode periods stabilising after the fourth or fifth episode. Often 5 years or more may elapse between the first and second episodes, although 50% of patients may experience another manic attack within 2 years of their initial episode. The periods between subsequent episodes usually narrow.[14]

Bipolar disorder causes substantial psychosocial morbidity that frequently affects the patient's marriage, children and occupation and many other domains of the patient's life. Divorce rates are three times higher in patients with bipolar disorder and the occupational status of patients with bipolar disorder is twice as likely to deteriorate as that of comparison subjects.[15]

As many as 15% of bipolar patients commit suicide,[3] and a third admit to having made a suicide attempt.[14] Suicide occurs more often among men than women and is most likely during a depressive episode, and comorbid substance abuse and anxiety disorders substantially increase the risk of suicide.[6]

Treatment of mania

In the UK episodes of mania are commonly treated with a variety of drugs, often in combination. These include lithium and antipsychotics such as chlorpromazine and haloperidol and, more recently, the atypical antipsychotics have been employed. These medications can cause side-effects such as extrapyramidal side-effects (EPS), which are associated with typical antipsychotics, weight gain, which is associated with atypical antipsychotics, and non-treatment-specific side-effects such as stiffness, shakiness, dry mouth and constipation. Additional medicines can be given to help alleviate the symptoms associated with these side-effects. In many cases sufferers need to be admitted to hospital in order to be treated.

In a recent investigation, it was estimated that the annual cost of managing bipolar disorder to the UK NHS was £199 million, 35% of which was attributable to hospital admissions.[16] Moreover, the annual direct non-healthcare cost was estimated to be £86 million, and the annual indirect societal cost was estimated to be £1770 million. Das Gupta and Guest[16] concluded that the annual cost to UK society attributable to bipolar disorder was £2 billion at 1999–2000 prices, allowing for 297000 people with the disorder. Overall, 10% of this cost was attributed to NHS resource use, 4% to non-healthcare resource use and 86% to indirect costs.

Description of new interventions

Olanzapine [Zyprexa® (Lilly)]

Olanzapine is licensed for use in schizophrenia and is also indicated for the treatment of moderate to severe manic episodes. Side-effects include mild, transient antimuscarinic effects, drowsiness, increased appetite, oedema, hyperprolactinaemia (but clinical manifestations are rare), occasionally blood dyscrasias, rarely bradycardia, rash, photosensitivity, hyperglycaemia, priapism, hepatitis and elevated creatine kinase concentration.[17] Contraindications include angle-closure glaucoma and breastfeeding. Dose has a usual, adjusted range of 5–20 mg daily, although doses of 15 mg daily or greater are recommended only after reassessment. Olanzapine is not recommended for patients under 18 years of age.

Olanzapine is a thienobenzodiazepine compound with high affinity for several serotonin and dopamine receptors, and it binds with high affinity with histamine and adrenergic receptors.[18] Olanzapine's effects on adrenergic receptors are associated with orthostatic changes, and its effects on histamine receptors may contribute to sedation and appetite stimulation, and olanzapine's procholinergic properties may explain its beneficial effects on cognition.[19] Importantly, although the precise mechanism of olanzapine's thymoleptic activity is unknown, it has been suggested that its dopamine antagonist properties correspond to antimanic activity.[19]

Quetiapine [Seroquel® (AstraZeneca)]

Quetiapine is indicated for the treatment of both positive and negative symptoms of schizophrenia. It is anticipated that quetiapine will have a licence for use in bipolar disorder by publication of National Institute for Clinical Excellence (NICE) guidance. Side-effects include drowsiness, dyspepsia, constipation, dry mouth, mild asthenia, rhinitis, hypertension, tachycardia; anxiety, fever, myalgia, ear pain, rash, leucopenia, elevated plasma triglyceride and cholesterol concentrations, reduced plasma thyroid hormone concentrations, possible QT interval prolongation and rarely oedema and very rarely priapism.[17] Breastfeeding is contraindicated. Dose is recommended at 25 mg twice daily on day 1, 50 mg twice daily on day 2, 100 mg twice daily on day 3, 150 mg twice daily on day 4 and then adjusted according to response. The usual range is 300–450 mg daily in two divided doses, to a maximum of 750 mg daily. Quetiapine is not recommended for patients under 18 years of age.

Quetiapine is a derivative of dibenzothiazepine. Quetiapine has weak affinity for dopamine, muscarinic, histamine and adrenergic receptors. Quetiapine's adrenergic and histamine atagonism are associated with orthostatic, sedative and appetite-stimulating properties.[19] Moreover, quetiapine's serotonergic and adrenergic actions may facilitate antidepressant activity and its dopamine receptor antagonism may confer antimanic effects.[20]

Valproate semisodium [Depakote® (Sanofi-Synthelabo)]

Valproate semisodium, or divalproex, is indicated for acute treatment of a manic episode associated with bipolar disorder. Side-effects include gastric irritation, nausea, ataxia and tremor, hyperammonaemia, increased appetite and weight gain, transient hair loss, oedema, thrombocytopenia, inhibition of platelet aggregation, impaired hepatic function leading rarely to fatal hepatic failure, rashes, EPS, dementia, leucopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction, irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi's syndrome, toxic epidermal necrolysis, Stevens–Johnson syndrome, vasculitis, hirsutism and acne.[17] Contraindications include hypersensitivity to active substance or excipients, active liver disease, personal or family history of severe hepatic dysfunction and porphyria. The initial dose is 750 mg daily in 2–3 divided doses, and increased according to response, with the usual dose being 1–2 g daily. The daily dosage should be established according to age and body weight. The safety and efficacy of valproate semisodium have not been established in patients under 18 years of age.

Valproic acid is a basic branched-chain carboxylic acid. Valproate inhibits pentylenetetrazol-induced and maximal electroshock seizures in animals and suppresses secondary generalised seizures without affecting focal activity in cortical cobalt- and alumina-lesioned animals.[21] Valproate also has antikindling properties and neuroprotective effects, and these properties have been proposed to be more directly relevant to the antimanic and mood-stabilising properties of valproate.[19,22]

The present review

The objective of this review is to establish the clinical and cost-effectiveness of olanzapine, quetiapine and valproate semisodium for bipolar affective disorder, within their licensed or proposed indications either as mono- or adjunctive therapy for the treatment of an acute manic episode. This report evaluates the effectiveness of these agents against acute episodes of mania only and, as such, implications regarding their potential use as prophylaxis against further episodes should not be drawn.

Chapter 2
Methods

Search strategy

The literature search was not limited to any specific study design, hence the searches were conducted without methodological filters and consisted of terms for the drug interventions combined with terms for bipolar disorder. Full details of the search strategies for this review are presented in Appendix 1.

The following databases were searched for relevant published literature: BIOSIS, Cochrane Controlled Trials Register (CCTR), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Health Economic Evaluations Databases (HEED), LILACS, MEDLINE, National Research Register (NRR), NHS Economic Evaluation Database (NHS EED), PsycINFO and Science Citation Index.

Searches were also carried out on the Internet using the medical search engine OMNI (http://omni.ac.uk/), meta-search engine Copernic (http://www.copernic.com/) and general search engines Alta Vista (http://www.altavista.com/) and Google (http://www.google.com/). Specialist mental health-related websites were also searched: the Royal College of Psychiatrists (http://www.rcpsych.ac.uk/index.htm), the American Psychiatric Association (http://www.psych.org/index.cfm) and the National Institute of Mental Health (http://www.nimh.nih.gov/home.cfm/).

In addition, the bibliographies of retrieved articles and industry submissions made to NICE were searched for further relevant studies.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full-paper manuscripts of potentially relevant titles and abstracts were obtained where possible and the relevance of each study was assessed according to the criteria below. Studies that did not fulfil all of the criteria were excluded and their bibliographic details listed with the reason for exclusion (Appendix 2). Any discrepancies were resolved by consensus and if necessary a third reviewer was consulted.

Study design

The following study designs were included:

- Randomised controlled trials (RCTs) where olanzapine, quetiapine or valproate semisodium were used either as mono- or adjunctive therapy for the treatment of an acute manic episode. Acute mania was taken to mean any duration of mania reported in the studies up to a maximum of 10 weeks. The most commonly reported duration of RCTs was 3 weeks; therefore, if a study reported data at 3 weeks and other time points, we extracted the 3-week data only.
- A broader range of studies were considered in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options, and considered both costs and consequences (including cost–effectiveness, cost–utility and cost-benefit analyses), were included.

Interventions

These were olanzapine, quetiapine or valproate semisodium used either as mono- or adjunctive therapy within their licensed indications for the treatment of an acute manic episode, although quetiapine is not currently licensed for treatment of mania associated with bipolar affective disorder. Comparators were any agents used for the treatment of an acute manic episode.

Participants

These were individuals with bipolar affective disorder who are experiencing an acute manic episode.

Outcomes

Data on the following outcome measures were included:

- response (e.g. measured by rating scales)
- suicide
- rates of hospitalisation/discharge/length of hospital stay

- adverse effects (e.g. gastrointestinal disturbances, weight gain and EPS)
- costs from all reported perspectives
- quality of life and personal preference, where reported
- attrition/leaving the study early.

Data extraction strategy

Data relating to study details (Appendix 3) and quality (Appendix 4) were extracted by one reviewer into an Access database and independently checked for accuracy by a second reviewer. Disagreements were resolved through discussion and, if necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study. Where possible, people who left the study early were added back in to dichotomous outcomes as having had the 'bad' outcome (e.g. for the outcome 'response', missing persons were assumed to be non-responders). A sensitivity analysis was carried out to assess whether including these people as having had the 'good' outcome made a substantial difference to the results. However this worst-case intention-to-treat (ITT) analysis was not possible for the majority of people who left the included studies early, as they had already been added back in by the trial authors using the last observation carried forward (LOCF) method and data reported for the group as a whole. We therefore could not separate the end-point data for people who completed the trial from the LOCF data for people who left the trial early.

Quality assessment strategy

The quality of the individual studies was assessed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and if necessary a third reviewer was consulted. The quality of clinical effectiveness studies was assessed using criteria based on *CRD Report* 4[23](Appendix 4). The quality of the cost-effectiveness studies was assessed using a checklist updated from that developed by Drummond and colleagues[24] (see Appendix 5). This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[25]

Methods of analysis/synthesis

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. The possible effects of study quality on the effectiveness data and review findings were examined. Where sufficient data were available, treatment effects were presented in the form of relative risk (RR) or mean differences (for continuous data) as appropriate. RR and mean difference data were presented as Forest plots but only pooled where this made sense clinically and statistically. Heterogeneity between studies was assessed by considering differences in (a) study population, (b) intervention, (c) outcome measures and (d) study quality. Studies were grouped by drug and, within each drug, by comparator used. We treated missing persons as non-responders as the base-case scenario. Where possible we carried out a sensitivity analysis using positive assumptions instead for missing persons. χ^2 tests of heterogeneity were performed for the outcomes if pooling was indicated.

Methods of analysis for economic studies

Details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables. This covered studies based on patient-level data and decision models and included any studies provided by manufacturers.

Patient-level data

For analyses based on patient-level data, the validity of the studies was assessed for the source of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and generalisability of results. Studies were classified as follows:

1. prospective resource use and patient outcome data
2. mixed prospective and retrospective data
3. retrospective data.

These categories were further subdivided as follows:

(a) RCT
(b) controlled trial (quasi- or no randomisation)
(c) cohort study with concurrent controls
(d) cohort study with historical controls.

Decision models

Critical appraisal was based on a range of questions, including

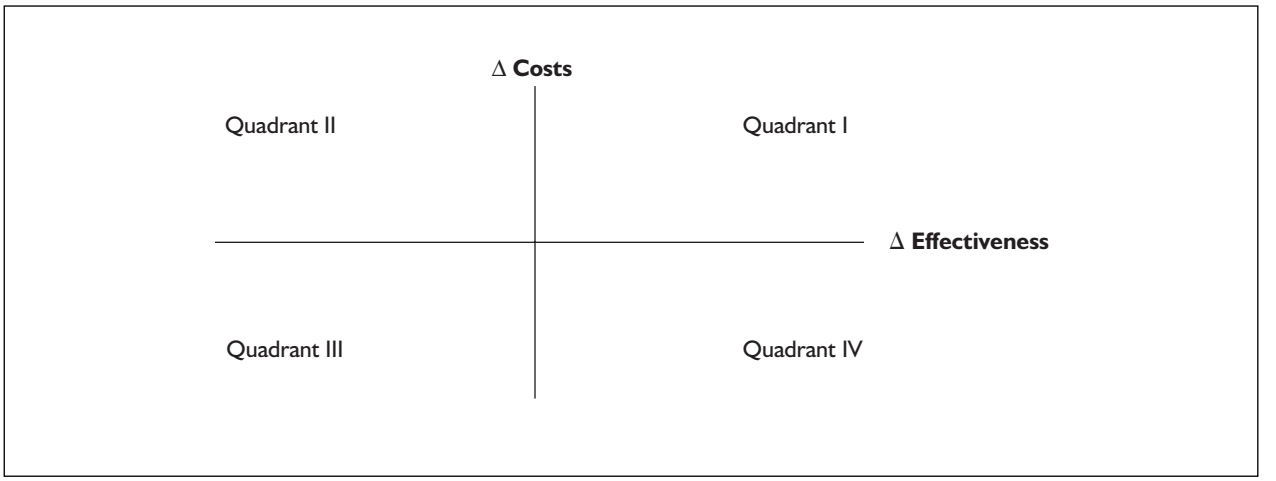

FIGURE 1 *Cost-effectiveness plane and quadrants*

1. structure of model
2. time horizon
3. details of key input parameters and their sources
4. methods of analysis (e.g. handling uncertainty).

For all types of economic study, evaluations were rated using a revised version of the Drummond checklist (Appendix 5).[24]

Part of the assessment process involved the location of each study in the appropriate quadrant of the cost-effectiveness plane (*Figure 1*). This indicated the direction of the differential costs and effects of the alternative treatment options considered, but did not address the uncertainty surrounding these estimates. Where possible, indications of the uncertainty underlying these estimates were assessed and an appropriate statistic such as confidence intervals around costs and effects or the incremental cost-effectiveness ratio (ICER), or cost-effectiveness acceptability curves were presented. These were produced from either published analyses, Monte Carlo simulation or per patient data on total costs and effects.

Key to quadrants

1. Quadrant I. Intervention increases costs and effectiveness. Incremental analysis required to assess cost-effectiveness compared with other interventions.
2. Quadrant II. Intervention is dominated as it increases costs and reduces effectiveness.
3. Quadrant III. Intervention reduces costs and effectiveness. Incremental analysis required.
4. Quadrant IV. Intervention is dominant as costs are reduced and effectiveness increased.

Chapter 3

Effectiveness results

Quantity of research available

A total of 1955 titles and abstracts were screened for inclusion in the review. Of these, 217 were ordered as full papers and assessed in detail. Fourteen of these papers were unobtainable. A total of 18 randomised trials (48 publications) met the criteria for inclusion in the review. There were 155 excluded studies, which are listed in Appendix 2 with the reason for exclusion. Studies are grouped and discussed according to drug type: quetiapine, olanzapine and valproate semisodium and direct comparisons between valproate semisodium and olanzapine. Full data extraction tables and quality assessment of trials for clinical effectiveness are presented in Appendices 6 and 7, respectively.

Quetiapine (Seroquel®)

Four unpublished studies were submitted by AstraZeneca and included in this section, namely Study 99, Study 100, Study 104 and Study 105.[26,27] Studies 99 and 100 compared quetiapine – as an adjunct to lithium or valproate semisodium – with lithium or valproate semisodium plus placebo. Study 104 compared quetiapine as monotherapy with haloperidol and placebo. Study 105 compared quetiapine as monotherapy with lithium and placebo. Some details of the design of Study 99 were published in a conference abstract, but no results.[28] The results of Study 99 were published in a later abstract.[29] Details of study design and results of Study 104 were also published later in a conference abstract.[30] Another conference abstract presented pooled results of studies 104 and 105.[31,32]

One published study was identified from the industry submission (DelBello 2002[33]) (note that all studies are referred to by just the first author and year). This study compared quetiapine as an adjunct to valproate semisodium with placebo with valproate semisodium.

Description of included trials

The five included trials (*Table 1*) included multiple comparisons. Two RCTs compared quetiapine with placebo (Studies 104 and 105), three compared quetiapine as an adjunct to lithium or valproate semisodium with placebo plus lithium or valproate semisodium (DelBello 2002,[33] Study 99[26–28] and Study 100[26,27]), one trial compared quetiapine with lithium (Study 105[31,34]) and one trial compared quetiapine with haloperidol (Study 104[30]). The dose of quetiapine ranged in both the DeBello 2002 study[33] and Study 99[26–28] from 200 to 800 mg/day. Study 99 was 3 weeks in duration and the DelBello 2002 study 6 weeks.

The DelBello 2002 study[33] recruited adolescents aged between 12 and 18 years (mean age 14.1–14.5 years). The numbers of males and females were approximately equal. A diagnosis of bipolar I (acute mania) was obtained with reference to DSM-IV. The minimum inclusion criterion was a YMRS score of no less than 20. Participants were excluded if they had received depot neuroleptic within the previous 3 months, antidepressant or antipsychotic medication within 1 week or antiepileptics, benzodiazepines or psychostimulants within 72 hours.

[Commercial-in-coinfidence (CIC) data from Studies 100, 104 and 105 have been removed.]

Validity

It was unclear whether allocation was adequately concealed in Study 99. Treatment groups were comparable at baseline and participants were blinded although the trial did not report whether the outcome assessors were blind. Modified ITT analysis (LOCF) was used for effectiveness data with standard ITT analysis for safety data. The trial conducted by DelBello and colleagues[33]used adequate randomisation procedures, but it was unclear to what extent treatment allocation was concealed. Although they reported that outcome assessors, administrators and participants were blinded, the success of blinding was not assessed. The trial was small, and a high proportion of participants withdrew early from the trial.

[CIC data from Studies 100, 104 and 105 have been removed.]

Quetiapine as monotherapy versus placebo

[CIC data from Study 105 have been removed.]

TABLE 1 *Quetiapine – included studies*

Study	Participants	Interventions	Outcomes
DelBello, 2002[33] (full paper)	*N* = 30 Adolescents (aged 12–18 years) Diagnosis: DSM-IV bipolar I disorder, mixed or manic YMRS score ≥ 20. 23 had mixed episode, 14 had psychosis, 18 had attention deficit hyperactivity disorder	6 weeks Quetiapine plus valproate semisodium (*n* = 15). Quetiapine dose max. 150 mg t.d.s., valproate semisodium serum level 80–130 mg/dl. Placebo plus valproate semisodium (*n* = 15) Valproate semisodium serum level 80–130 mg/dl	Attrition Adverse events YMRS scores, response; CDRS, CGAS, PANSS-P; AIMS, SAS, BAS scores; receipt lorazepam
Study 99 (full paper)[26–28]	*N* = 191 Diagnosis: DSM-IV bipolar I disorder, acute mania. YMRS score ≥ 20. 34.7% manic moderate, 22.9% manic severe with no psychotic features, 42.4% manic severe with psychotic features	3 weeks Quetiapine plus mood stabiliser (lithium or valproate semisodium, *n* = 91). Quetiapine dose 200–800 mg/day, lithium serum concentration 0.7–1.0 mEq/l, valproate semisodium serum concentration 50–100 μg/ml Placebo plus mood stabiliser (lithium or valproate semisodium, *n* = 100)	Attrition Adverse events YMRS scores, response, remission; CGI-BP scores, response; PANSS scores, GAS scores; SAS scores; emergent depression (MADRS scores)
Study 100 **[CIC data removed]**			
Study 104 **[some CIC data removed]**[30]	*N* = 302 Diagnosis: DSM-IV bipolar I disorder, acute mania. YMRS score ≥ 20. 29% manic moderate, 29% manic severe with no psychotic features, 42% manic severe with psychotic features	3 weeks Quetiapine (*n* = 102), 200–800 mg/day Haloperidol (*n* = 99), 2–8 mg/day Placebo (*n* = 101)	Attrition Adverse events YMRS scores, response, remission; CGI-BP scores, response; PANSS scores, GAS scores; emergent depression (MADRS scores)
Study 105 **[some CIC data removed]**[31,34]	*N* = 302 Diagnosis: DSM-IV bipolar I disorder, acute mania. YMRS score ≥ 20.	3 weeks Quetiapine (*n* = 107), 200–800 mg/day Lithium (*n* = 98), serum concentration 0.6–1.4 mEq/l Placebo (*n* = 97)	Attrition Adverse events YMRS scores, response, remission; CGI-BP scores, response; PANSS scores, GAS scores; emergent depression (MADRS scores)

AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Scale; CDRS, Children's Depression Rating Scale; CGAS, Children's Global Assessment Scale; CGI-BP, Clinical Global Impression – Bipolar; GAS, Global Assessment Scale; MADRS, Montgomery Asberg Depression Rating Scale; PANSS, Positive and Negative Symptom Scale; SAS, Simpson – Augus Scale; YMRS, Young Mania Rating Scale.

Studies 104 and 105 compared quetiapine as monotherapy with a placebo arm. Study 104 also included a haloperidol arm and Study 105 a lithium arm.

Global effects

Study 104 reported GAS scores but without a measure of variance, so we could not calculate 95% confidence intervals (CIs) around the mean difference of 5.94 (reported $p = 0.023$) in favour of quetiapine. Study 105 did not report GAS scores in its published form but reported that the mean increase from baseline was significantly greater for quetiapine than for placebo. Study 104 also reported CGI-BP scores, again with no measure of variance so we could not calculate 95% CIs around the mean difference (MD) of 0.12 in Study 104. Study 105 reported that mean change in CGI-BP score from baseline was significantly greater for quetiapine than placebo.

Both studies reported CGI-BP response rate (as 'improved' or 'much improved' on the CGI-BP scale) (*Figure 2*). The pooled result is in favour of quetiapine but there is significant heterogeneity in this result. Study 104 showed no significant difference between groups (RR 1.24, 95% CI 0.88 to 1.76) whereas Study 105 significantly favoured quetiapine (RR 2.05, 95% CI 1.48 to 2.86). Sensitivity analysis using positive assumptions for missing persons did not affect this result (Study 104, RR 1.24, 95% CI 0.88 to 1.76; Study 105, RR 2.05, 95% CI 1.48 to 2.86).

Effects on mania

Both studies reported YMRS change scores but no measure of variance, so we could not calculate 95% CIs around the mean difference of 3.97 in Study 104 (reported $p = 0.0096$ in favour of quetiapine) and 7.91 in Study 105 (reported $p < 0.0001$ in favour of quetiapine). Both studies also reported response rates using YMRS criteria. Response was defined as at least a 50% decrease in YMRS score.

The pooled result for response is in favour of quetiapine but there is significant heterogeneity in this result. Study 104 showed no significant difference between groups (RR 1.22, 95% CI 0.86 to 1.73) whereas Study 105 significantly favoured quetiapine (RR 1.91, 95% CI 1.33 to 2.76) (*Figure 3*). Sensitivity analysis using positive assumptions for missing persons did not affect this result (Study 104, RR 1.22, 95% CI 0.86 to 1.73; Study 105, RR 1.91, 95% CI 1.33 to 2.76). **[CIC data on YMRS remission (*Figure 4*) have been removed.]**

Other psychiatric assessments

Study 104 reported PANSS total change scores and PANSS agitation and aggression scores, without any measures of variance. We could not calculate 95% CIs around the MD of 5.32 for PANSS total (reported $p = 0.006$ in favour of quetiapine) or of 1.44 ($p = 0.046$ for quetiapine) and 1.59 ($p = 0.41$) for PANSS agitation and aggression scores.

Study 105 reported that the mean reduction from baseline in PANSS total score, MADRS score and in PANSS positive, activation and supplemental aggression risk subscale scores was significantly greater for quetiapine compared with placebo ($p < 0.001$).

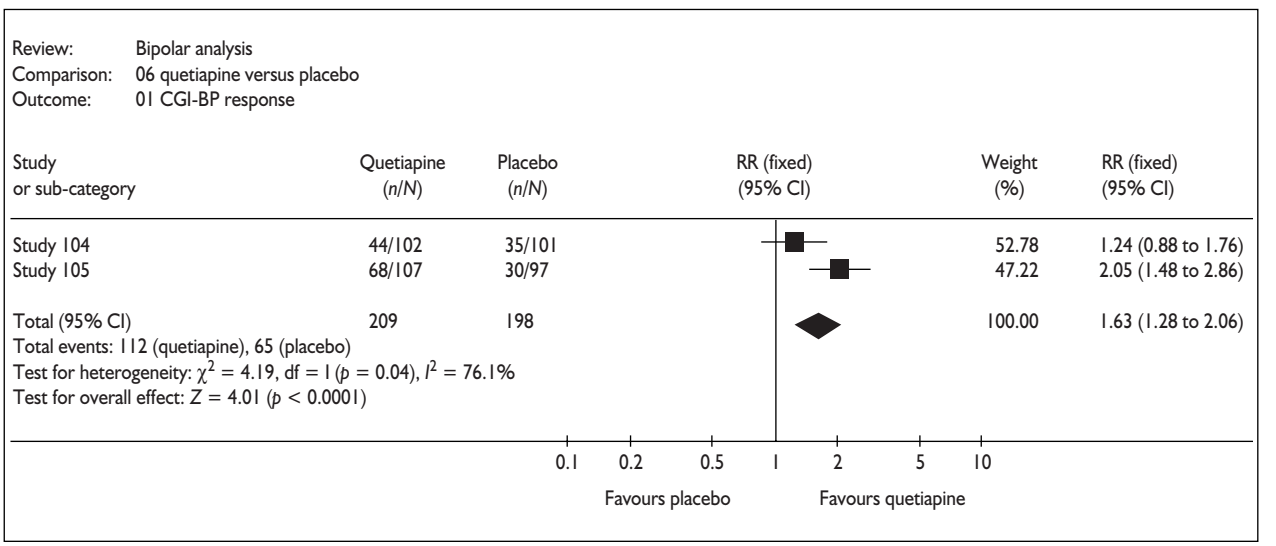

FIGURE 2 *CGI-BP 'response': quetiapine monotherapy versus placebo*

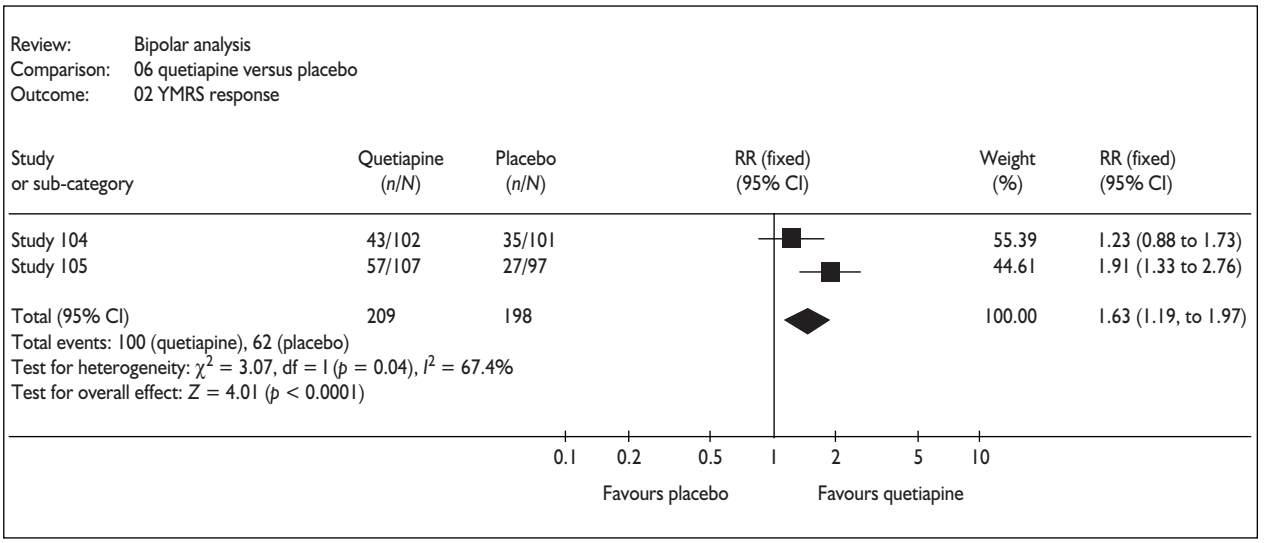

FIGURE 3 *YMRS response: quetiapine monotherapy versus placebo*

FIGURE 4 *YMRS remission.* ***[CIC data removed.]***

There was no significant difference between groups in risk of emergent depressive symptoms, defined on the MADRS scale (pooled RR 0.31, 95% CI 0.09 to 1.06) (*Figure 5*).

Leaving the study early

Both studies reported this outcome. People in the placebo group were more likely to leave the study early for any reason (RR 0.64, 95% CI 0.53 to 0.79), due to disease progression (RR 0.46, 95% CI 0.26 to 0.82) or due to lack of efficacy (RR 0.54, 95% CI 0.35 to 0.81) (*Figure 6*).

Adverse effects

Both studies reported some adverse effects. People in the quetiapine group were more likely to experience dry mouth (RR 11.79, 95% CI 2.87 to 48.36), somnolence (RR 4.03, 95% CI 1.90 to 8.53), weight gain (RR 14.50, 95% CI 1.96 to 107.34) or dizziness (RR 5.89, 95% CI 1.36 to 25.45) than people in the placebo group (*Figure 7*).

Quetiapine as adjunct to lithium or valproate semisodium versus placebo plus lithium or valproate semisodium

[CIC data from Study 100 have been removed.]

Two studies (99 and 100) compared quetiapine as an adjunct to a mood stabiliser with mood stabiliser plus placebo in adults.

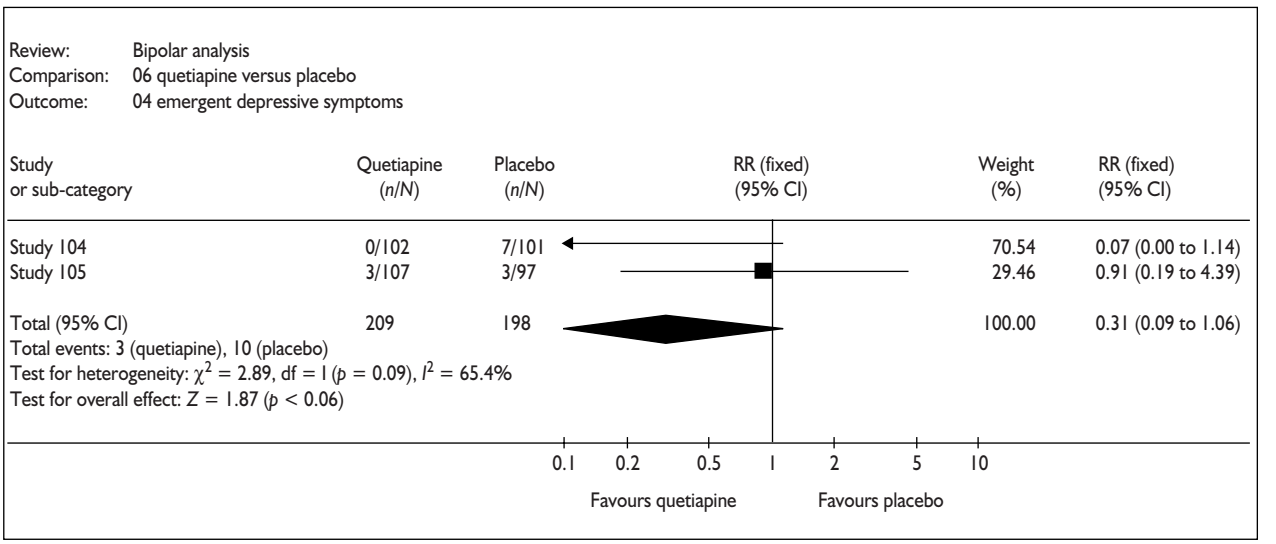

FIGURE 5 *Emergent depressive symptoms: quetiapine monotherapy versus placebo*

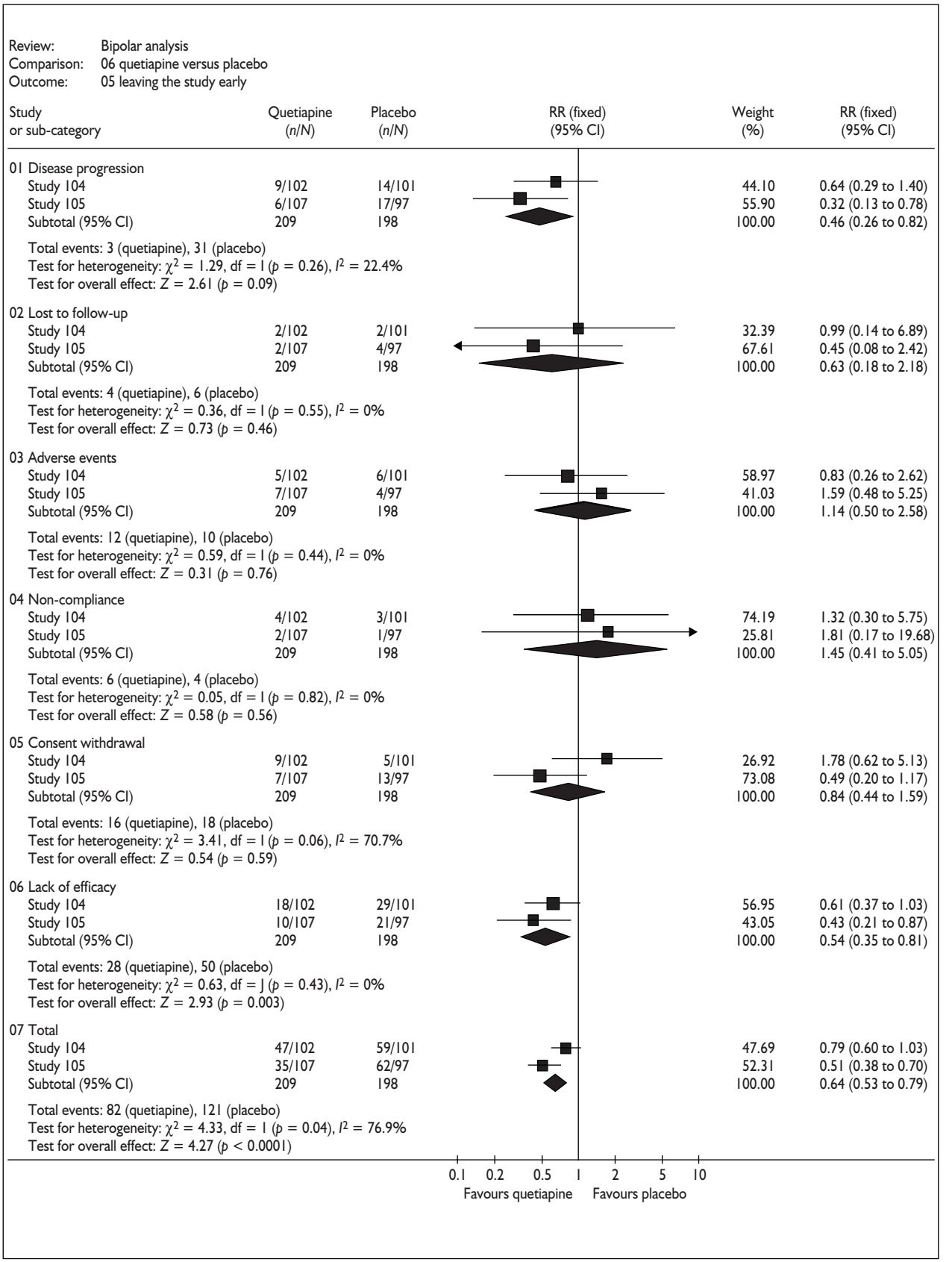

FIGURE 6 *Leaving the study early – quetiapine monotherapy versus placebo*

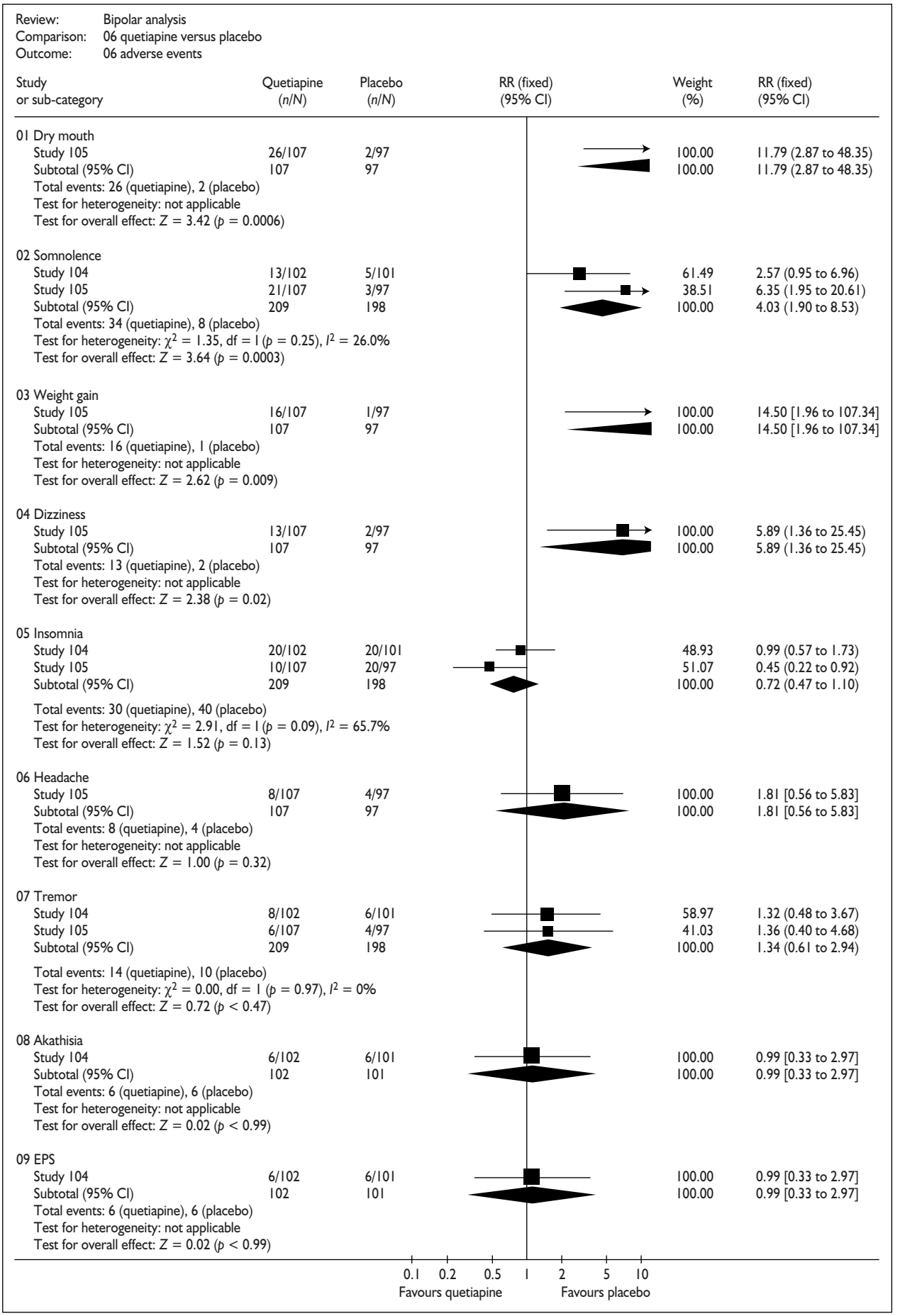

FIGURE 7 *Adverse events – quetiapine monotherapy versus placebo*

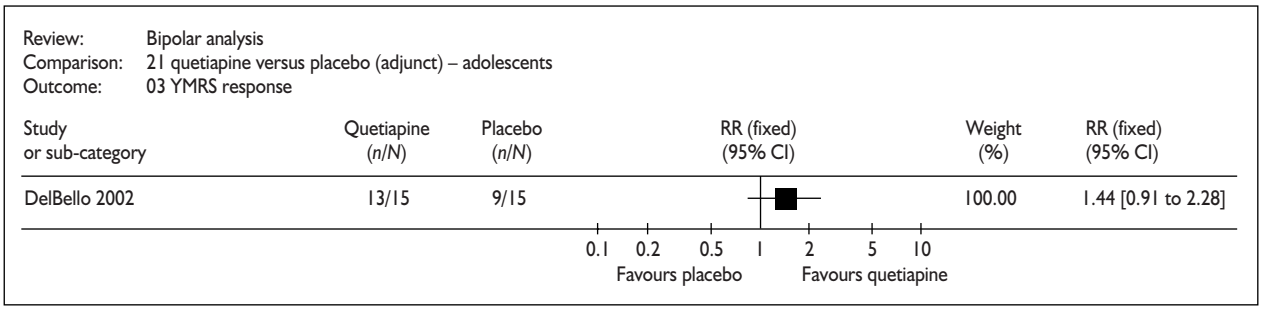

FIGURE 8 *YMRS response – adolescents – quetiapine adjunct therapy versus placebo*

Study 99 was of 3 weeks duration but no results were reported in the published abstract.[28]

One study (DelBello 2002[33]) compared quetiapine as an adjunct to valproate semisodium with placebo adjunct to valproate semisodium in adolescents. The duration of this study was 6 weeks.

Global effects

Adults

Study 99[26,27] reported CGI-BP change scores with standard errors. The result showed no significant difference between groups [mean difference (MD) –0.60, 95% CI –3.81 to 2.61].

Study 99[26,27] also reported CGI-BP response rates. The result found in favour of the quetiapine adjunct arm (RR 1.61, 95% CI 1.09 to 2.37).

Effects on mania

Adults

Study 99[26,27] reported YMRS change scores with standard errors. The result showed no significant difference between trial arms (MD –3.83, 95% CI –8.09 to 0.43).

Study 99[26,27] also reported YMRS response (defined as at least a 50% decrease in YMRS score). The result favours the quetiapine adjunct arm (RR 1.67, 95% CI 1.15 to 2.42).

Remission (defined as a YMRS score of 12 and a score of ≤ 2 on each subscale: irritability, speech, content, disruptive/aggressive behaviour) favoured quetiapine (RR 1.77, 95% CI 1.14 to 2.73). **[CIC data have been removed.]**

Adolescents

YMRS scores were measured in DelBello 2002[33] but not reported fully. The trial authors reported that the quetiapine adjunct group had a significantly greater reduction in YMRS score than the control group ($p = 0.03$). YMRS response (defined as at least a 50% decrease in YMRS score) showed a trend towards favouring quetiapine but this was not statistically significant (RR 1.44, 95% CI 0.91 to 2.28) (*Figure 8*).

[CIC data from Study 99 have been removed.]

Other psychiatric assessments

Adults

Study 99[26,27] reported PANSS total change scores and PANSS agitation and aggression scores, without any measures of variance. We could not calculate 95% CIs around the MD of 2.33 for PANSS total in Study 99 (reported $p = 0.323$) or of 1.8 ($p = 0.02$ in favour of the quetiapine arm) for PANSS agitation and aggression scores in Study 99.

In Study 99[26,27] there was no significant difference between groups in the risk of emergent depressive symptoms, defined on the MADRS scale (RR 1.37, 95% CI 0.68 to 2.78).

Adolescents

In DelBello 2002,[33] measurements were taken on the CDRS, the PANSS-positive scale and the CGAS; however, data are not reported. The trial authors report that there were no significant differences between groups in change from baseline to end-point in the CDRS ($p = 1.0$), PANSS-P ($p = 0.8$) and CGAS ($p = 0.2$) scales.

Leaving the study early

Adults

In Study 99,[26,27] there was no significant difference between trial arms in attrition for any reason.

Adolescents

Although more people left the study early in the quetiapine adjunct group (7/15) than the placebo group (1/15), this difference was not statistically significant (RR 7.00, 95% CI 0.98 to 50.16) (*Figure 9*).

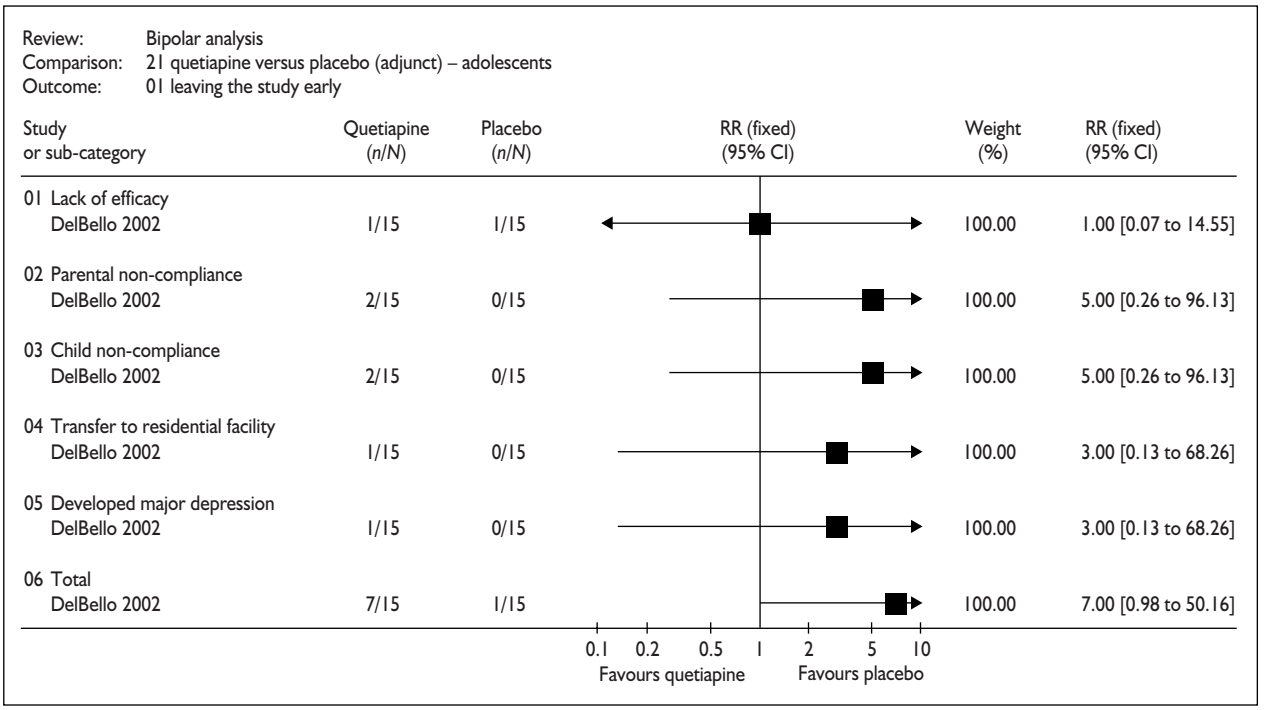

FIGURE 9 *Leaving the study early – adolescents – quetiapine adjunct therapy versus placebo*

Adverse effects

Adults

Study 99[26,27] reported some adverse events. People in the quetiapine adjunct arm were more likely to experience dry mouth (RR 4.67, 95% CI 1.63 to 13.37), somnolence (RR 3.96, 95% CI 2.08 to 7.51), postural hypotension (RR 3.66, 95% CI 1.04 to 12.90) and asthenia (RR 3.66, 95% CI 1.04 to 12.90). No adverse event occurred more frequently in the placebo arm.

Adolescents

In DelBello 2002,[33] sedation was significantly more likely to occur in the quetiapine group than the placebo group (RR 2.40, 95% CI 1.12 to 5.13) (*Figure 10*). The other reported adverse events of nausea/vomiting, dizziness, headache, gastrointestinal irritation, joint pain and dry mouth were no more or less likely to occur in the quetiapine than the placebo group. Measures of movement disorder (SAS, BAS and AIMS scores) showed no significant differences between groups (*Figure 11*).

Receipt of lorazepam

Adolescents

People in the quetiapine group were no more or less likely to receive additional lorazepam than people in the placebo group (RR 0.67, 95% CI 0.13 to 3.44) (*Figure 12*).

Quetiapine versus lithium

One study (Study 105) compared quetiapine with lithium. **[Some CIC data from Study 105 have been removed.]**

Global effects

CGI-BP response rate was reported (as 'improved' or 'much improved' on the CGI-BP scale). The result showed no significant difference between quetiapine and lithium groups (RR 0.99, 95% CI 0.80 to 1.21) (*Figure 13*).

Effects on mania

YMRS change scores were reported but with no measure of variance, so we could not calculate 95% CIs around the MD of 0.58. Response rates were also reported using YMRS criteria. Response was defined as at least a 50% decrease in YMRS score.

The result for response does not favour lithium or quetiapine (RR 1.02, 95% CI 0.79 to 1.33) (*Figure 14*).

Other psychiatric assessments

There was no significant difference between groups in risk of emergent depressive symptoms, defined on the MADRS scale (RR 1.37, 95% CI 0.23 to 8.05) (*Figure 15*).

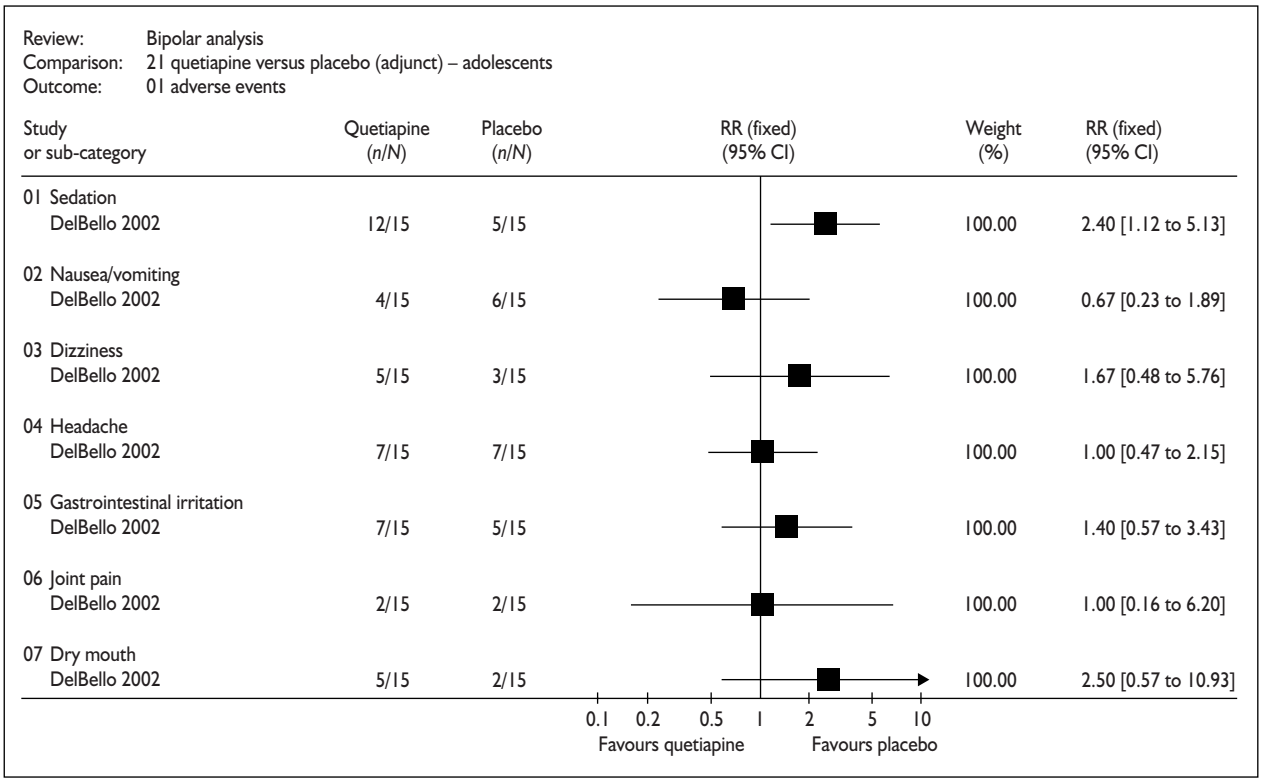

FIGURE 10 *Adverse events – adolescents – quetiapine adjunct therapy versus placebo*

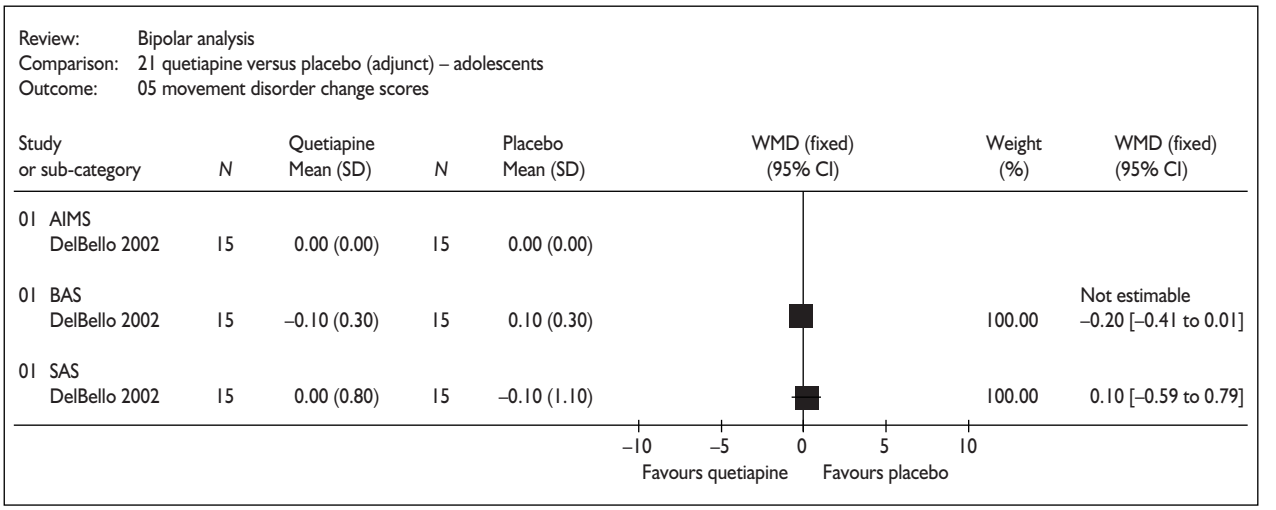

FIGURE 11 *Movement disorder change scores – adolescents – quetiapine adjunct therapy versus placebo*

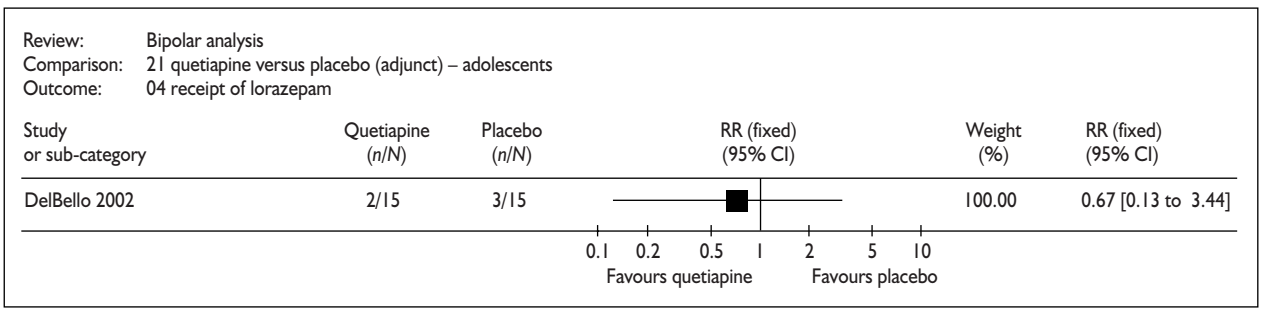

FIGURE 12 *Receipt of lorazepam – adolescents – quetiapine adjunct therapy versus placebo*

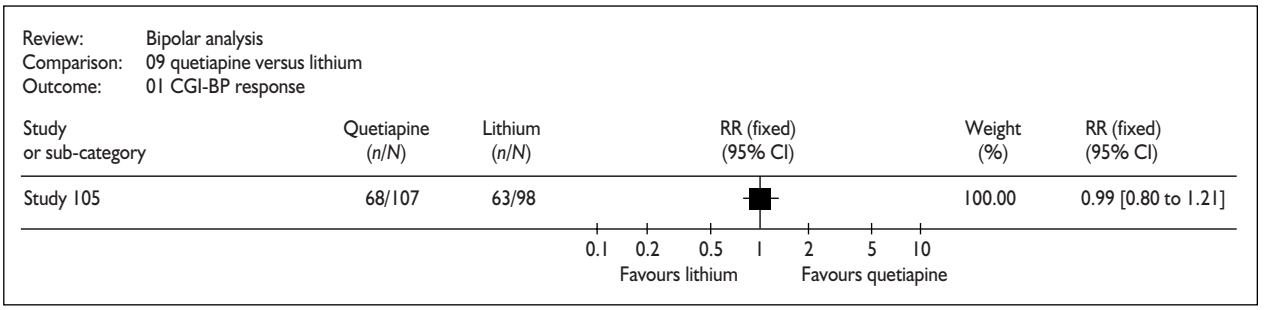

FIGURE 13 *CGI-BP response – quetiapine versus lithium*

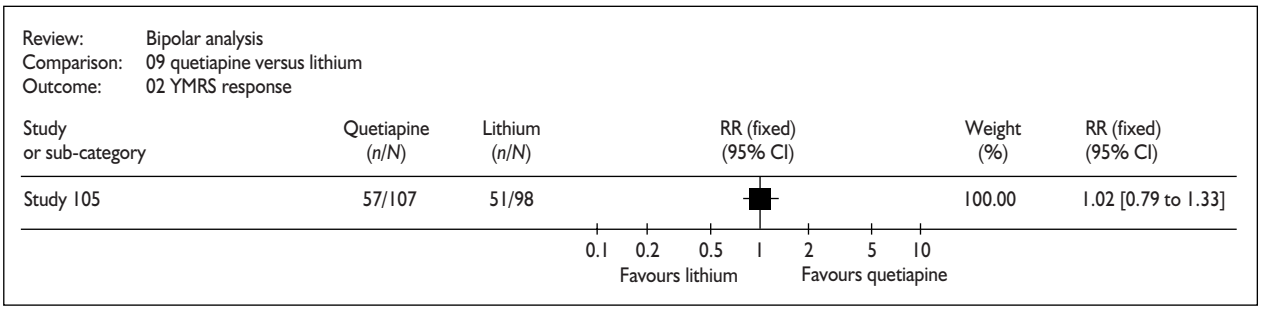

FIGURE 14 *YMRS response – quetiapine versus lithium*

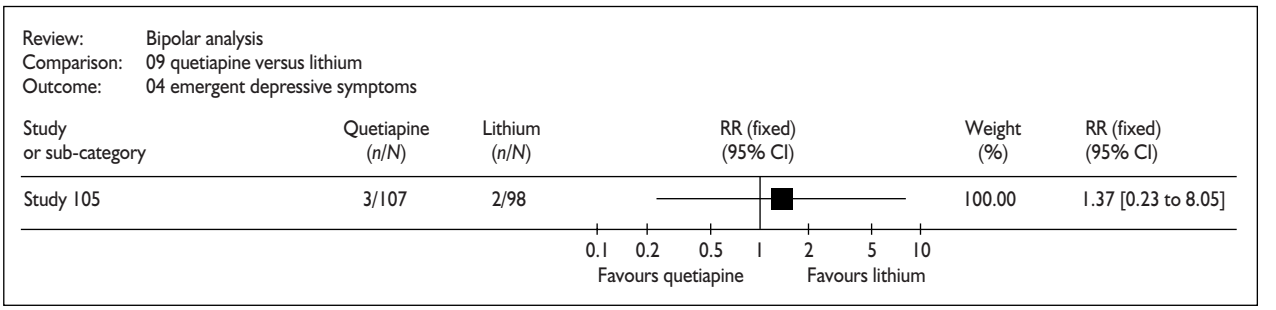

FIGURE 15 *Emergent depressive symptoms – quetiapine versus lithium*

Leaving the study early

There was no significant difference between quetiapine and lithium arms in likelihood of leaving the study early for any reason (*Figure 16*).

Adverse effects

People in the quetiapine arm were more likely to experience dry mouth (RR 3.97, 95% CI 1.71 to 9.23), somnolence (RR 2.14, 95% CI 1.03 to 4.44) or weight gain (RR 2.44, 95% CI 1.00 to 5.99) than people in the lithium arm. People in the lithium arm were more likely to experience tremor (RR 0.31, 95% CI 0.13 to 0.74) than people in the quetiapine arm (*Figure 17*).

Quetiapine versus haloperidol

One study (Study 104) compared quetiapine with haloperidol. **[Some CIC data from Study 104 have been removed.]**

Global effects

CGI-BP response rate was reported (as 'improved' or 'much improved' on the CGI-BP scale). The result showed no significant difference between quetiapine and haloperidol groups (RR 0.82, 95% CI 0.61 to 1.10). Sensitivity analysis using positive assumptions for missing persons did not substantially affect this result (RR 0.82, 95% CI 0.61 to 1.10) (*Figure 18*).

Effects on mania

YMRS change scores were reported but with no measure of variance, so we could not calculate 95% CIs around the MD of 3.42. Response rates were also reported using YMRS criteria. Response was defined as at least a 50% decrease in YMRS score.

The result for response does not statistically favour haloperidol or quetiapine although there is a

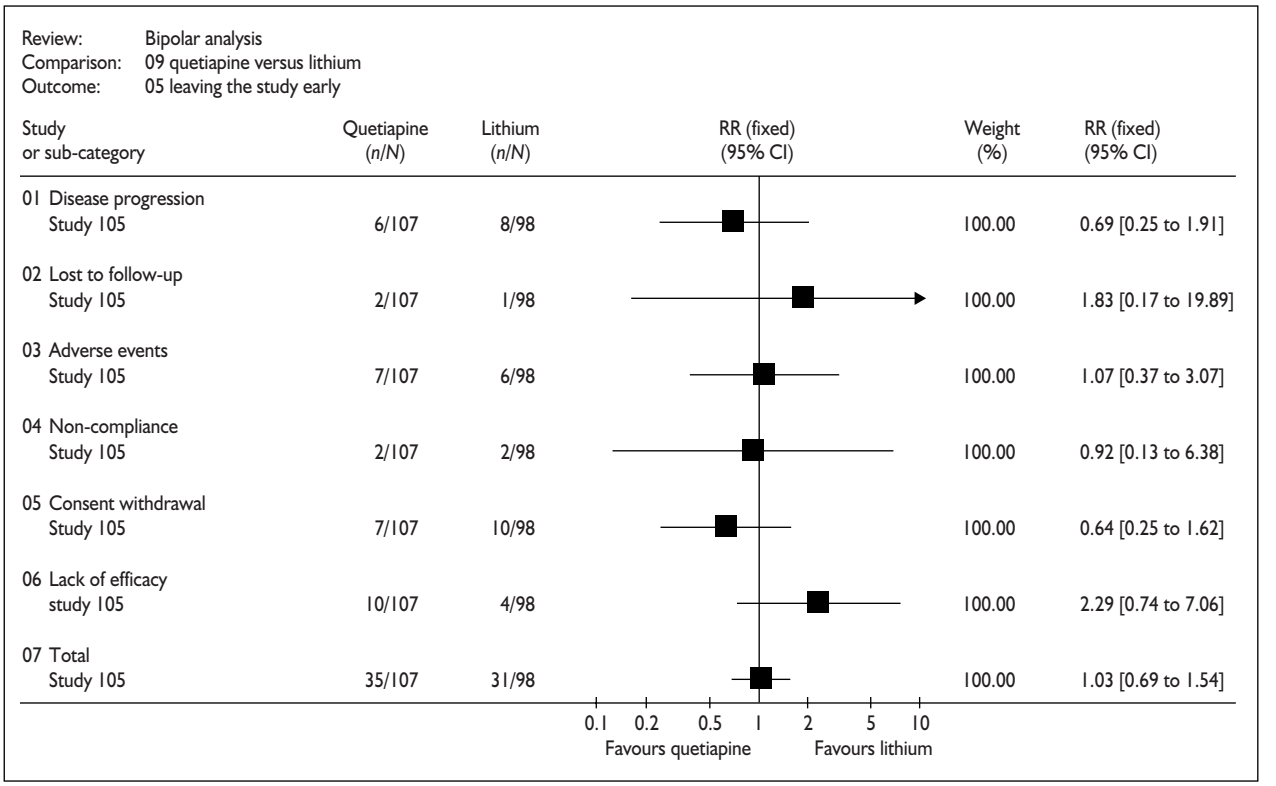

FIGURE 16 *Leaving the study early – quetiapine versus lithium*

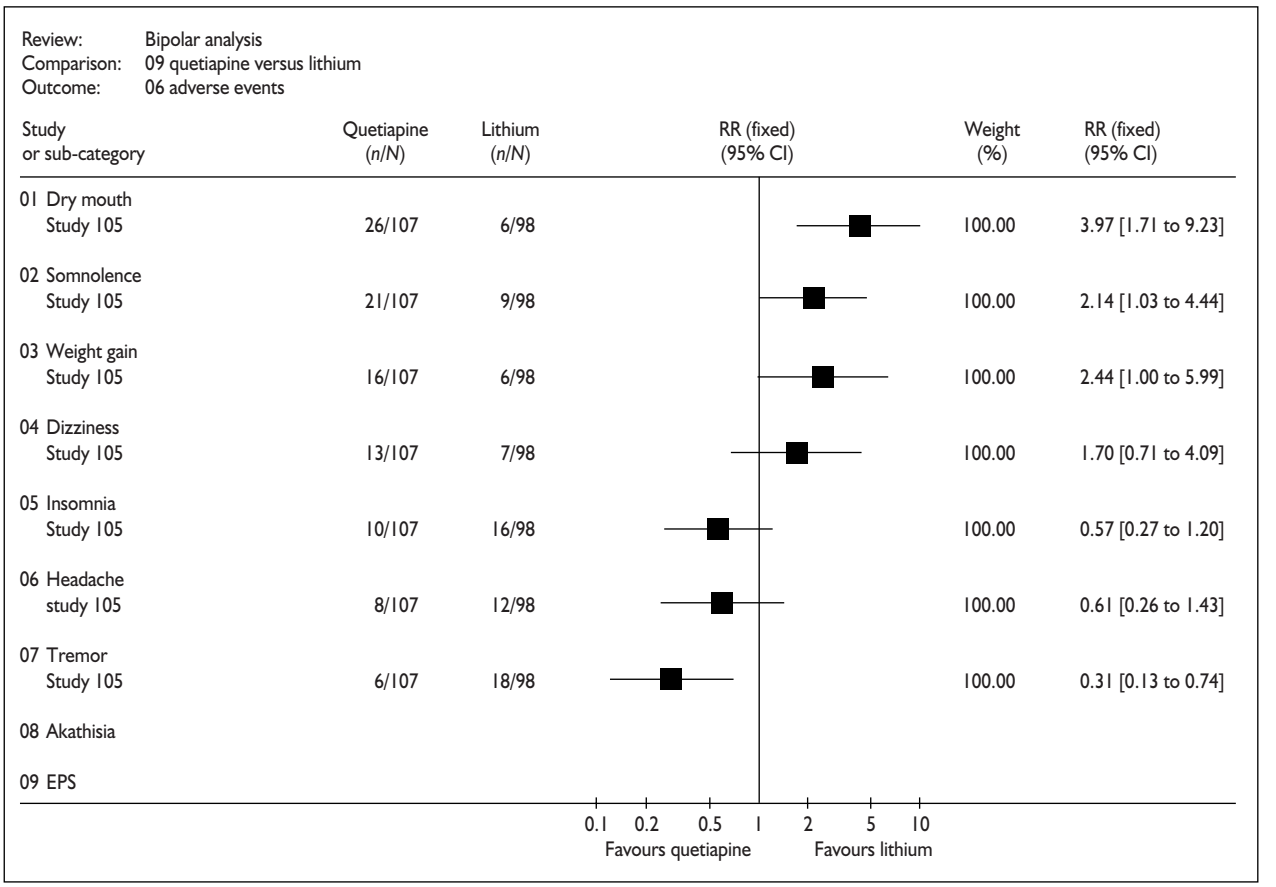

FIGURE 17 *Adverse events – quetiapine versus lithium*

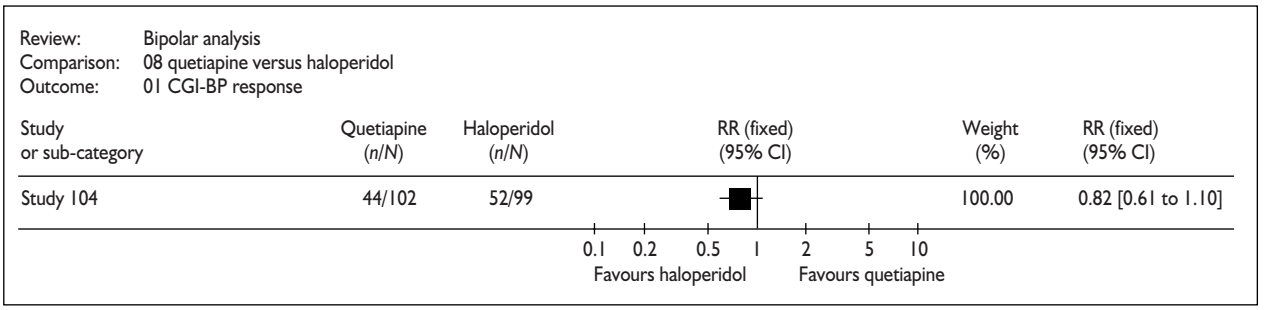

FIGURE 18 *CGI-BP response – quetiapine versus haloperidol*

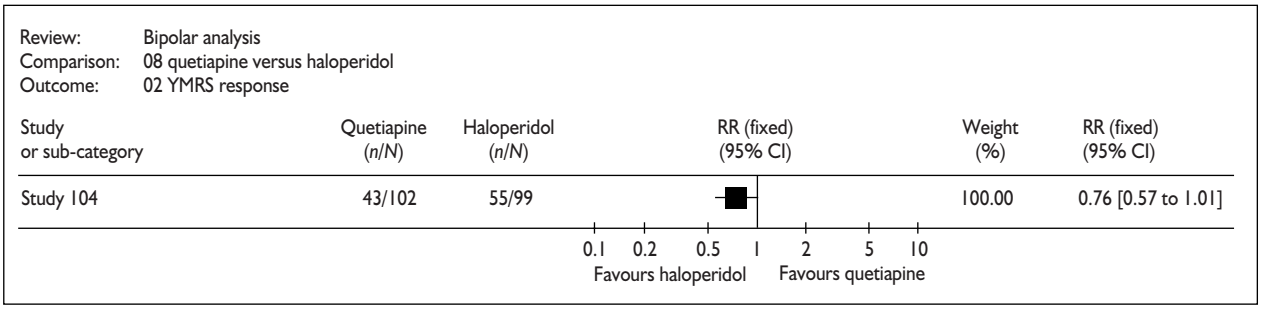

FIGURE 19 *YMRS response – quetiapine versus haloperidol*

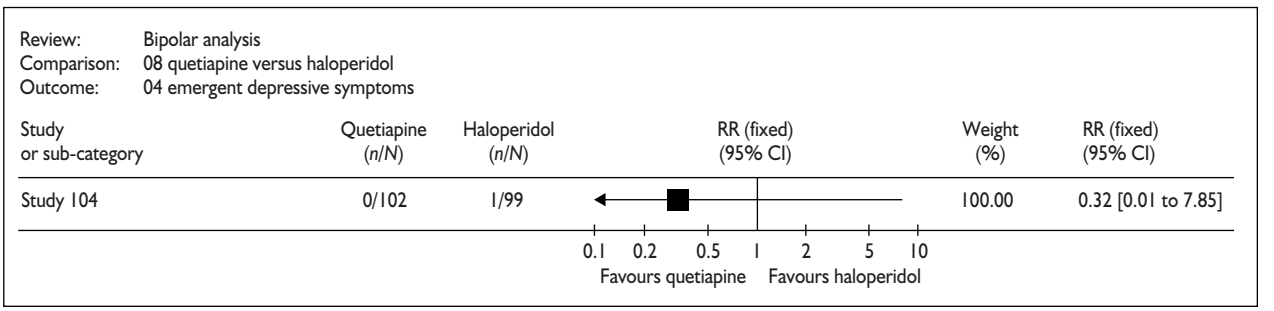

FIGURE 20 *Emergent depressive symptoms – quetiapine versus haloperidol*

trend in favour of haloperidol (RR 0.76, 95% CI 0.57 to 1.01). Sensitivity analysis using positive assumptions for missing persons did not substantially affect this result (RR 0.76, 95% CI 0.57 to 1.01) (*Figure 19*).

Other psychiatric assessments

There was no significant difference between groups in risk of emergent depressive symptoms, defined on the MADRS scale (RR 0.32, 95% CI 0.01 to 7.85) (*Figure 20*).

Leaving the study early

There was no significant difference between haloperidol and quetiapine groups in likelihood of leaving the study early for any reason (*Figure 21*).

Adverse effects

People in the haloperidol group were significantly more likely than people in the quetiapine group to experience tremor (RR 0.26, 95% CI 0.12 to 0.54), akathisia (RR 0.18, 95% CI 0.08 to 0.40) and EPS (RR 0.17, 95% CI 0.07 to 0.38) (*Figure 22*).

Olanzapine (Zyprexa®)

Six RCTs are included in this section: Tohen 1999,[35] Tohen 2000,[36] Tohen 2001,[37,38,39,44] Berk 1999,[40] Tohen 2002[41,45–47] and Meehan 2001[42,43] (*Table 2*).

Description of included trials

Two RCTs compared olanzapine with placebo,[35,36]

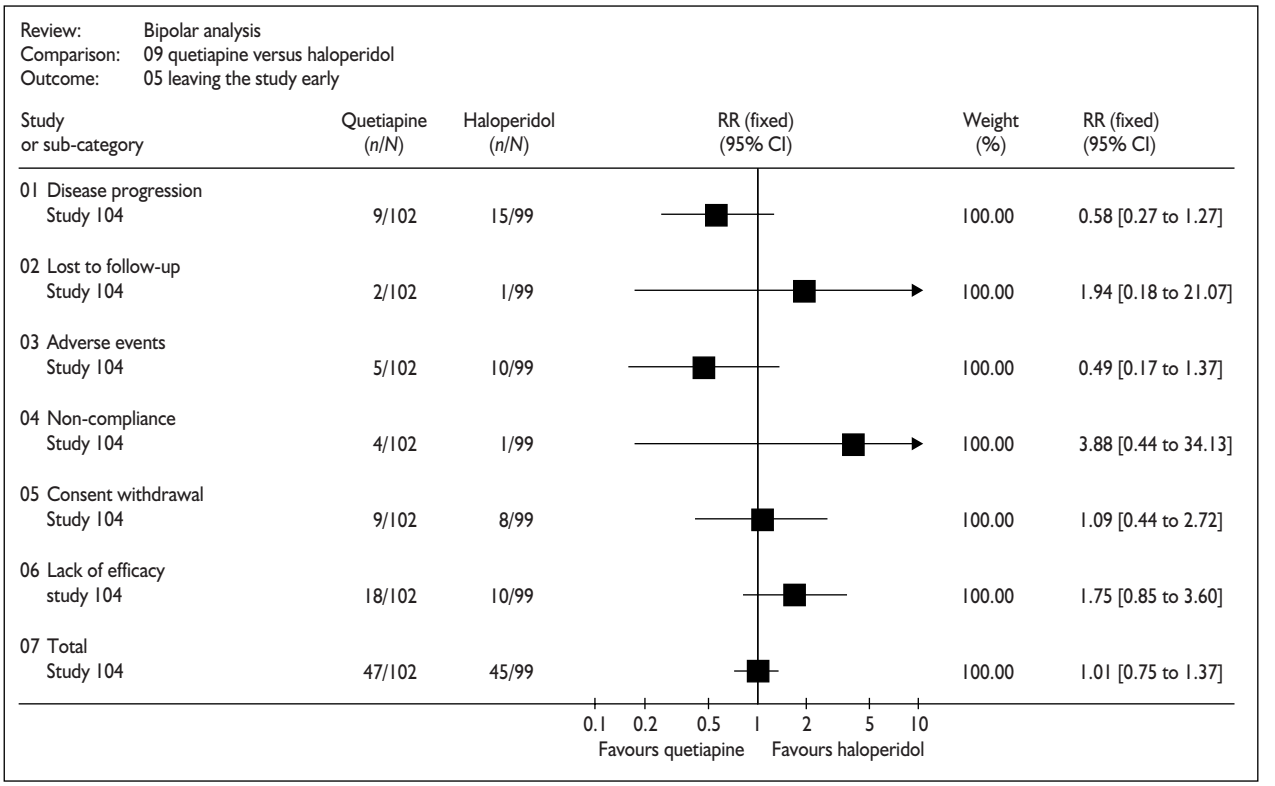

FIGURE 21 *Leaving the study early – quetiapine versus haloperidol*

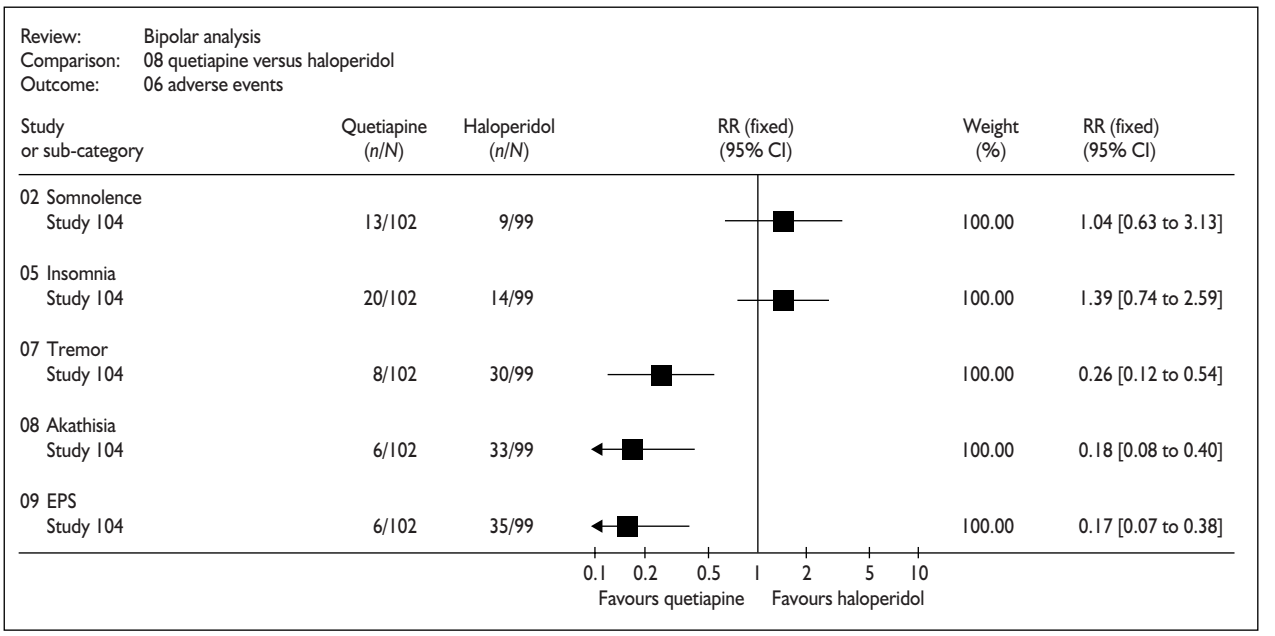

FIGURE 22 *Adverse events – quetiapine versus haloperidol*

one compared olanzapine with lithium,[40] one compared olanzapine plus valproate semisodium or lithium with placebo plus valproate semisodium or lithium,[41,45–47] one compared olanzapine with haloperidol[37–39,44] and one compared intramuscular olanzapine with lorazepam and with placebo.[42,43] The dose of olanzapine ranged, as clinically indicated, from 5 to 20 mg/day in five RCTs[35–37,40,41] and from 10 to 25 mg/day in one RCT.[42,43]

TABLE 2 *Included studies – olanzapine*

Study	Participants	Interventions	Outcomes
Berk 1999[40] (full paper)	*N* = 30 Diagnosis: DSM-IV bipolar disorder, acute manic episode. Severely ill (baseline BPRS mean 53.3, MAS 35.1)	4 weeks Olanzapine (*n* = 15) 10 mg/day Lithium carbonate (*n* = 15) 10 mg/day	Attrition EPS BPRS scores; CGI-I and CGI-S scores; MAS scores; GAF scores
Meehan 2001[42,43] (full paper)	*N* = 201 Diagnosis: DSM-IV bipolar disorder, manic or mixed. PANSS-EC score ≥ 14. Mean 16 years duration. 52.3% manic mixed with psychotic features, 87.5% mood congruent, 52.2% rapid cycling	24 hours Olanzapine (*n* = 99): 1–3 intramuscular injections (based on clinical judgment, 1st and 2nd 10 mg, 3rd 5 mg) Lorazepam (*n* = 51): 1–3 intramuscular injections (based on clinical judgment, 1st and 2nd 2 mg, 3rd 1 mg) Placebo (*n* = 51): 2 placebo injections (10 mg) and, if necessary, a third injection of olanzapine (10 mg)	Adverse events PANSS-EC scores; ABS scores; ACES scores
Tohen 1999[35] (full paper)	*N* = 139 Diagnosis: DSM-III-R bipolar disorder, manic or mixed episode. YMRS score ≥ 20. 82.7% manic episode, 17.3% mixed episode, 53.2% displayed psychotic features, 32.4% met DSM-IV criteria for rapid cycling	3 weeks Olanzapine (*n* = 70): 5–20 mg/day Placebo (*n* = 69): 5–20 mg/day	Attrition Adverse events YMRS scores; YMRS response
Tohen 2000[36] (full paper)	*N* = 115 Diagnosis: DSM-IV bipolar disorder, manic or mixed, with or without psychotic features. YMRS score ≥ 20. Mean duration 15–18 years. 43% mixed episode, 56% psychotic features	4 weeks Olanzapine (*n* = 55): 5–20 mg/day Placebo (*n* = 60): 5–20 mg/day	Attrition Adverse events YMRS scores
Tohen 2001[37–39,44] (poster, full paper)	*N* = 453 Diagnosis: DSM-IV bipolar I disorder, acute manic or mixed episode (with or without psychotic features). YMRS score ≥ 20. Mean age 38.0–40.3 years	6 weeks Olanzapine (*n* = 234): 5–20 mg/day Haloperidol (*n* = 219): 3–15 mg/day	Attrition Adverse events YMRS response, remission; MADRS, HAM-D scores; HAM-D treatment emergent depression; HRQoL (SF-36) scores; work status
Tohen 2002[41,45–47] (full paper)	*N* = 344 Diagnosis: DSM-IV bipolar disorder, manic or mixed, with or without psychotic features. YMRS score ≥ 16	4 weeks Olanzapine plus valproate or lithium (*n* = 229): max. 15 mg/day Placebo plus valproate or lithium (*n* = 115): max. 15 mg/day	Attrition Adverse events YMRS score; MRS remission; YMRS response

ABS, Agitated Behaviour Scale; ACES, Agitated Calmness Evaluation Scale; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Seventy; GAF, Global Assessment of Functioning; HAM-D, Hamilton Depression Rating Scale; HRQoL, health-related quality of life; MAS, Mania Assessment Scale; MRS, Mania Rating Scale; PANSS-EC, Positive and Negative Symptom Scale – Excited Component; SF-36, Short Form with 36 Items.

All trials recruited adults, with a mean age range of 31.2–40.6 years. Across four RCTs[35,36,41,42] male patients accounted for between 48 and 55% of participants, in one RCT 60% of participants were female[37] and in one trial the number of male and female patients was unclear.[40] In all trials, a diagnosis of bipolar disorder was established with reference to DSM-IV. In five trials patients with manic or mixed episodes were included,[35–37,41,42] and in one trial only patients experiencing an acute manic episode were included.[40] For participants to be included, three trials set a minimum score of 20 using the YMRS,[35–37] in one trial a minimum score of 16 on the YMRS was necessary[41] and in another trial a minimum score of 14 on the PANSS-EC was required for entry.[42]

In three trials, participants were excluded if they had serious, unstable medical illness, DSM-IV substance dependence (excluding nicotine and caffeine) within the past 3 months, and if they were at serious risk of suicide.[35–37] In one trial, patients were excluded if they had abnormal liver functions, thyroid function or haematological findings, acute medical disorder, medical disorder requiring frequent changes in medication, pre-existing cardiac disease, neuroleptic depot preparation in the last month, fluoxetine within 5 weeks, a history of recent drug or alcohol abuse, or if they were unable to comply with requirements of informed consent or treatment protocol.[40]

Validity

Only one RCT reported adequate randomisation procedures, although it was unclear in this trial whether allocation was adequately concealed.[36] The remaining five trials did not provide sufficient information to determine the adequacy or otherwise of randomisation and concealment of allocation.[35,37,40–42] In five trials, treatment groups were comparable at baseline,[35,37,40–42] whereas in one trial treatment groups were not comparable at baseline.[36] Participants were blinded in all trials, but none of the trials reported clearly that outcome assessors were also blinded. ITT analysis was used in four trials,[35–37,41] although in one trial ITT analysis was limited to adverse events and was not employed for effectiveness.[35] In two trials, it was unclear whether ITT analysis was used,[40,42] though the authors of one trial state that it was.[42]

Olanzapine versus placebo

Two studies compared olanzapine with placebo.[35,36] Olanzapine was given at a dose of between 5 and 20 mg/day in both trials. Participants in both trials were described as manic or mixed episode, and in one trial treatment duration was 3 weeks[35] whereas in the other it was 4 weeks.[36]

Global effects

Both trials reported data on global effects using the CGI-BP. The scale provides an assessment of severity of bipolar illness (total score), and contains two subscales relating to severity of mania and depression. Pooled results indicated significant differences in favour of olanzapine for total severity of bipolar illness (WMD –0.58, 95% CI –0.93 to –0.24), and on the mania subscale (–0.75 95% CI –1.12 to –0.38) (*Figure 23*). There was no significant difference between groups on the depression subscale. There was significant heterogeneity between scores on both the Clinical Global Impression (CGI) Scale total and its depression subscale. The source of this heterogeneity was unknown, and the results are of questionable reliability. However, with regard to the total score on the CGI Scale, the larger trial showed no statistically significant difference between the groups.

Effects on mania

Both trials reported change scores in the YMRS from baseline to end-point, including standard deviations (SDs). A WMD of –5.95 (95% CI –9.05 to –2.86) in favour of olanzapine was calculated when results were pooled (*Figure 24*).

Both trials[35,36] reported response to treatment, defined as ≥ 50% decrease in YMRS score. The pooled RR was in favour of olanzapine: 1.80 (95% CI 1.33 to 2.43). Sensitivity analysis using positive assumptions for missing persons did not substantially affect this result (RR 1.71, 95% CI 1.28 to 2.30) (*Figure 25*).

One trial[36] reported remission (defined as a YMRS score of ≤ 12). The result favoured olanzapine: RR 1.80 (95% CI 1.19 to 2.73). Sensitivity analysis using positive assumptions for missing persons did not substantially affect this result (RR 1.71, 95% CI 1.13 to 2.58) (*Figure 26*).

Other psychiatric assessments

Other psychiatric assessments were not reported.

Leaving the study early

Both studies reported the number of participants who left the study early. Significantly fewer participants in the olanzapine treatment group withdrew from the study before completion (pooled RR 0.62, 95% CI 0.48 to 0.80) (*Figure 27*).

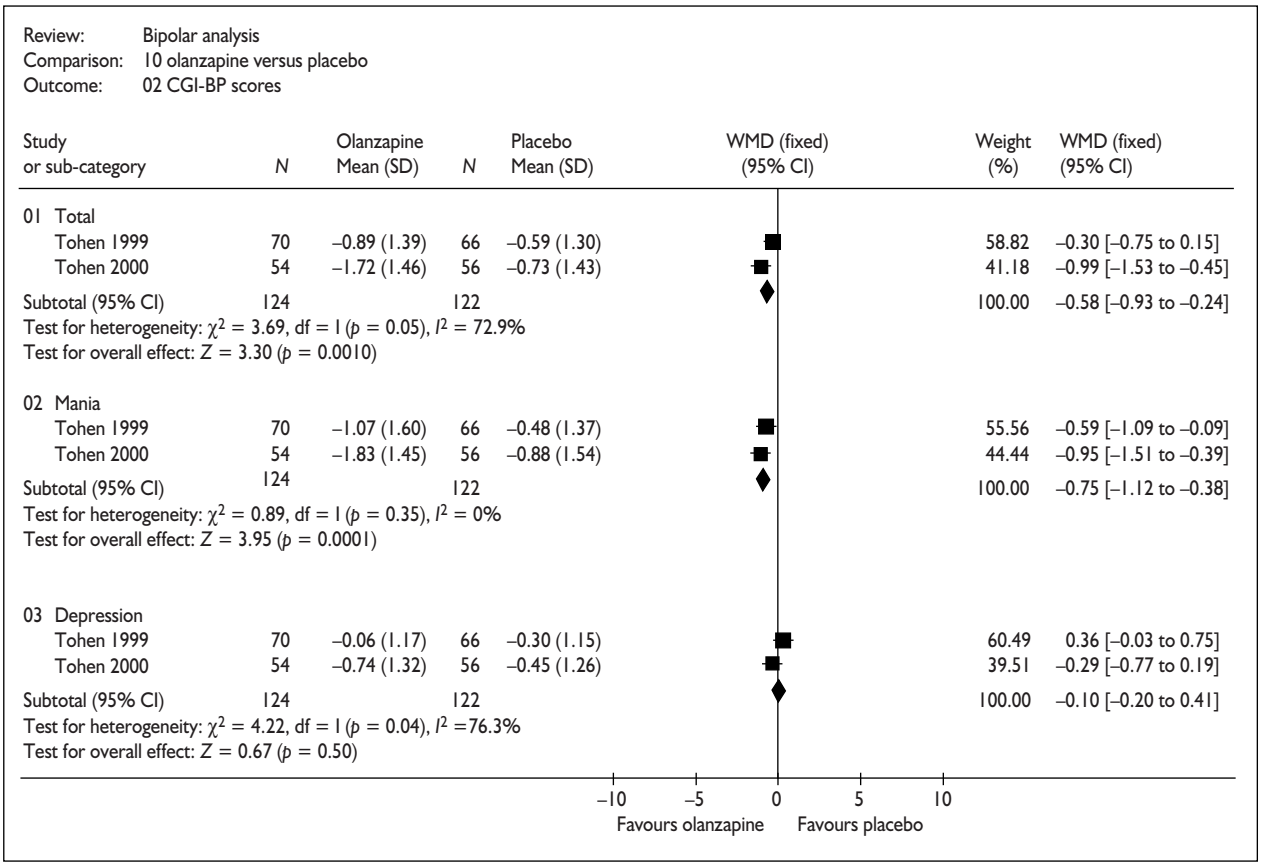

FIGURE 23 *CGI-BP scores*

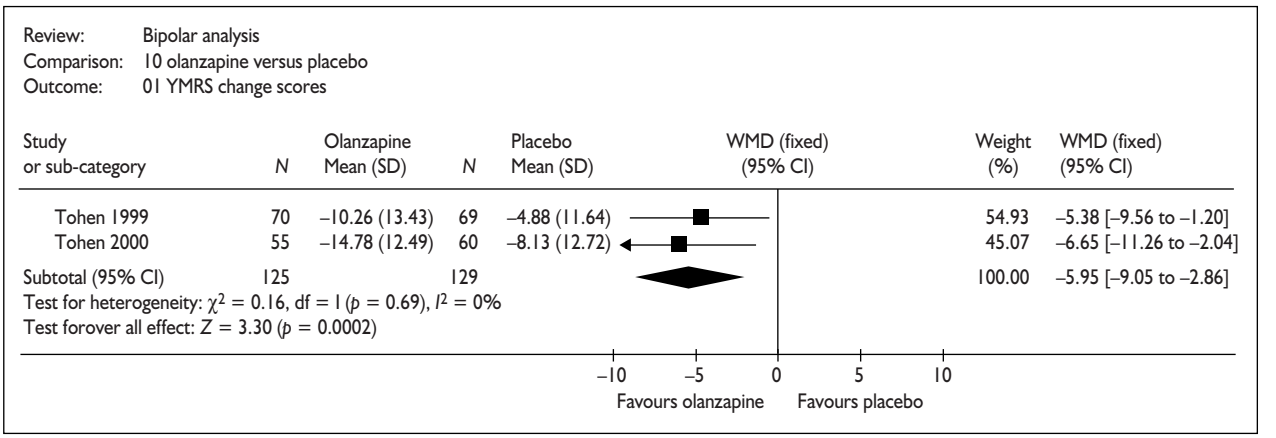

FIGURE 24 *YMRS change scores*

Length of stay

Neither study reported explicitly on length of stay in hospital.

Receipt of lorazepam

Receipt of lorazepam was not reported.

Adverse effects

One study reported adequate data on adverse events.[35] There were significant differences favouring the placebo group on measures of somnolence (RR 1.89, 95% CI 1.02 to 3.49), dry mouth (RR 2.96, 95% CI 1.25 to 7.00), dizziness (RR 3.94, 95% CI 1.39 to 11.20) and weight gain (RR 7.89, 95% CI 1.01 to 61.39). There were trends towards significance favouring the placebo group on measures of asthenia (RR 2.56, 95% CI 0.97 to 6.80), constipation (RR 3.94, 95% CI 0.87 to 17.91) and pain (RR 2.63, 95% CI 0.73 to 9.50) (*Figure 28*). There were no significant differences

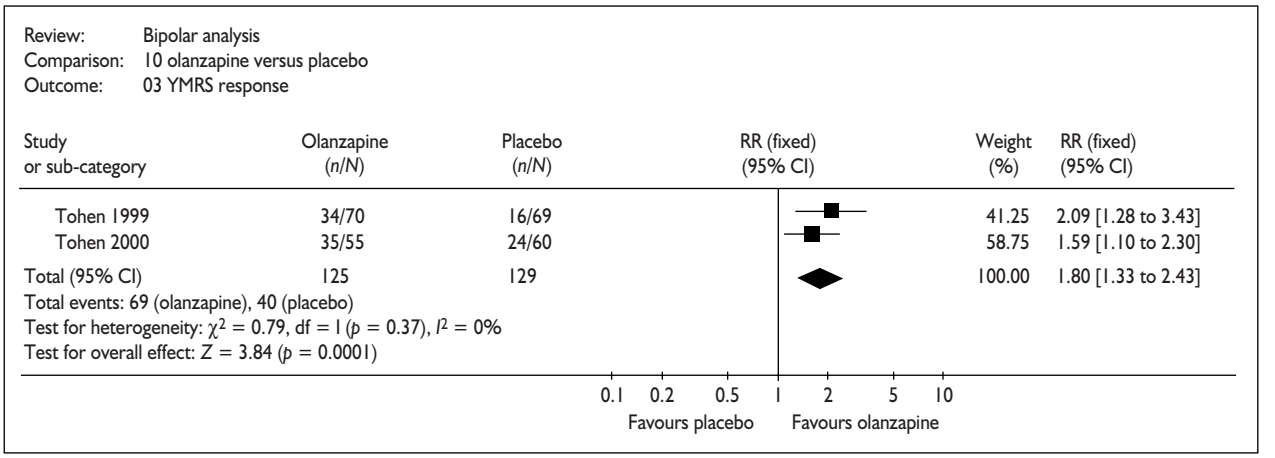

FIGURE 25 *YMRS response*

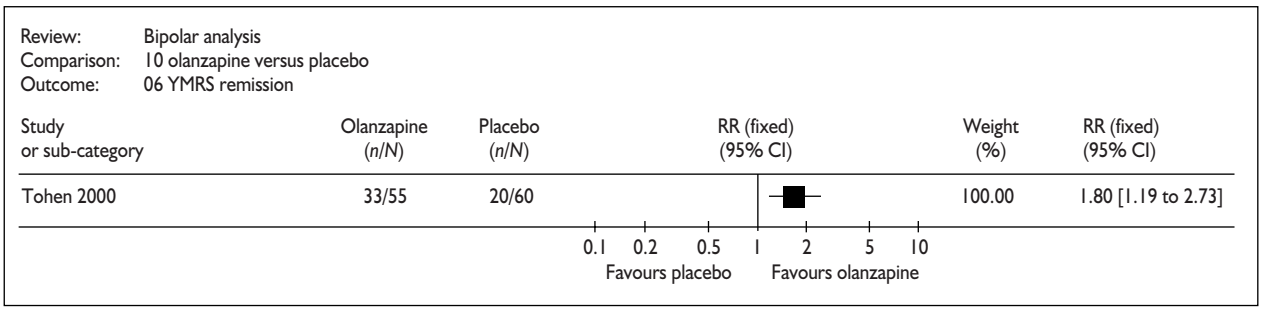

FIGURE 26 *YMRS remission*

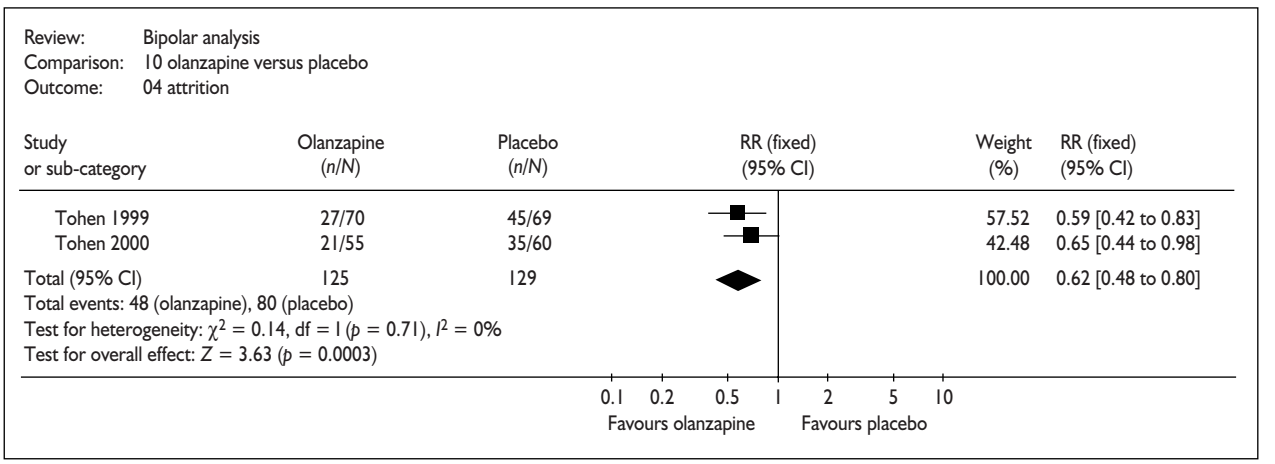

FIGURE 27 *Attrition*

between the olanzapine and placebo groups on measures of agitation, headache, anxiety, depression, hostility, nervousness and personality disorder.

The second study[36] reported that somnolence in the olanzapine group was significantly greater than in the placebo group ($p < 0.001$), whereas agitation was greater in the placebo group ($p = 0.03$).

Olanzapine versus lithium

One study compared olanzapine with lithium.[40] Olanzapine was given at a dose of 10 mg/day and lithium carbonate was given at 400 mg b.d. Participants were described as experiencing an

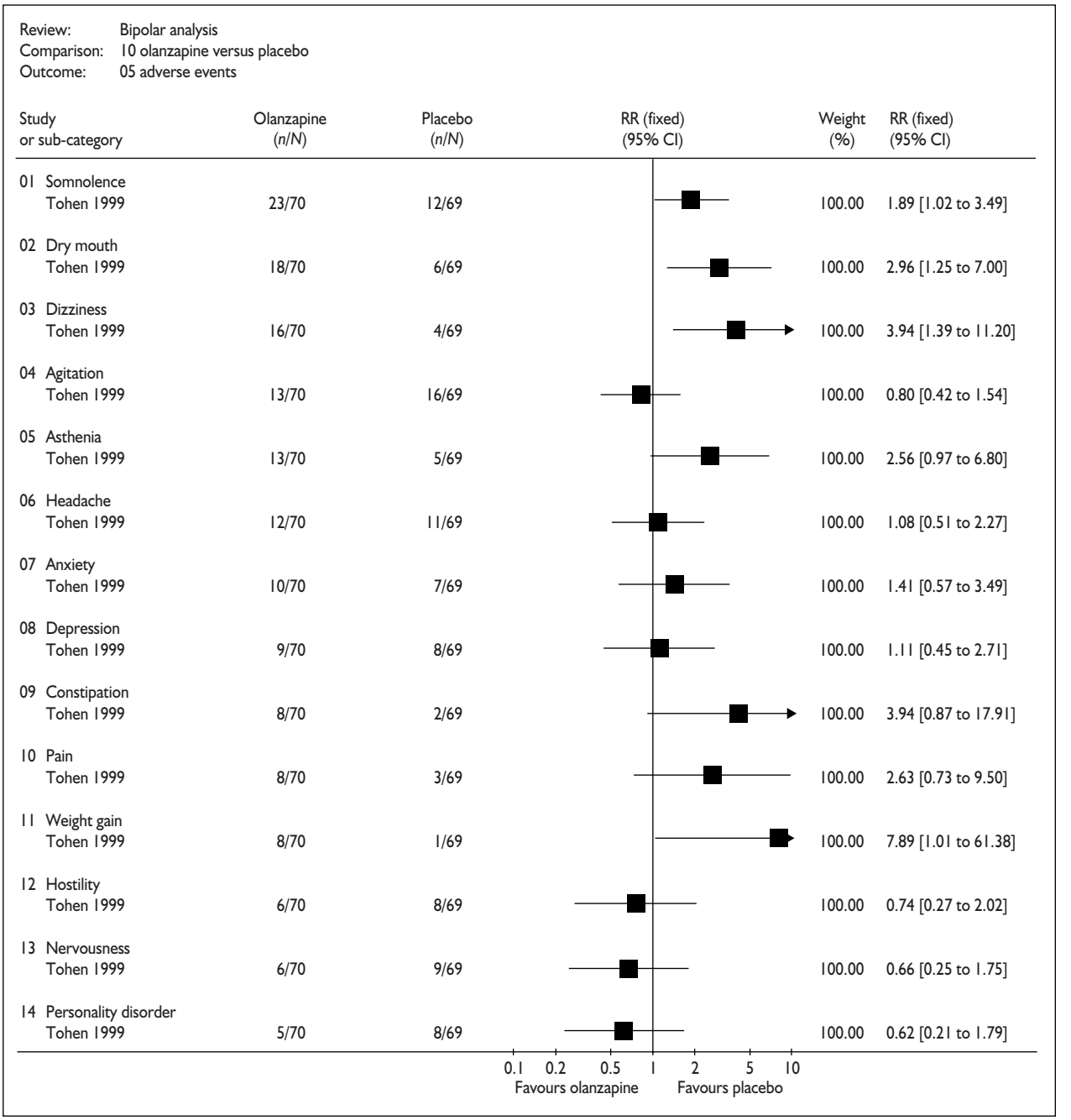

FIGURE 28 *Adverse events*

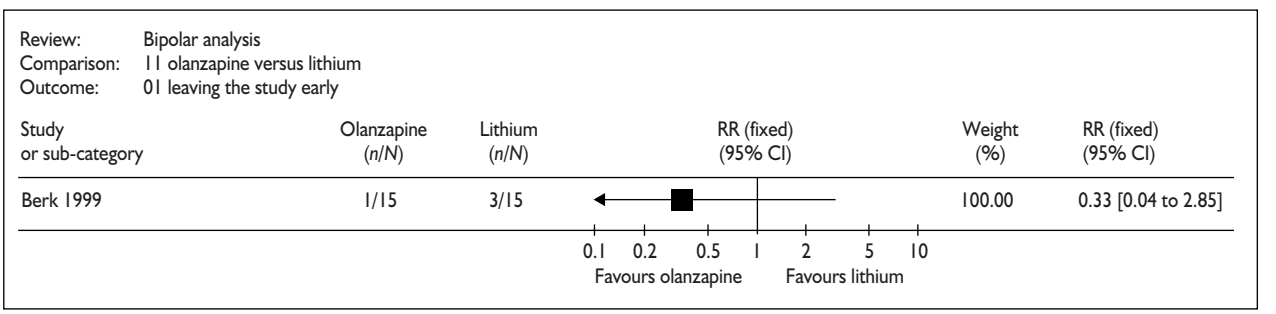

FIGURE 29 *leaving the study early – olanzapine versus lithium*

acute manic episode, and the duration of the trial was 4 weeks.

Global effects

Global effects were reported using the CGI-I, CGI-S and GAF scales. For the CGI-I and CGI-S scales, 4-week follow-up scores were presented for both groups with a *p*-value for the difference which was in favour of olanzapine for severity ($p = 0.025$) but not for improvement ($p = 0.163$). No estimates for variance in the results were presented. Therefore, the corresponding CIs for MDs in end-point scores between the groups (of 0.54 in favour of olanzapine for severity and 0.39 in favour of olanzapine for improvement) cannot be presented. For the GAF scale only 4-week follow-up scores for both groups with a *p*-value for the difference were presented. The MD in end-point scores was 1.7 in favour of olanzapine but this difference was not statistically significant ($p = 0.583$). No measures of variance were presented so we cannot calculate the 95% CI around this difference.

Effects on mania

Effects on mania were reported using the MAS. Again, no estimates for variance in the results were presented. Therefore, 95% CIs cannot be presented. However, the MD in end-point scores at 28 days was 3.0 and this difference was not statistically significant ($p = 0.315$).

Other psychiatric assessments

BPRS scores were reported. However, no estimates for variance in the results were presented. Therefore, 95% CIs cannot be presented. However, the MD in end-point scores at 28 days was 0.2 and this difference was not statistically significant ($p = 0.439$).

Leaving the study early

In the olanzapine group one withdrawal was reported for agitation, whereas in the lithium group two persons withdrew consent and one person withdrew because of an epileptic seizure. This did not amount to a statistically significant difference between groups (RR 0.33, 95% CI 0.04 to 2.85) (*Figure 29*).

Length of stay

Length of stay was not reported.

Receipt of lorazepam

According to the protocol, lorazepam, 4–12 mg daily, was given when necessary for control of aggression. Actual receipt of lorazepam during the intervention period was not reported.

Adverse effects

Olanzapine did not differ from lithium in terms of treatment-emergent EPS as measured by the SAS. Actual data were not reported.

Olanzapine plus valproate semisodium or lithium versus placebo plus valproate semisodium or lithium

One study compared olanzapine plus valproate semisodium or lithium with placebo plus valproate semisodium or lithium.[41] Olanzapine was given at a dose of two 5-mg capsules titrated up in increments of one capsule or down by any number of decrements at the investigator's discretion according to patient tolerance. The modal dose of olanzapine was 10.4 mg/day. Participants had manic or mixed episodes, and the duration of the trial was 4 weeks.

Global effects

Global effects were reported using the CGI-BP scale. Change scores after 28 days for olanzapine with valproate or lithium were significantly better then those for placebo with valproate or lithium (MD –0.31, 95% CI –0.60 to –0.02) (*Figure 30*).

Effects on mania

Effects on mania were reported using the YMRS. Again, change scores after 28 days for olanzapine with valproate or lithium were significantly better than those for placebo with valproate or lithium (MD –4.01, 95% CI –6.06 to –1.96) (*Figure 31*).

Response was reported as an improvement of ≥ 50% in YMRS scores and remission as a YMRS score of ≤ 12. The result for response found in favour of olanzapine (RR 1.47, 95% CI 1.17 to 1.84) (*Figure 32*), whereas the result for remission showed a trend in favour of olanzapine (RR 1.16, 95% CI 0.99 to 1.35) (*Figure 33*). Sensitivity analysis using positive assumptions for missing persons did not substantially affect the result for response (RR 1.51, 95% CI 1.21 to 1.89). The result for remission was in favour of olanzapine when the positive assumption for missing data was used (RR 1.20, 95% CI 1.03 to 1.39).

Time to response and time to remission were significantly ($p < 0.002$) lower in the olanzapine group than the placebo group.

Other psychiatric assessments

PANSS change scores significantly favoured olanzapine over placebo (MD –5.94, 95% CI –9.60 to –2.28) (*Figure 34*).

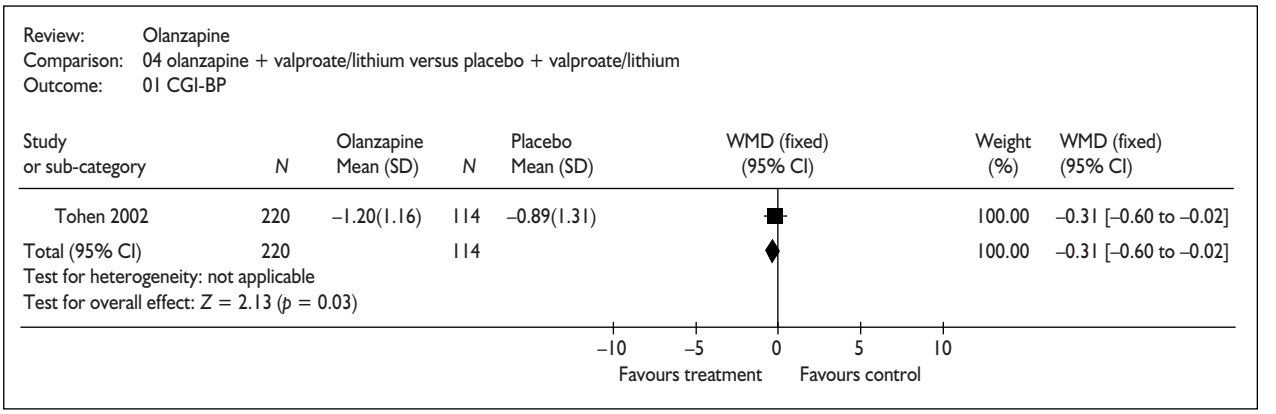

FIGURE 30 *CGI-BP change scores – olanzapine versus placebo (adjunct)*

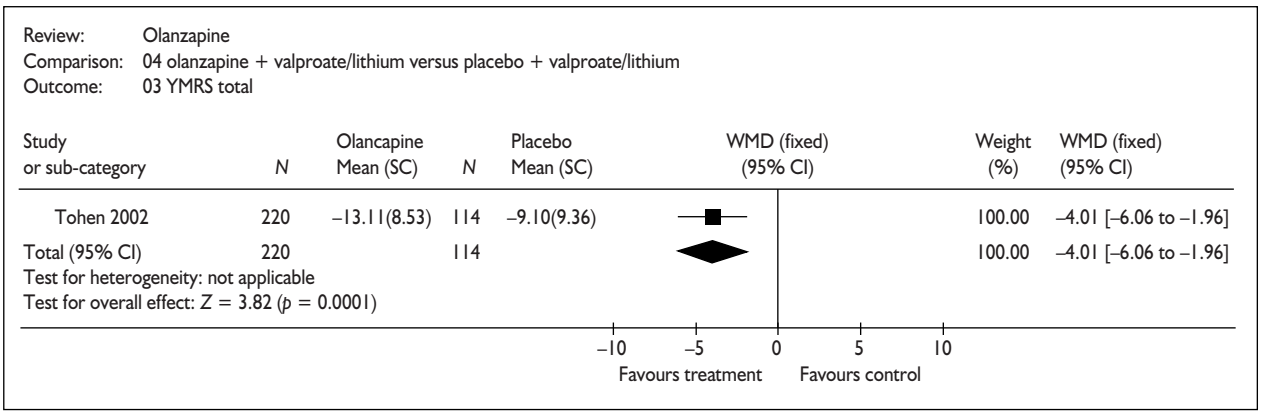

FIGURE 31 *YMRS change scores – olanzapine versus placebo (adjunct)*

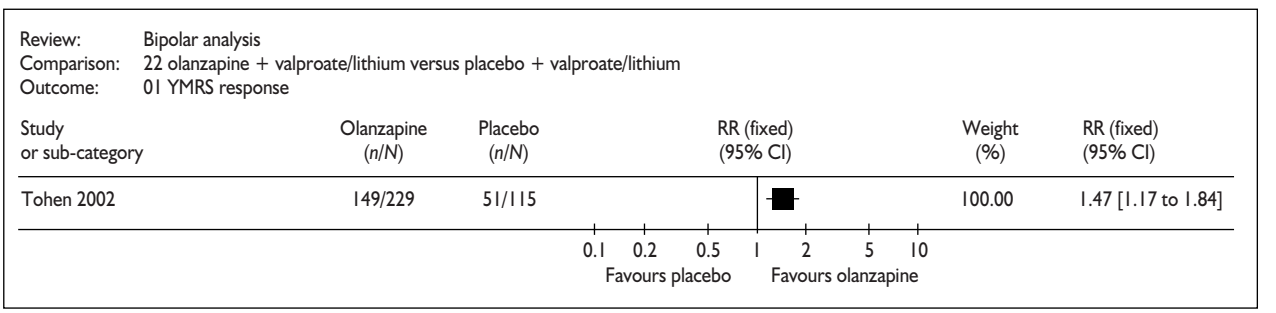

FIGURE 32 *YMRS response – olanzapine versus placebo (adjunct)*

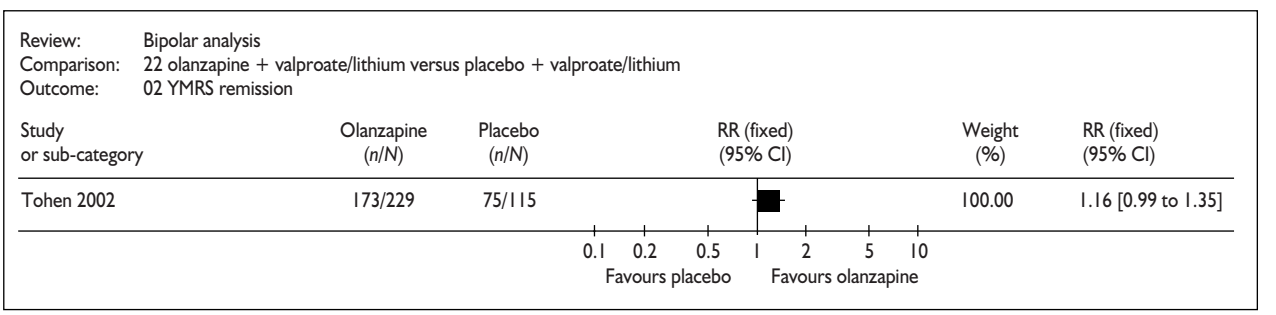

FIGURE 33 *YMRS remission – olanzapine versus placebo (adjunct)*

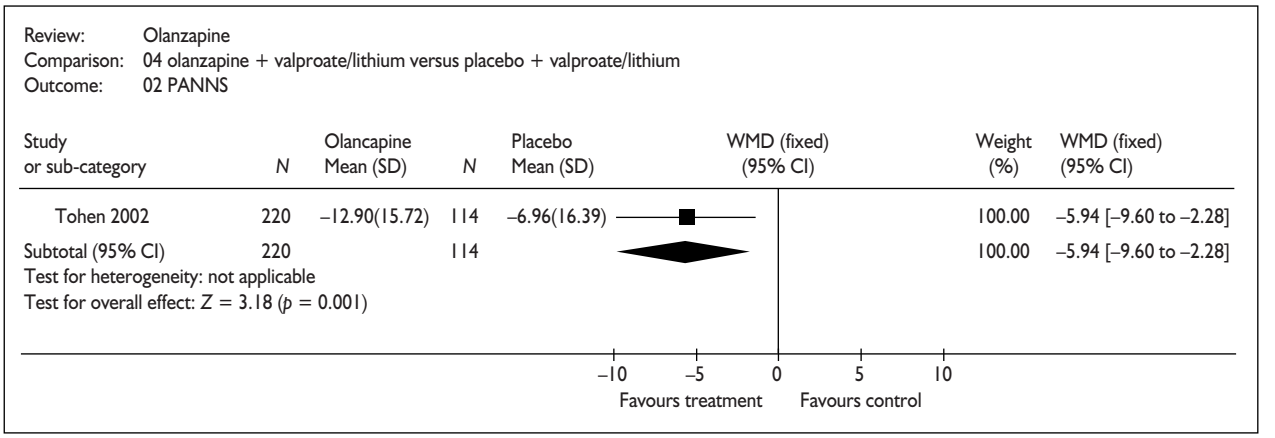

FIGURE 34 *PANSS change scores – olanzapine versus placebo (adjunct)*

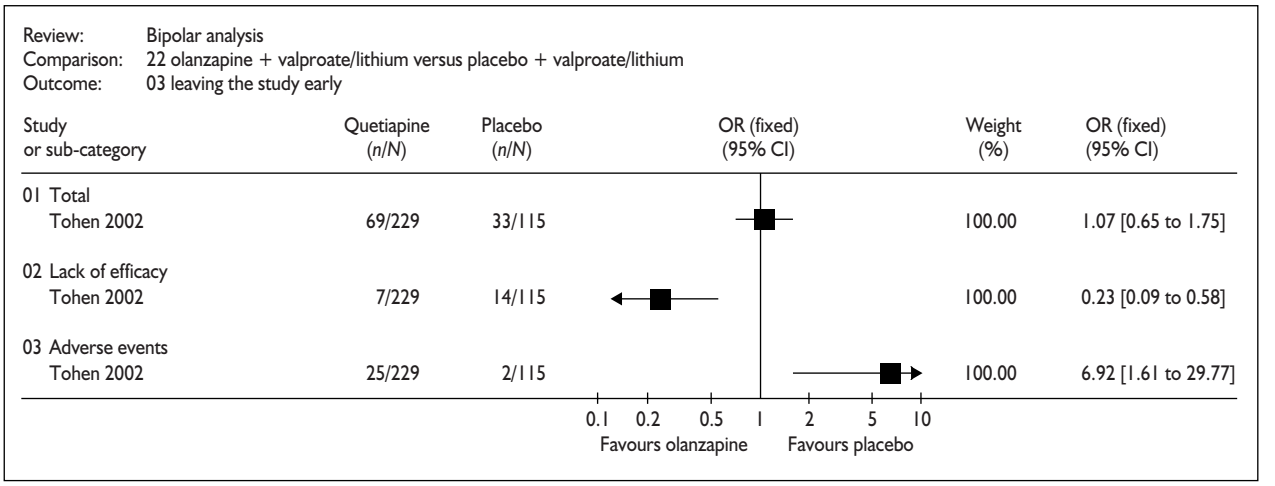

FIGURE 35 *Leaving the study early – olanzapine versus placebo (adjunct)*

Leaving the study early

In the olanzapine group, 69 respondents (30.1%) did not complete the study, compared with 33 (28.7%) in the placebo group (RR 1.05, 95% CI 0.74 to 1.49). Significantly more patients in the control group discontinued treatment owing to lack of efficacy (RR 0.25, 95% CI 0.10 to 0.60), whereas significantly more patients in the intervention group withdrew owing to adverse events (RR 6.28, 95% CI 1.51 to 26.04) (*Figure 35*).

Length of stay

Length of stay was not reported.

Receipt of lorazepam

Receipt of lorazepam was not reported.

Adverse effects

A number of adverse events occurred significantly more often in the olanzapine group: somnolence (RR 1.91, 95% CI 1.38 to 2.65), dry mouth (RR 4.07, 95% CI 2.12 to 7.84), weight gain (RR 3.77, 95% CI 1.86 to 7.61), increased appetite (RR 3.01, 95% CI 1.54 to 5.88), tremor (RR 1.77, 95% CI 1.05 to 3.01) and speech disorder (RR 7.53, 95% CI 1.01 to 56.32) (*Figure 36*).

Intramuscular olanzapine versus lorazepam versus placebo

One study compared intramuscular olanzapine with lorazepam with placebo.[42] Based on clinical judgement, patients received 1–3 intramuscular (i.m.) injections of olanzapine within 24 hours. The first and second injections were given at a dose of 10 mg and the third at 5 mg. Participants had manic or mixed episodes, and the duration of the trial was 24 hours.

Global effects

Global effects were reported using the CGI-S scale. Scores for olanzapine were not significantly different from those for lorazepam (MD –0.14,

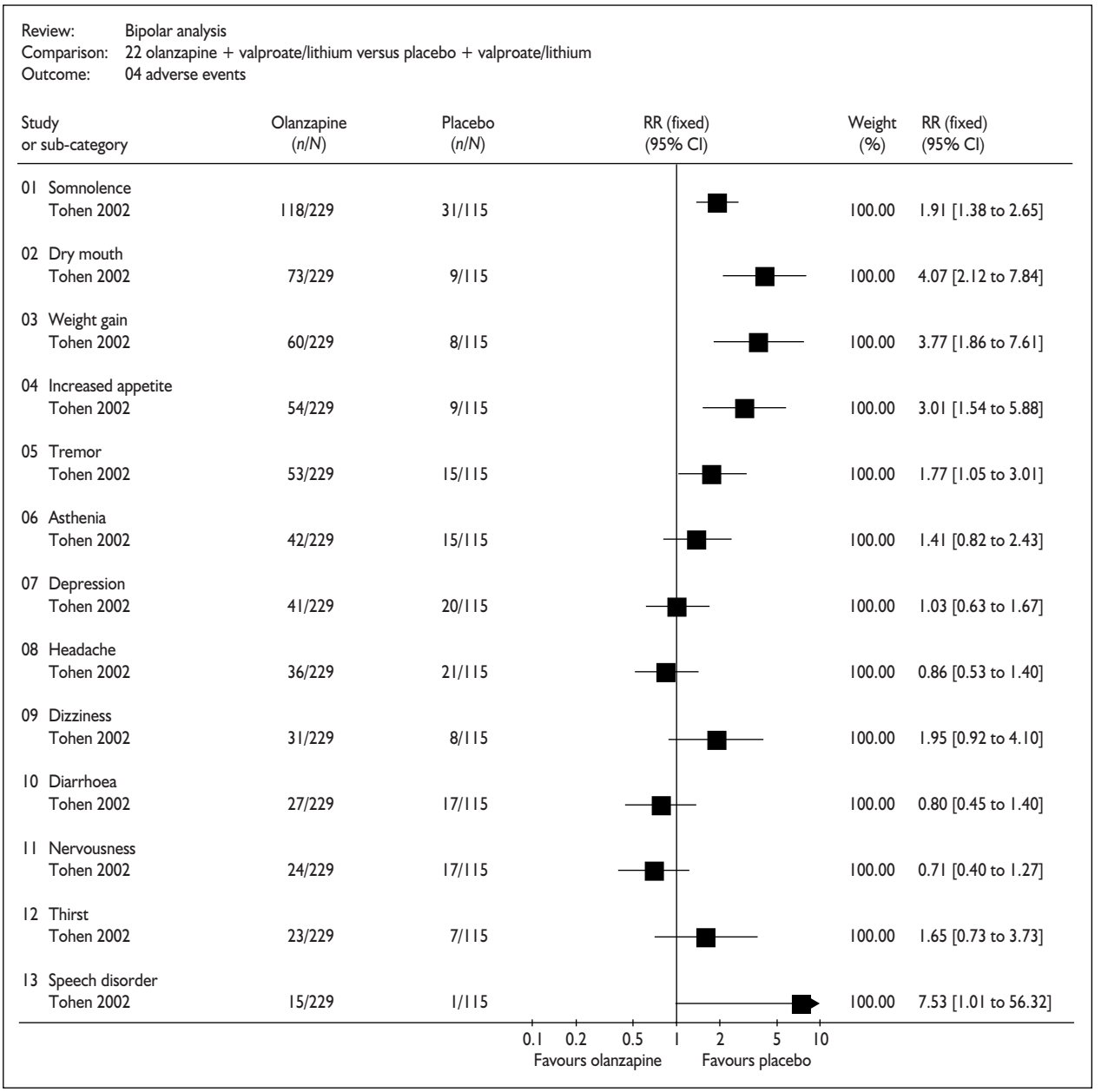

FIGURE 36 *Adverse events – olanzapine versus placebo (adjunct)*

95% CI –0.43 to 0.15) (*Figure 37*) or placebo (MD –0.07, 95% CI –0.58 to 0.44) (*Figure 38*).

Effects on mania

Agitation was measured using the PANNS-EC, two additional agitation scales, namely: the ABS and the ACES and also the YMRS.

None of these measures showed significant differences between olanzapine and lorazepam (PANNS-EC, MD –0.13, 95% CI –1.84 to 1.58; ABS, MD –0.12, 95% CI –2.13 to 1.89; ACES, MD –0.02, 95% CI –0.29 to 0.25; YMRS, MD –0.53, 95% CI –3.44 to 2.38. Comparisons between olanzapine and placebo groups showed significant differences in favour of olanzapine for scores on PANNS-EC, MD –1.84, 95% CI –3.36 to –0.32; ABS, MD –3.16, 95% CI –5.03 to –1.29; ACES, MD 0.48, 95% CI 0.16 to 0.80, but not for scores on YMRS, MD –1.54, 95% CI –5.39 to 2.31 (*Figures 39–46*).

Other psychiatric assessments

A PANNS-derived BPRS was assessed. This measure showed no significant difference between the olanzapine and the lorazepam group (MD –1.42, 95% CI –5.08 to 2.24 (*Figure 47*), but there was a significant difference favouring the

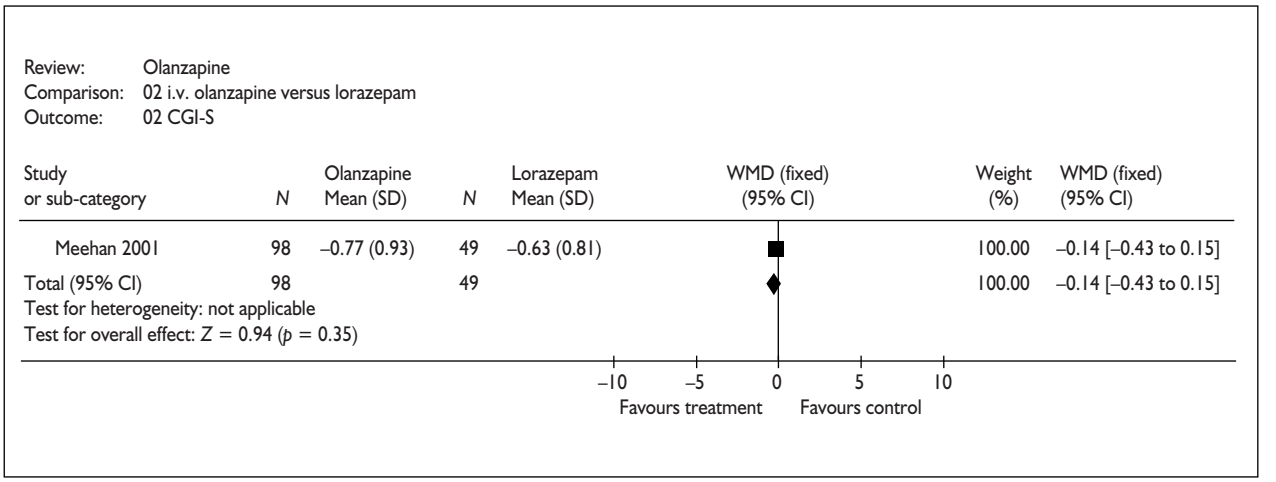

FIGURE 37 *CGI-S scores – i.m. olanzapine versus lorazepam*

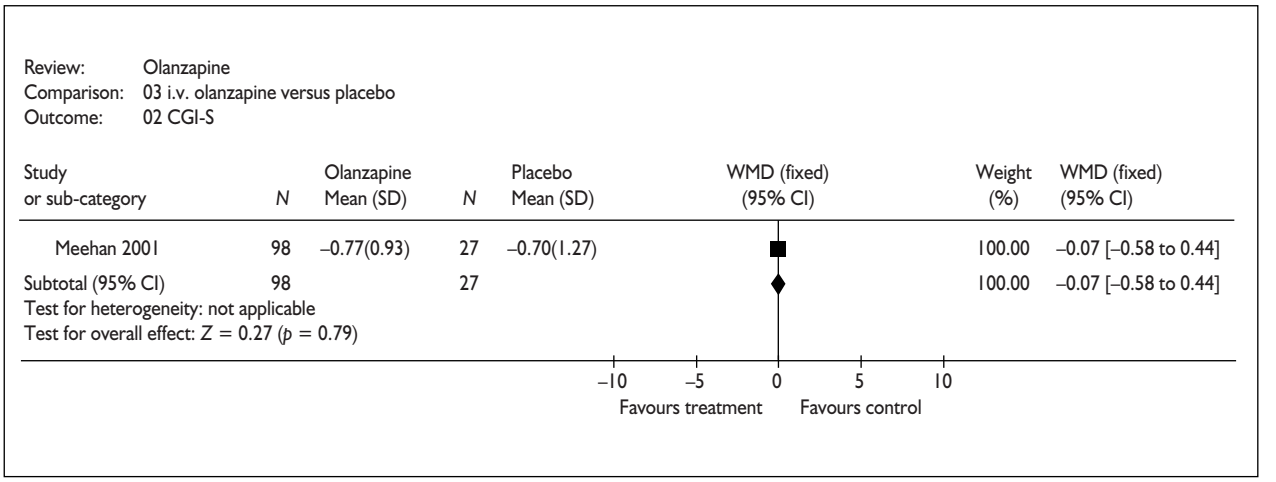

FIGURE 38 *CGI-S scores – i.m. olanzapine versus placebo*

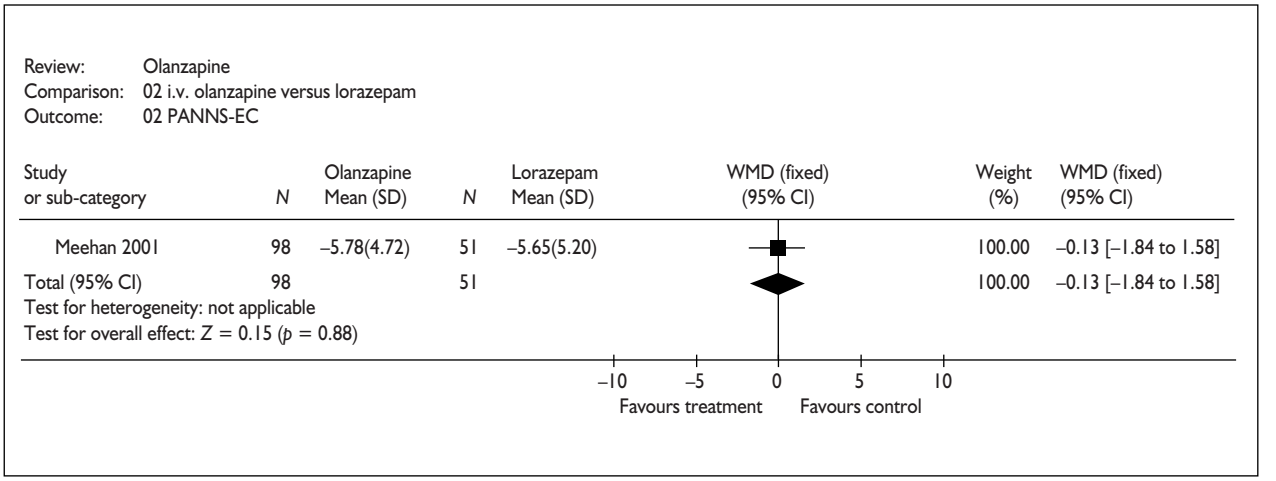

FIGURE 39 *PANSS-EC scores – i.m. olanzapine versus lorazepam*

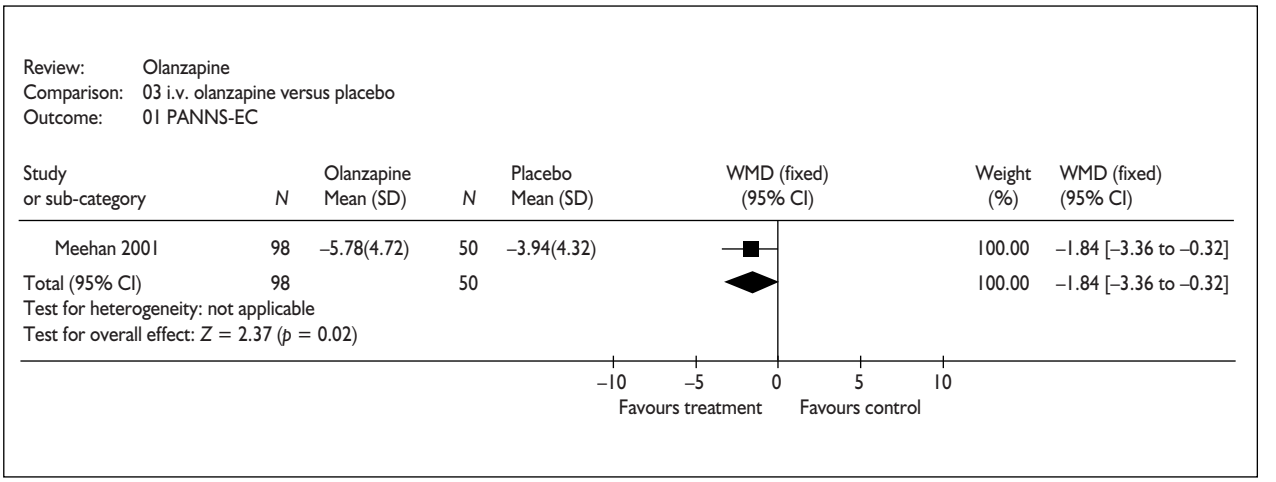

FIGURE 40 *PANSS-EC scores – i.m. olanzapine versus placebo*

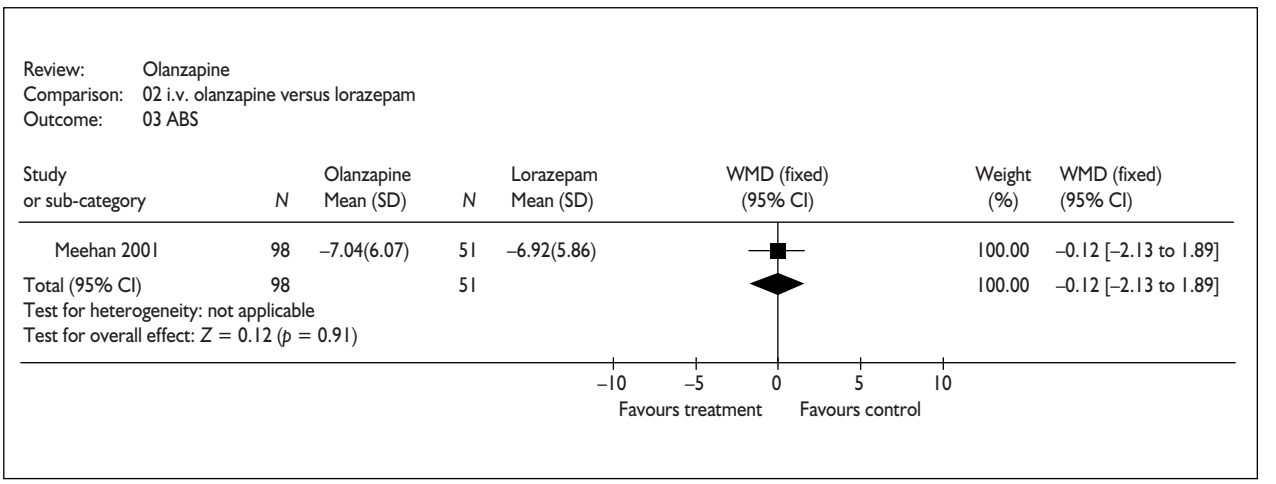

FIGURE 41 *ABS scores – i.m. olanzapine versus lorazepam*

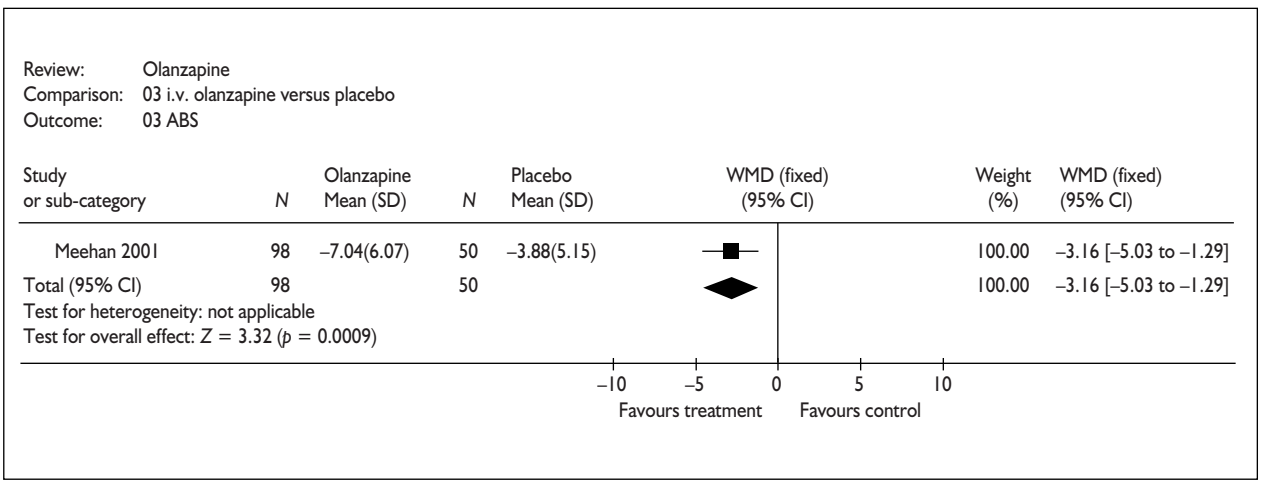

FIGURE 42 *ABS scores – i.m. olanzapine versus placebo*

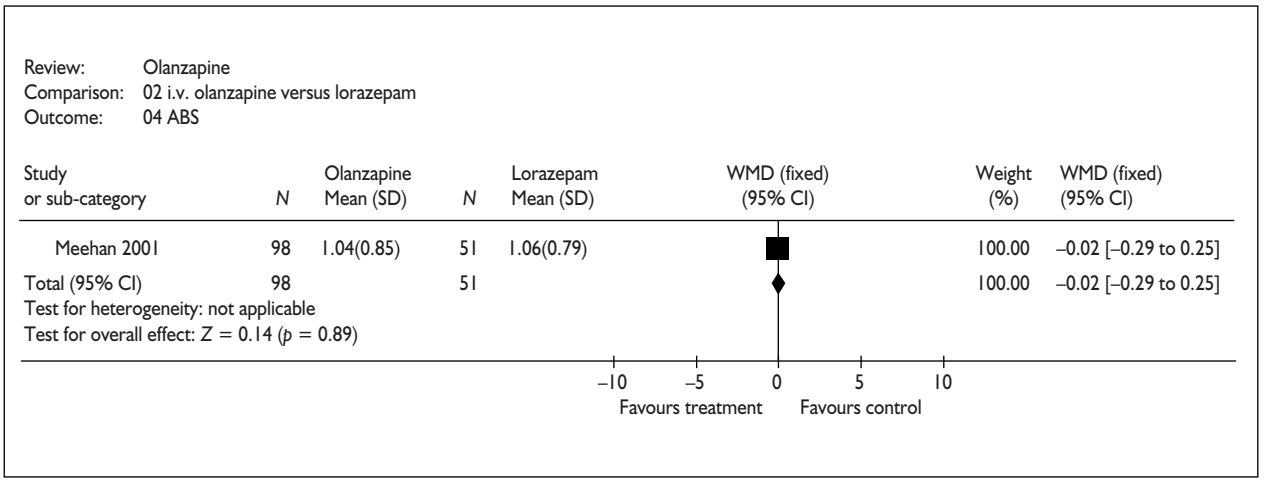

FIGURE 43 *ACES scores – i.m olanzapine versus lorazepam*

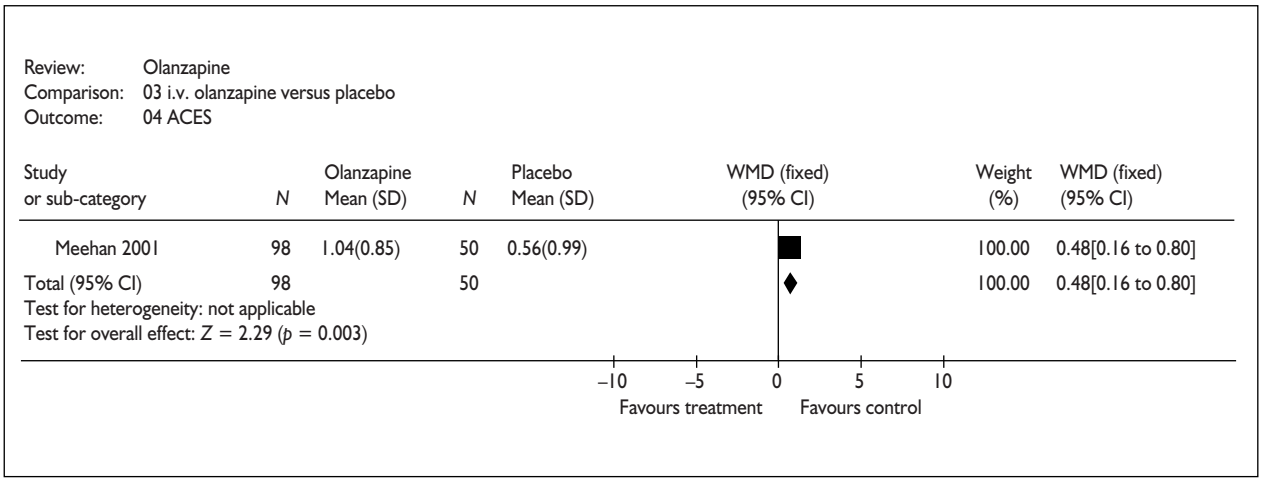

FIGURE 44 *ACES scores – i.m. olanzapine versus placebo*

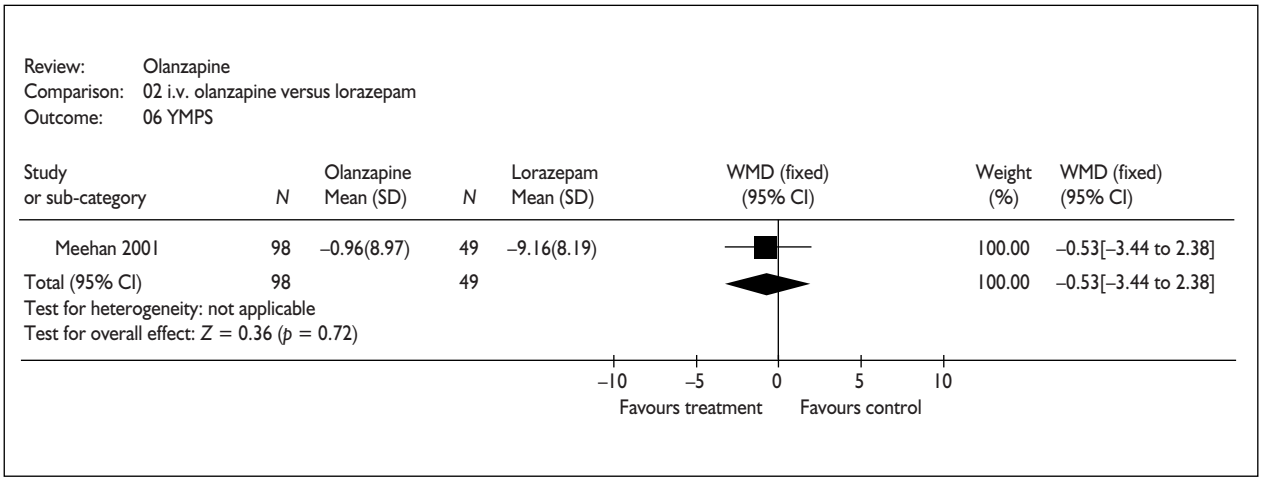

FIGURE 45 *YMRS scores – i.m. olanzapine versus lorazepam*

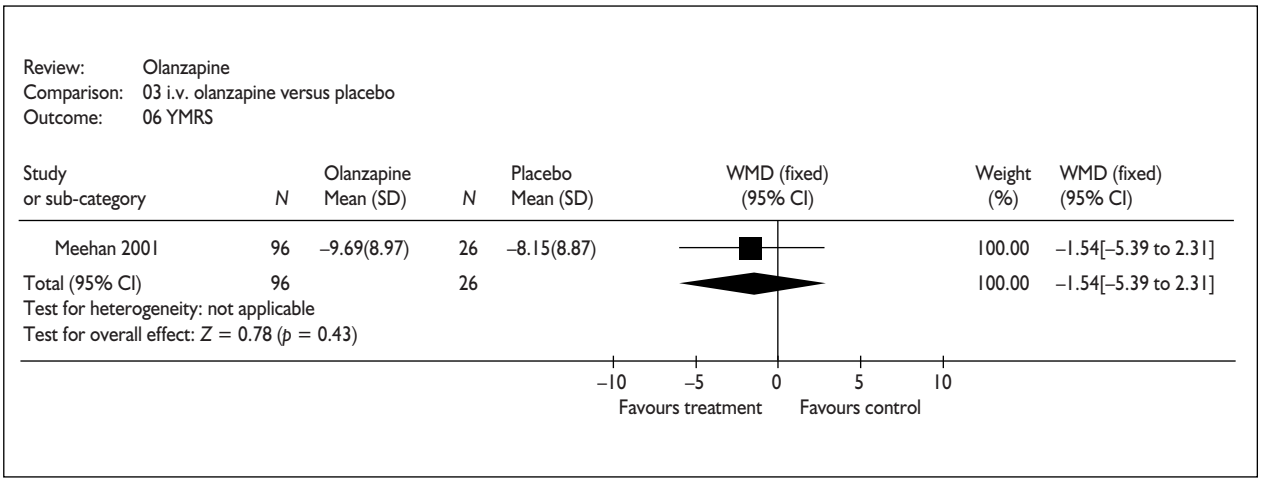

FIGURE 46 *YMRS scores – i.m. olanzapine versus placebo*

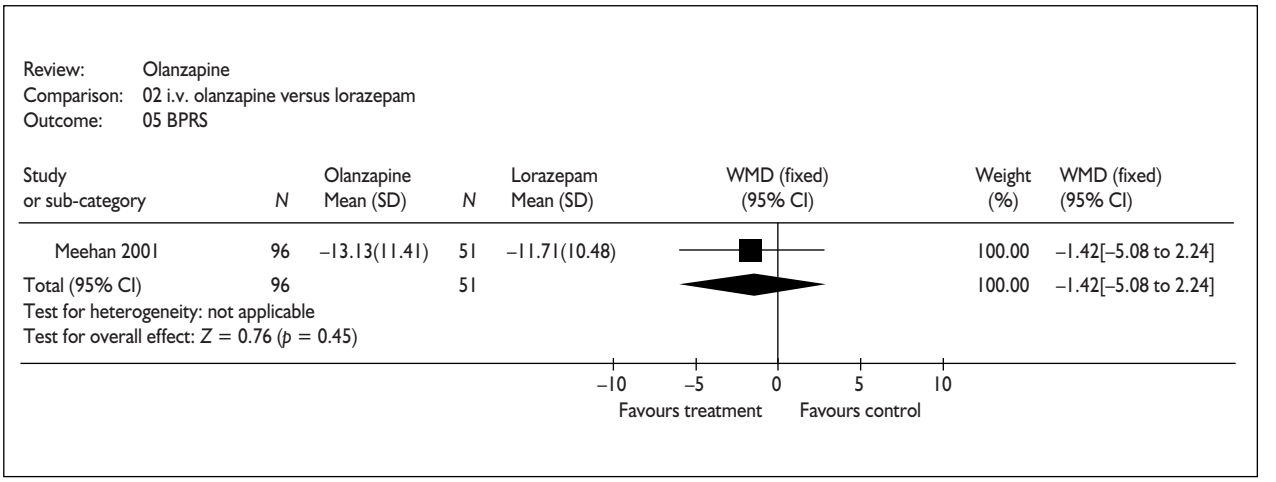

FIGURE 47 *BPRS scores – i.m. olanzapine versus lorazepam*

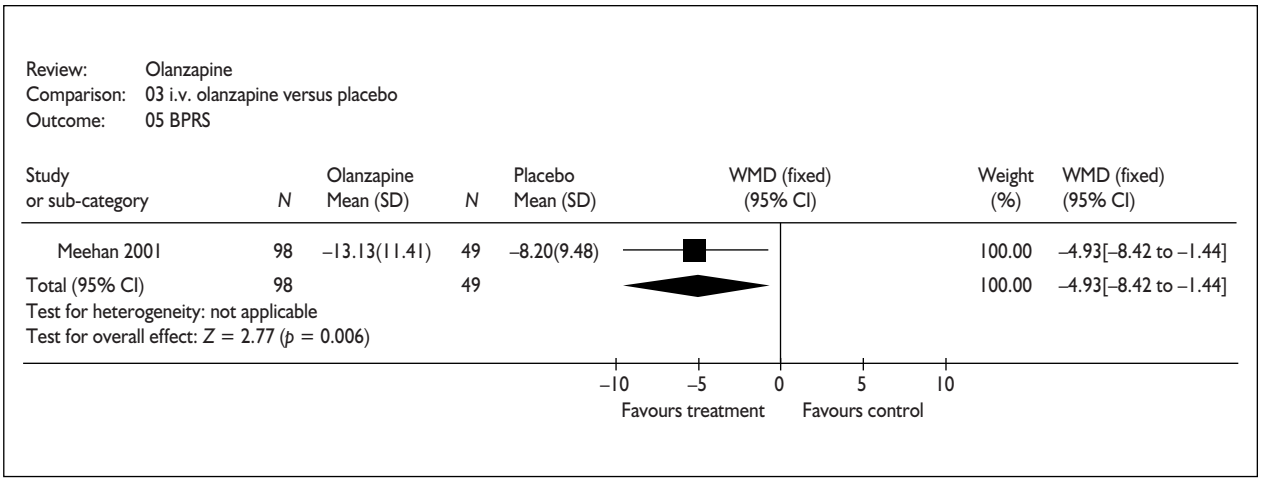

FIGURE 48 *BPRS scores – i.m. olanzapine versus placebo*

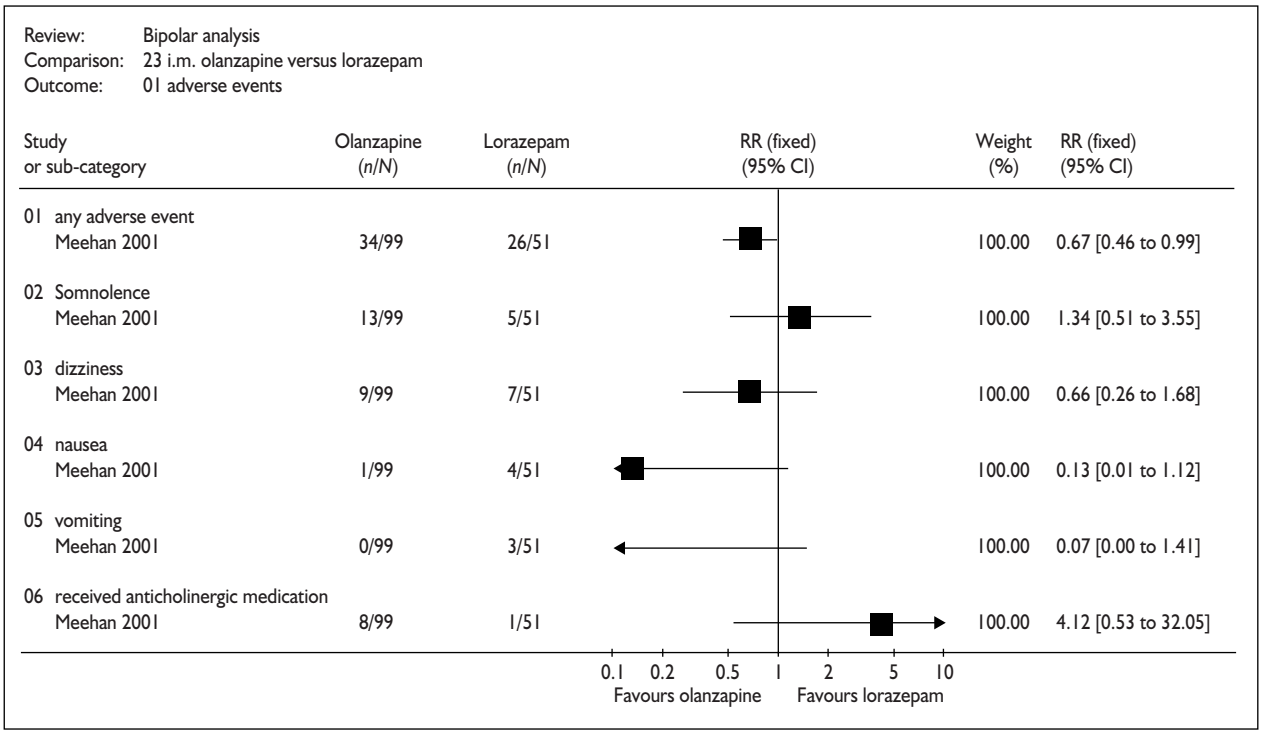

FIGURE 49 *Adverse events – i.m. olanzapine versus lorazepam*

olanzapine group when compared with placebo (MD –4.93, 95% CI –8.42 to –1.44) (*Figure 48*).

Leaving the study early

Data for withdrawals are not reported. However, data for 1–4 respondents are missing on various measures for the olanzapine group, for 1–2 respondents for the lorazepam group and for 1–25 respondents for the placebo group.

Length of stay

Length of stay was not reported.

Receipt of lorazepam

As lorazepam was a comparator, it was not allowed for respondents in both other groups.

Adverse effects

The lorazepam group had a significantly larger proportion of treatment-emergent adverse events than olanzapine (RR 0.67, 95% CI 0.46 to 0.99) (*Figure 49*). There was no significant difference between olanzapine and lorazepam or placebo groups in incidence of somnolence, nausea, vomiting, dizziness or receipt of anticholinergic medication (*Figure 50*).

Olanzapine versus haloperidol

One large study (Tohen 2001[37,38]) compared olanzapine (5–20 mg/day) with haloperidol (3–15 mg/day). The study was of 6 weeks' duration with a 6-week continuation phase for responders. Only data from the 6-week timepoint are reported here.

Effects on mania

Response (defined as at least a 50% reduction in YMRS score) was not significantly more likely to occur in the olanzapine than the haloperidol group (RR 0.99, 95% CI 0.88 to 1.11) (*Figure 51*).

Remission (defined as a YMRS score of ≤ 12 and a HAM-D score of ≤ 8) showed a trend favouring the olanzapine group, but this was not statistically significant (RR 1.13, 95% CI 0.94 to 1.37) (*Figure 52*).

When the remission rates were divided into subgroups with psychotic and without psychotic features, there was no statistically significant difference between treatments in remission rates in the psychotic subgroup (RR 0.98, 95% CI 0.77 to 1.26), but remission rates in the non-psychotic subgroup marginally favoured olanzapine (RR 1.36, 95% CI 1.01 to 1.84) (*Figure 53*).

Other psychiatric assessments

Mean change scores were reported for the MADRS and HAM-D scales but no measure of variance was reported so we cannot calculate a 95% CI around

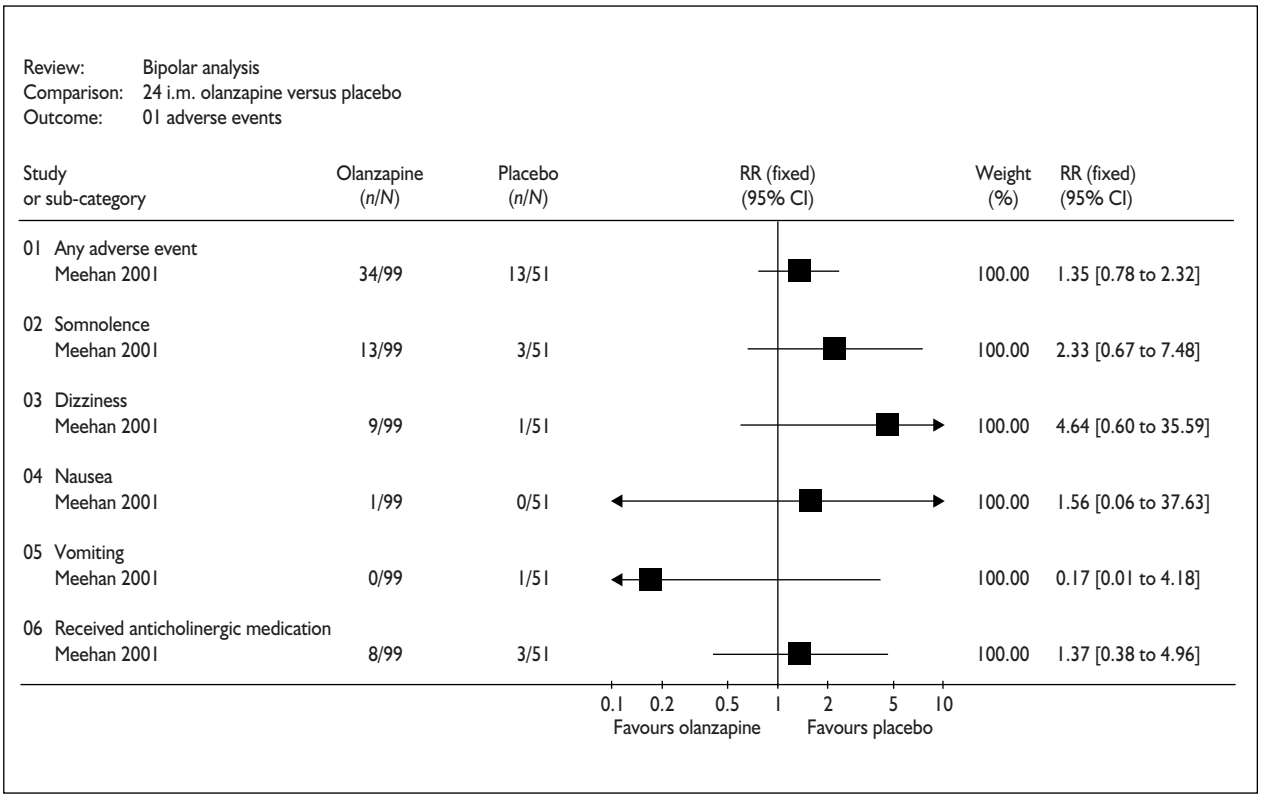

FIGURE 50 *Adverse events – i.m. olanzapine versus placebo*

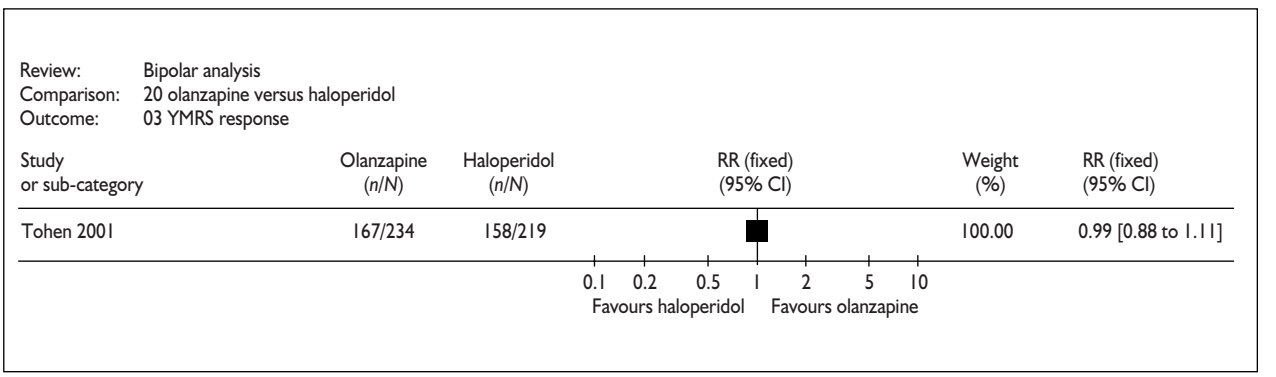

FIGURE 51 *YMRS response – olanzapine versus haloperidol*

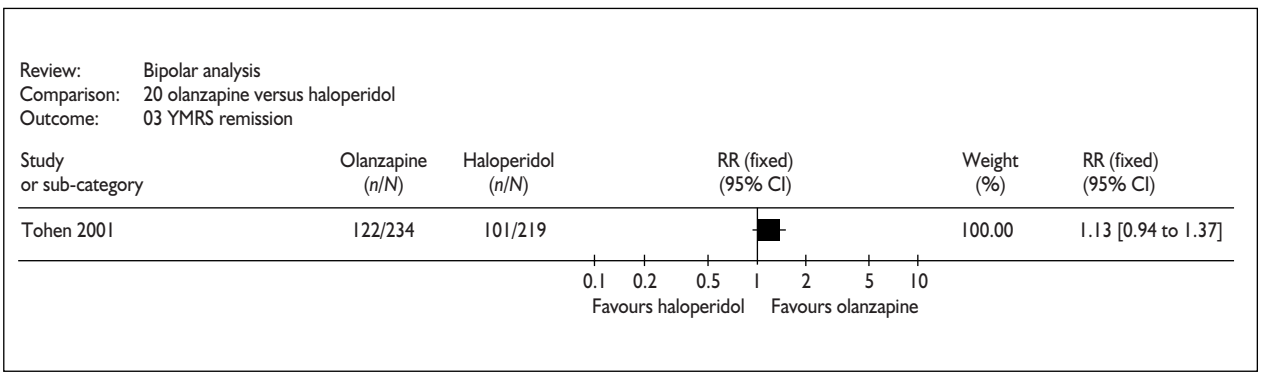

FIGURE 52 *YMRS remission – olanzapine versus haloperidol*

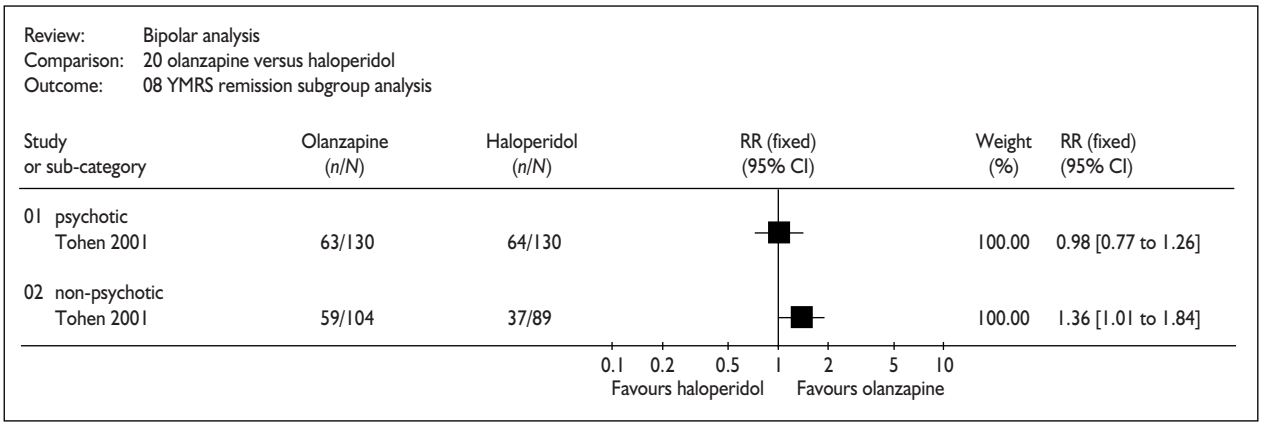

FIGURE 53 *YMRS remission – subgroup analysis – olanzapine versus haloperidol*

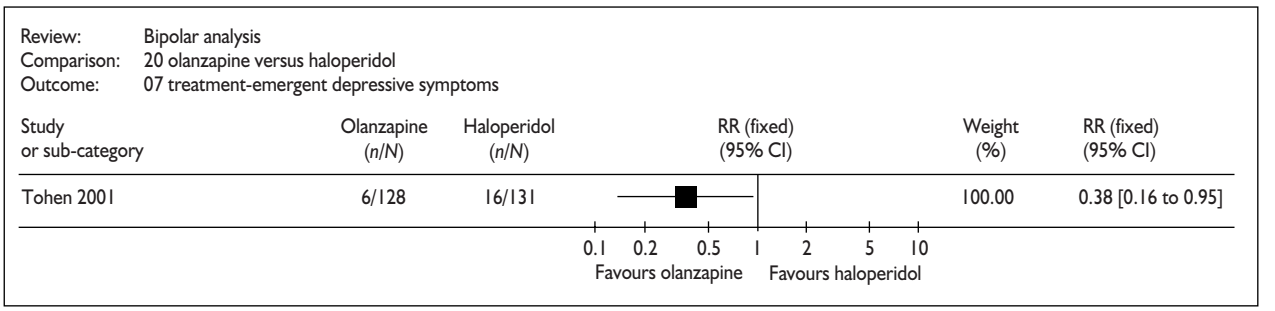

FIGURE 54 *Treatment-emergent depressive symptoms – olanzapine versus haloperidol*

the MD of 1.47 between treatment groups on the MADRS scale (trial authors' p-value = 0.028 in favour of olanzapine) and 1.01 on the HAM-D scale (p-value not reported).

The incidence of 'switching to depression' (defined as a HAM-D score of ≤ 15 at any point during the study in people whose HAM-D score was ≤ 8 at baseline) was significantly higher in the haloperidol group than the olanzapine group (RR 0.38, 95% CI 0.16 to 0.95) (*Figure 54*).

Leaving the study early

There was no significant difference between the olanzapine and haloperidol groups in likelihood of leaving the study early for any reason, adverse events or lack of efficacy (*Figure 55*).

Adverse events

Weight gain (RR 3.59, 95% CI 1.49 to 8.64) and infection (9.36, 95% CI 1.21 to 72.51) were significantly more likely to occur in the olanzapine than the haloperidol group. Akathisia (RR 0.21, 95% CI 0.12 to 0.36), tremor (RR 0.33, 95% CI 0.17 to 0.64), hypertonia (RR 0.22, 95% CI 0.11 to 0.45), EPS (RR 0.10, 95% CI 0.04 to 0.24), dystonia (RR 0.20, 95% CI 0.06 to 0.69), hypokinesia (RR 0.12, 95% CI 0.01 to 0.83) and increased salivation (RR 0.08, 95% CI 0.01 to 0.47) were significantly more likely to occur in the haloperidol group than the olanzapine group (*Figure 56*). The adverse events of insomnia, somnolence and dyskinesia were not significantly more likely to occur in either group.

Work status

The number of people in work was not statistically significantly different between treatment groups but showed a trend towards favouring olanzapine (RR 1.06, 95% CI 0.93 to 1.19) (*Figure 57*).

Health-related quality of life (HRQoL)

SF-36 mean change scores were reported with SDs. These were translated into standard errors and the MD between groups with 95% CI calculated (*Figure 58*). Most measures favoured olanzapine over haloperidol (physical and mental summary scores, general health, mental health, physical functioning, role limitations due to emotional problems, role limitations due to physical problems, social functioning and vitality dimensions). The strongest effects were seen in the physical summary score, the physical functioning dimension and the role limitations due to physical

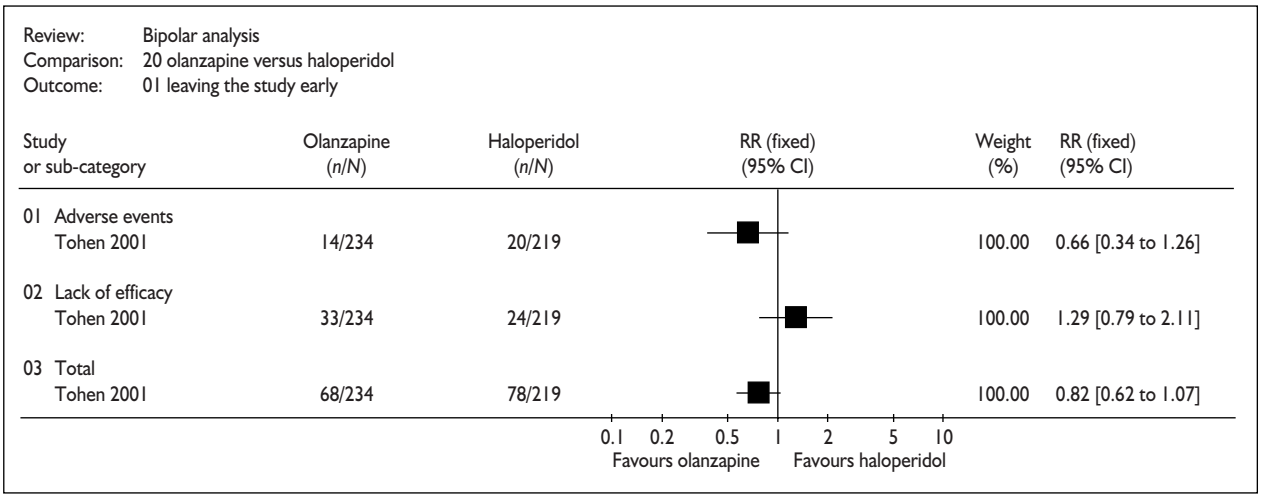

FIGURE 55 *Leaving the study early – olanzapine versus haloperidol*

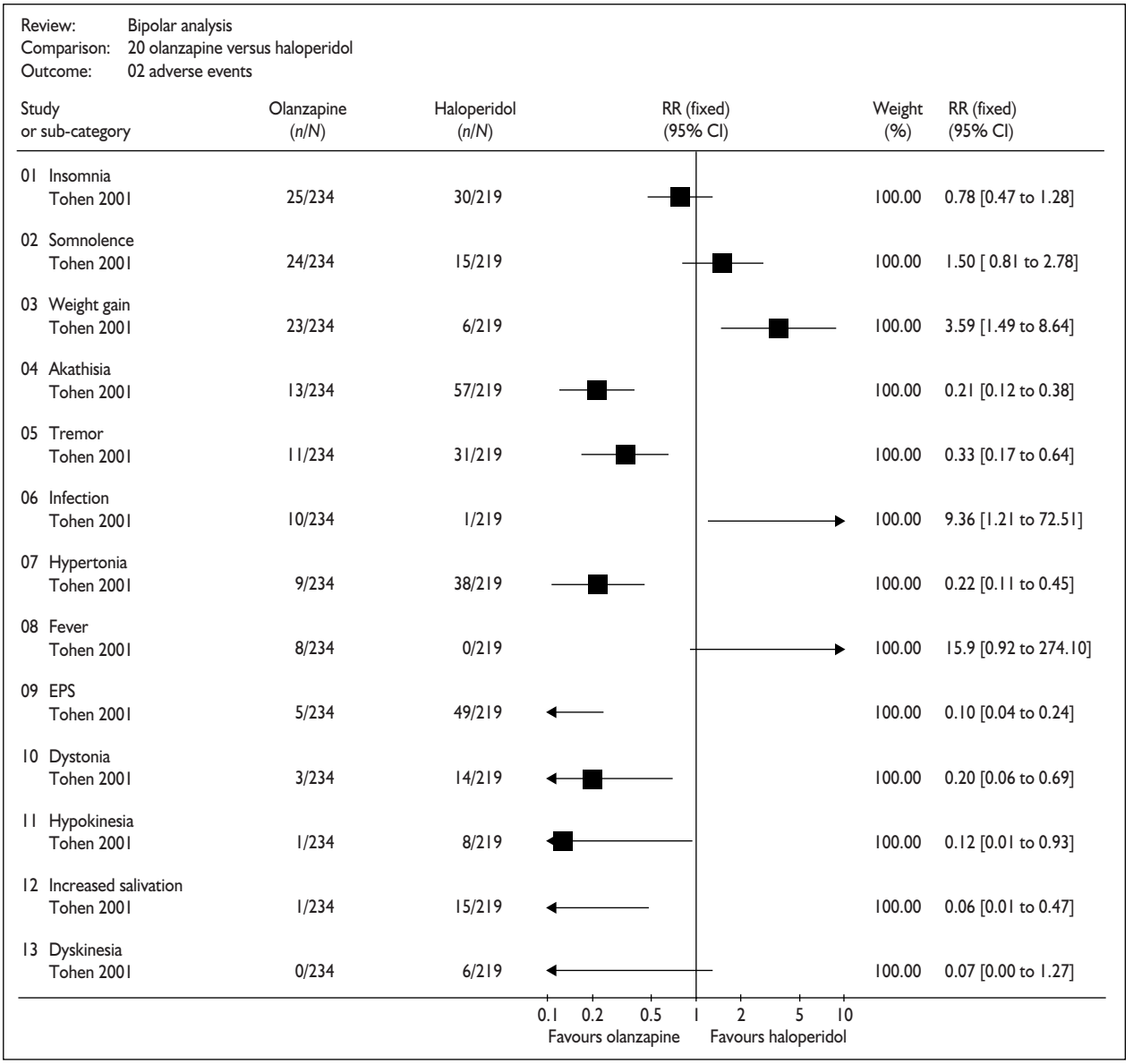

FIGURE 56 *Adverse events – olanzapine versus haloperidol*

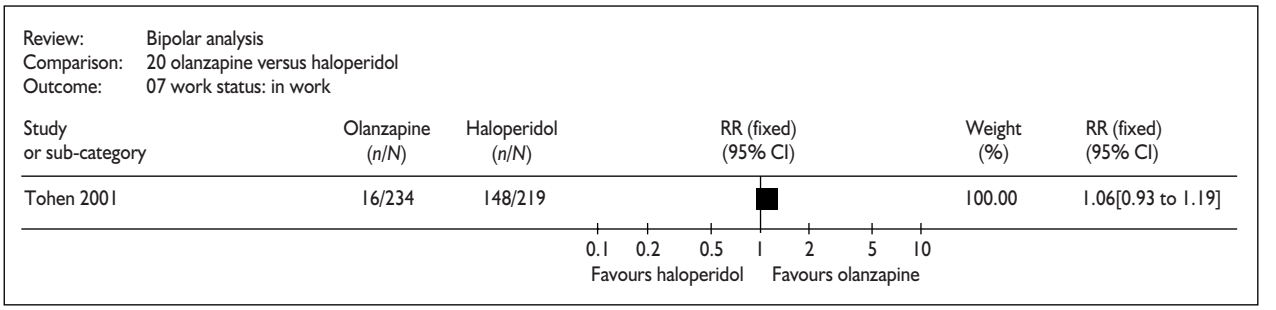

FIGURE 57 *Work status – olanzapine versus haloperidol*

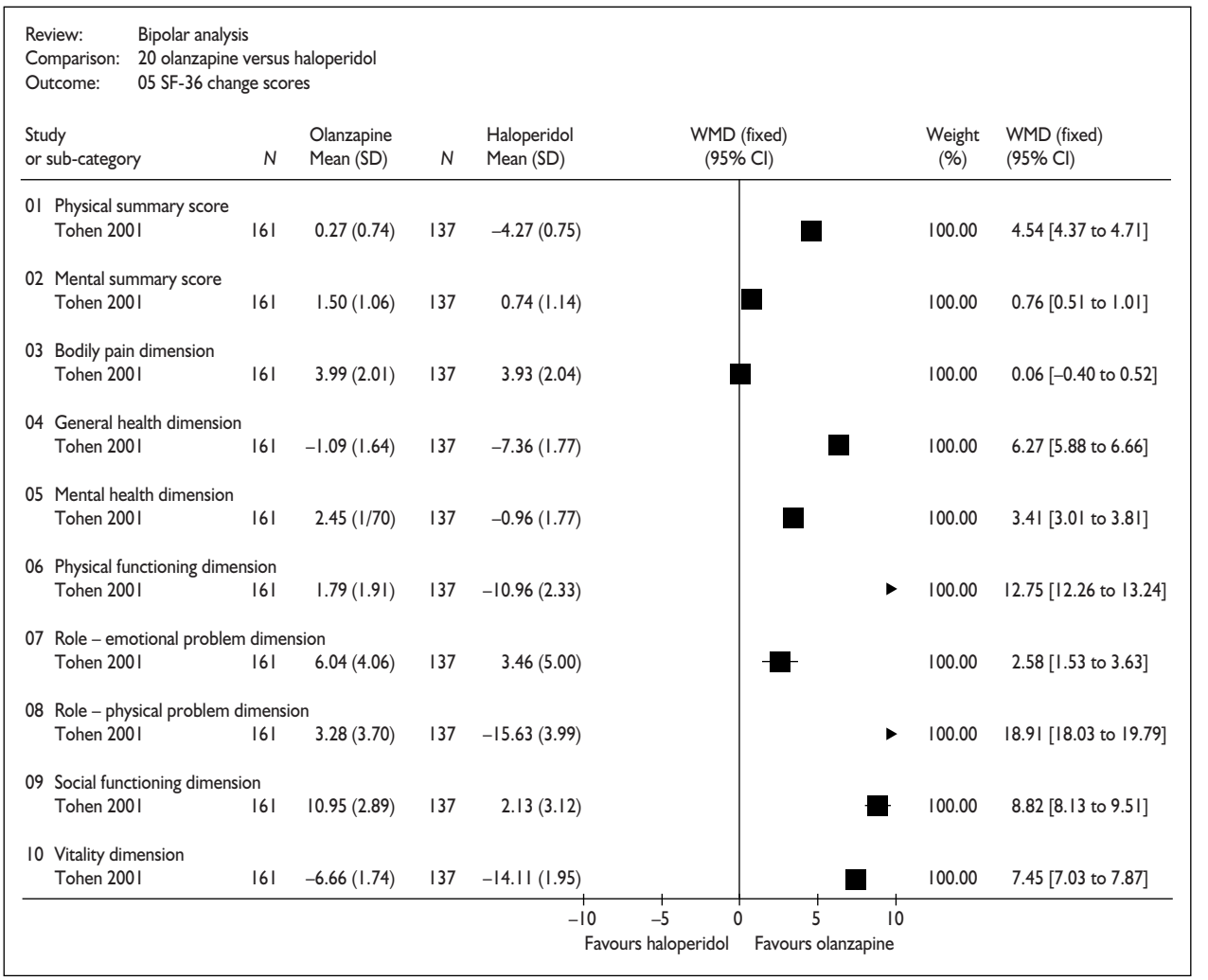

FIGURE 58 *SF-36 change scores – olanzapine versus haloperidol*

problems dimension. No measure favoured haloperidol over olanzapine.

Valproate semisodium (divalproex)

Five RCTs are included in this section: Pope 1991,[48] Bowden 1994,[49–52] Hirschfeld 1999,[53] Kowatch 2000,[54] and McElroy 1996[55] (*Table 3*). A further two trials comparing valproate semisodium to olanzapine are reported in a later section.[56,57]

Description of included trials

Two RCTs[48,49] compared valproate semisodium with placebo, three compared valproate semisodium with lithium,[49,53,54] and one compared

TABLE 3 *Valproate semisodium – included studies*

Study	Participants	Interventions	Outcomes
Pope 1991[48] (full paper)	*N* = 43 Diagnosis: DSM-III-R bipolar disorder, manic phase. Lithium-resistant or intolerant. Duration of illness 11.2–12.2 years	1–3 weeks Valproate semisodium (*n* = 20): 3 50 mg tablets per day Placebo (*n* = 23): 3 250 mg tablets per day	Attrition Adverse events YMRS scores; GAS scores; BPRS-A scores; receipt of lorazepam
Bowden 1994[49–52] (full paper)	*N* = 212 Diagnosis: 'manic disorder' diagnosed using Research Diagnostic Criteria and SADS rating scale. MRS scores ≥ 14 Duration of illness: 16.1–18 years	3 weeks Valproate semisodium (*n* = 69) initial dose 750 mg/day (3 divided doses). On day 3, dose increased to 1000 mg Lithium carbonate (*n* = 36) initial dose 750 mg/day (3 divided doses). On day 3, dose increased to 1000 mg Placebo (*n* = 74)	Attrition Adverse events SADS-C mania rating scale score; GAS score; ADRS score; Behaviour-Ideation Scale
Hirschfeld 1999[53] (full paper)	*N* = 60 Diagnosis: DSM-IV bipolar disorder (manic or mixed), acute manic episode. YMRS ≥ 14, hospitalised Duration of illness 8.7–19.9 years	10 days Valproate semisodium loading (*n* = 20): 30 mg/kg/day on days 1 and 2, 20 mg/kg/day days 3–10 Valproate semisodium non-loading (*n* = 20): 250 mg t.d.s. days 1 and 2 then standard dose titration days 3–10 Lithium carbonate (*n* = 20): 30 mg/kg/day days 1 and 2, 20 mg/kg/day days 3–10	Attrition Adverse events YMRS scores; GAS scores; receipt of lorazepam; serum concentration
Kowatch 2000[54] (full paper)	*N* = 42. Children, mean age 11.4 years Diagnosis: DSM-IV bipolar I or II disorder, mixed or manic episode. YMRS score ≥ 14 Duration of illness 4.6 years	4–8 weeks Valproate semisodium (*n* = 15): initial dose 20 mg/kg/day in 3 divided doses. After 1 week, titrated to serum level 85–110 μg/l Lithium (*n* = 14): initial dose 20 mg/kg/day in 3 divided doses. After 1 week, titrated to serum level 85–110 μg/l Carbamazepine (*n* = 13): 15 mg/kg/day	Attrition Adverse events CGI-I score; YMRS score; YMRS 'response'
McElroy 1996[55] (full paper)	*N* = 42 Diagnosis: DSM-III-R bipolar disorder, manic or mixed phase with psychotic features. Duration of illness 6.9–9.3 years	6 days Valproate semisodium (*n* = 21), 20 mg/kg/day Haloperidol (*n* = 15), 20 mg/kg/day	Adverse events Receipt of lorazepam; YMRS score; 'response'; SADS score; length of stay

ADRS, Affective Disorder Rating Scale; BPRS-A, Brief Psychiatric Rating Scale, Augmented; SADS, Schedule for Affective Disorders and Schizophrenia; SADS-C, Schedule for Affective Disorder and Schizophrenia, Change version.

valproate semisodium with haloperidol.[55] The Hirschfeld 1999[53] study compared a 'loading' and 'non-loading' strategy for valproate semisodium with lithium. The dose of valproate semisodium was 750 mg/day in one of the placebo-controlled studies,[48] 1000 mg/day in the placebo- and lithium-controlled study,[49] >500 mg/day in the non-loading arm of Hirschfeld 1999[53] and 20 mg/kg/day in the non-loading arm of Hirschfeld 1999[53] and in the other studies. The

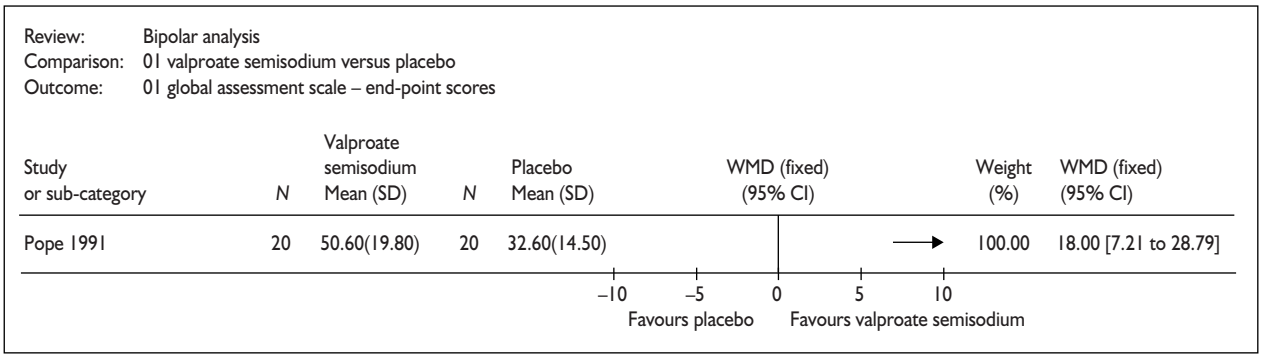

FIGURE 59 *GAS scores – valproate semisodium versus placebo*

lithium dose was 200 mg/day maximum in Bowden 1994[49] and 20 mg/kg/day in the other two studies. The haloperidol dose was 20 mg/kg/day in McElroy 1996.[55] The Kowatch 2000[54] study recruited children aged between 6 and 18 years (mean age 11.4 years). The other four RCTs recruited adults aged 18–65 years (mean age ranged from 32.4 to 40.4 years). More than half (52–72%) were male. Participants in the McElroy 1996[55] trial, which used haloperidol as a comparator, were diagnosed with DSM-III-R bipolar disorder, manic or mixed phase, with psychotic features. People who had been treated with valproate before were excluded from this trial. Participants in the Bowden 1994[49] trial were diagnosed with 'manic disorder' with a YMRS score of ≥ 14, in Hirschfeld 1999[53] with an acute manic episode (defined as a YMRS score of ≥ 14) of DSM-IV bipolar disorder, manic or mixed and in Kowatch 2000[54] children were diagnosed with DSM-IV bipolar I or II disorder, mixed or manic episode with a YMRS score of ≥ 14. People who were intolerant to lithium or had received valproate before were excluded from the Bowden 1994[49] trial. Participants in the Pope 1991[48] trial were diagnosed with DSM-III-R bipolar disorder, manic phase and were resistant or intolerant to lithium. People who drank more than three alcoholic drinks per day or had received more than 250 mg of valproate before were excluded from this trial.

Validity

Two of the included RCTs (Pope 1991[48] and Bowden 1994[49]) reported details of method of randomisation and allocation concealment and these were adequate in both of these trials. The treatment groups were stated to be comparable at baseline in McElroy 1996[55] and Pope 1991.[48] This was not stated in Kowatch 2000,[54] and in Bowden 1994[49] and Hirschfeld 1999[53] the treatment groups were not comparable at baseline. The Bowden 1994,[49] Hirschfeld 1999[53] and Pope 1991[48] trials were stated to be double-blind, but only in Pope 1991[48] was it clear from the report that participants, investigators and outcome assessors were blind to treatment group. ITT analysis was carried out in the Kowatch 2000[54] and McElroy 1996[55] but not in the Bowden 1994[49] and Pope 1991[48] trials. It was unclear whether ITT analysis was carried out in the Hirschfeld 1999[53] trial. The dose of comparator drug given seemed to be appropriate in all five RCTs.

Valproate semisodium versus placebo

Two studies compared valproate semisodium with placebo: Bowden 1994[49] and Pope 1991.[48] Valproate semisodium was given at a dose of 750 mg/day in Pope 1991[48] and 1000 mg/day in Bowden 1994.[49] Participants in the Pope 1991[48] trial were stated to be lithium-resistant or -intolerant. Participants in the Bowden 1994[49] trial were stated to have 'manic disorder'. The Bowden 1994[49] trial gave treatment for 3 weeks and Pope 1991[48] for 1–3 weeks.

Global effects

Both trials reported GAS scores. Pope 1991[48] reported GAS scores at baseline and end-point with SDs. An MD of 18.00 (95% CI 7.21 to 28.79) in favour of valproate semisodium was calculated in this study (*Figure 59*). Change scores in this study were 20.6 in the valproate semisodium group and 1.0 in the placebo group.

The Bowden 1994[49] trial reported change scores of 7.6 in the valproate semisodium group compared with 3.8 in the placebo group and reported that the difference was non-significant ($p = 0.06$). No measure of variance was given so we cannot calculate a 95% CI around the MD in change scores of 3.8. The different results in the two trials may have been due to differences in diagnosis (participants in the Pope 1991[48] trial were lithium-resistant or -intolerant and this was a trial of second-line treatment; the Bowden 1994[49]

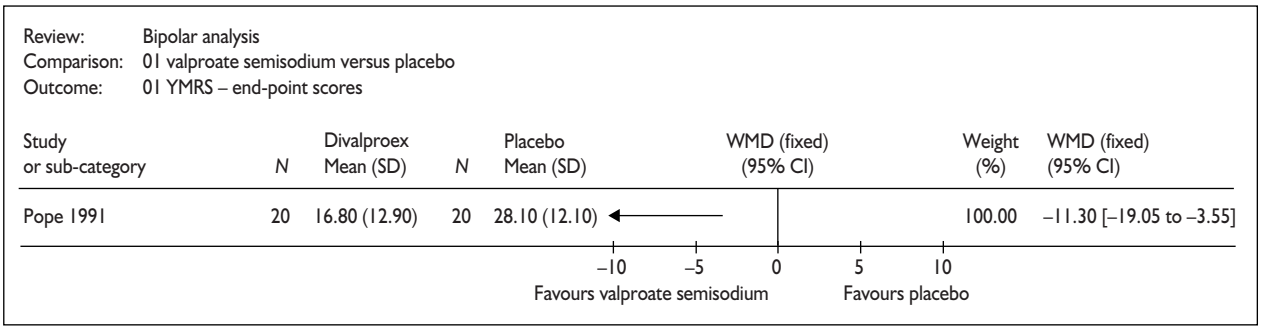

FIGURE 60 *YMRS scores – valproate semisodium versus placebo*

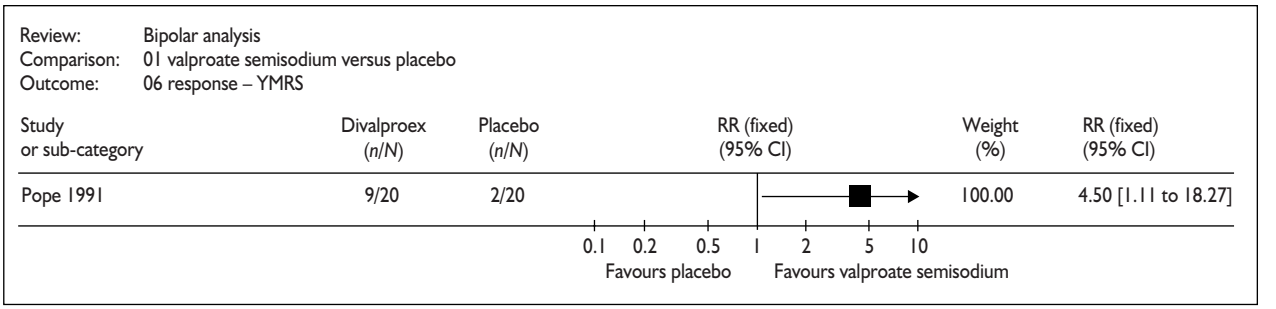

FIGURE 61 *YMRS 'response' – valproate semisodium versus placebo*

study excluded people who were intolerant or resistant to lithium and this was a trial of first-line treatment).

Effects on mania

The Pope 1991[48] study reported YMRS scores and Bowden 1994[49] reported SADS-C manic rating scores. The Pope 1991[48] trial reported YMRS scores at baseline and end-point with SDs. An MD of –11.30 (95% CI –19.05 to –3.55) in favour of valproate semisodium was calculated (*Figure 60*). It is worth noting, however, that the mean end-point score in the valproate semisodium group was 16.8 and entry criteria for some of the other RCTs were a YMRS score of ≥ 14: participants in this group would still be suffering from mania if these criteria were applied. Change scores in this study were –11.4 in the valproate semisodium group and –0.7 in the placebo group.

The Pope 1991[48] study also reported 'response' as being at least a 50% improvement in the YMRS score. Response was significantly more likely to occur in the valproate semisodium group (RR 4.50, 95% CI 1.11 to 18.27) (*Figure 61*). Sensitivity analysis using positive assumptions for missing persons did not substantially affect this result (RR 5.03, 95% CI 1.26 to 20.10).

The Bowden 1994[49] study reported SADS-C MRS change scores separately for lithium responders (–7.4 in the valproate semisodium group and –4.0 in the placebo group) and lithium non-responders (–10.8 in the valproate semisodium group and –3.2 in the placebo group). No measure of variance was given so we cannot calculate a 95% CI around the MD in change scores of –3.4 in lithium responders and –7.6 in lithium non-responders. A significantly greater improvement (compared with placebo) was reported for subscales of elevated mood, less need for sleep, excessive activity and motor hyperactivity. An effect size analysis[52] of this trial did report SD scores for the total MRS and subscales for the whole group. The total MD was in favour of valproate semisodium (5.30, 95% CI 1.47 to 9.13), as were all reported subscales (*Figure 62*).

The Bowden 1994[49] trial also reported 'response' as being at least a 50% improvement on the SADS-C MRS score. Response was significantly more likely to occur in the valproate semisodium group (RR 1.91, 95% CI 1.19 to 3.07) (*Figure 63*). Sensitivity analysis using positive assumptions for missing persons did not substantially affect this result (RR 1.91, 95% CI 1.19 to 3.06).

A subgroup analysis from this study[51] reported that antimanic response to treatment diverged sharply as the number of lifetime episodes of affective disorder increased. Values for improvement with a low number of episodes were

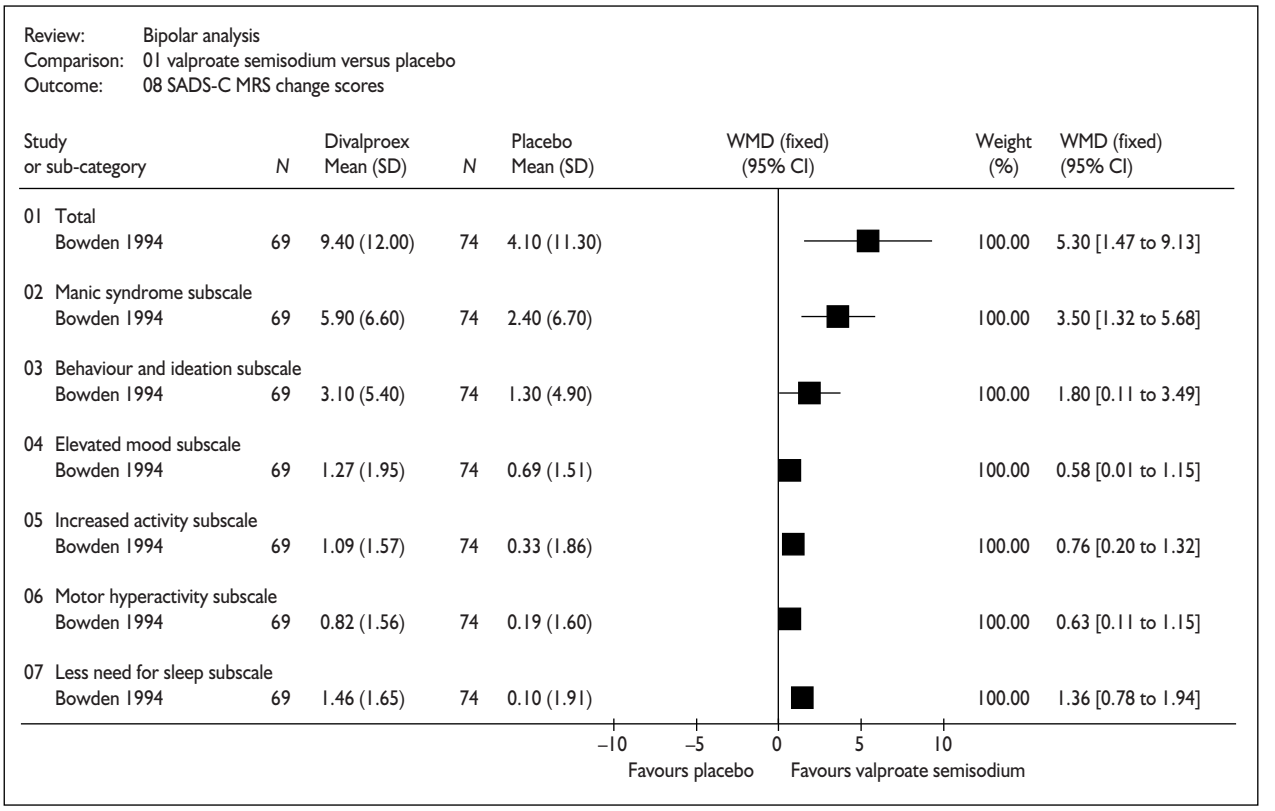

FIGURE 62 *SADS-C mania rating scale scores – valproate semisodium versus placebo*

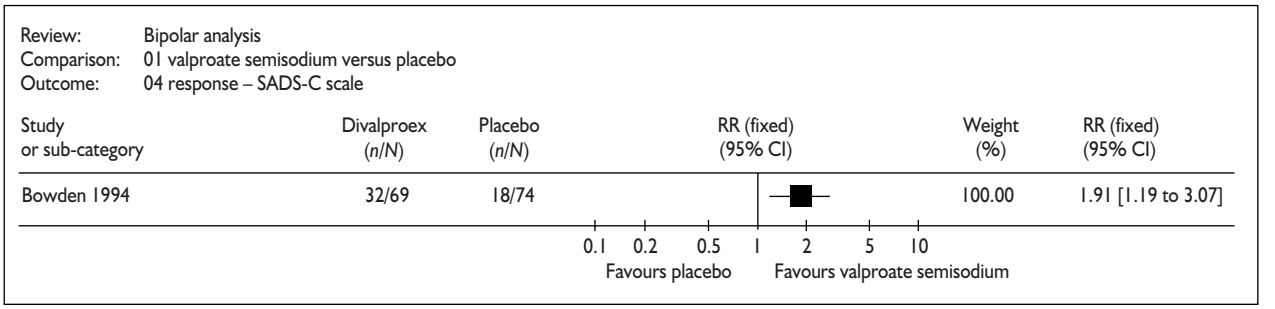

FIGURE 63 *SADS-C 'response' – valproate semisodium versus placebo*

5.9 (SD 1.1) for valproate semisodium and 2.4 (SD 0.7) for placebo ($p < 0.005$). There was no significant difference between valproate semisodium- and placebo-treated groups in transition between high and low response.

Other psychiatric assessments

The Pope 1991[48] trial reported BPRS-A total median end-point scores as a 17-point improvement in the valproate semisodium group compared with a 3-point improvement in the placebo group. This difference was reported as significant ($p = 0.001$). No measure of variance was reported so we could not calculate a 95% CI around the MD of 14 points. The trial authors also reported that on four of the 18 BPRS subscales (conceptual disorganisation, tension, hostility and excitement), people receiving valproate semisodium improved significantly more than those receiving placebo ($p < 0.005$) and that no subscale produced a significant change in favour of placebo. The Bowden 1994[49,52] study reported ADRS change scores. Valproate semisodium was reported to give significantly greater improvement than placebo for the subscales mania (MD 4.70, 95% CI 1.24 to 8.16), elation/grandiosity (MD 1.90, 95% CI 0.50 to 3.30) and psychosis (MD 2.10, 95% CI 0.10 to 4.10) (*Figure 64*).

A subgroup analysis from this study,[50] which compared three definitions of depressive mania, reported that depressive presentation was

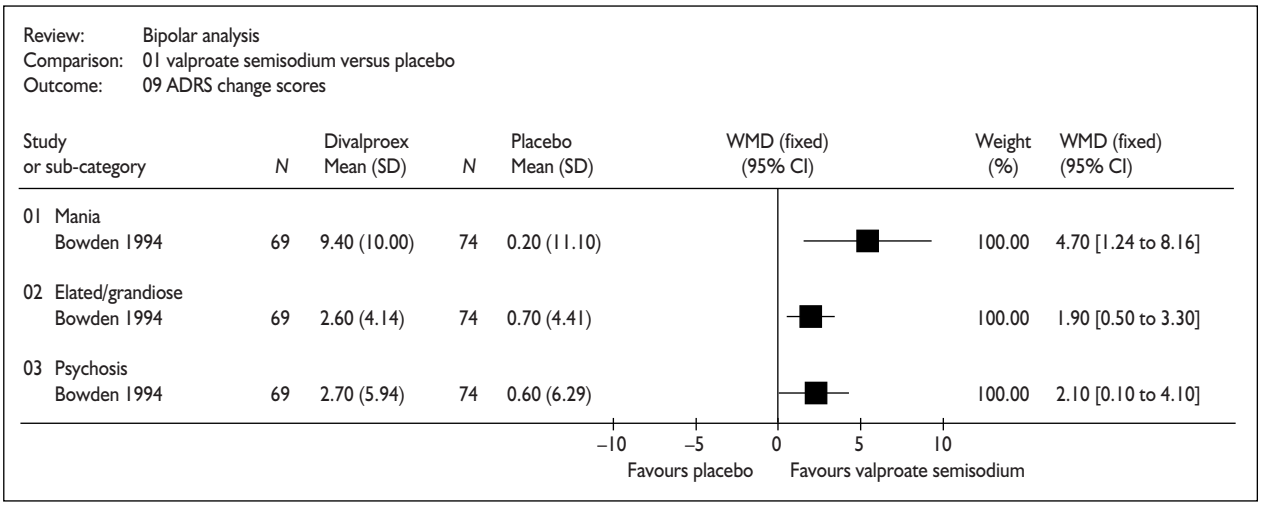

FIGURE 64 *ADRS scores – valproate semisodium versus placebo*

associated with a poorer response to lithium with less improvement (or even slight deterioration) in the Behavioural Ideation Scale compared with classic mania. Depressive symptoms had no significant effect on response to valproate semisodium. People experiencing depressive mania were reported to have better response to valproate semisodium than to lithium, but the reverse was true for classic mania.

Leaving the study early

Significantly fewer people in the valproate semisodium group than in the placebo group left the study early in both studies, both in total (pooled RR 0.78, 95% CI 0.62 to 0.97) and owing to lack of efficacy (pooled RR 0.53, 95% CI 0.36 to 0.78) (*Figure 65*).

Length of stay

Neither trial reported explicitly the length of stay in hospital.

Receipt of lorazepam

The Pope 1991[48] trial reported that on average people in the placebo group received more lorazepam than people in the valproate semisodium group (MD –8.10, 95% CI –13.56 to –2.64) (*Figure 66*).

Adverse effects

Both studies reported adverse events. No significant differences were seen between valproate semisodium and placebo groups in risk of any adverse event, headache, sedation, fatigue or somnolence, constipation, local swelling or pain, ataxia, dysuria, palpitations, diplopia, tightness in chest, dry eyes, sinus pressure, dysarthria, depression, diarrhoea, anorexia, agitation, bruising, lump in throat, panic attacks, asthenia, fever or twitching. People receiving valproate semisodium were significantly more likely than those receiving placebo to experience gastrointestinal symptoms (pooled RR 1.66, 95% CI 1.04 to 2.67). There was a trend for people receiving valproate semisodium to experience more dizziness than those receiving placebo (RR 2.95, 95% CI 0.99 to 8.83) (*Figure 67*).

Valproate semisodium versus lithium

Three trials included a comparison between valproate semisodium and lithium: Bowden 1994,[49] Hirschfeld 1999[53] and Kowatch 2000.[54] The Bowden 1994[49] and Hirschfeld 1999[53] trials recruited adults with manic disorder (Bowden 1994[49]) or an acute manic episode of DSM-IV manic or mixed bipolar disorder (Hirschfeld 1999[53]), whereas the Kowatch 2000[54] trial recruited children aged 6–18 years with a mixed or manic episode of DSM-IV bipolar I or II disorder. Hirschfeld 1999[53] compared a 'loading' (20 mg/kg/day) and 'non-loading' strategy for valproate semisodium with lithium (>500 mg/day). Bowden 1994[49] compared 1000 mg/day valproate semisodium with 1200 mg/day lithium and Kowatch 2000[54] compared 20 mg/kg/day of either drug.

Global effects

Adults

Bowden 1994[49] and Hirschfeld 1999[53] both measured change on the GAS. In the Hirschfeld 1999[53] study the results were presented graphically but means and SDs were not reported. In this study the authors reported that similar improvements were seen in all three groups: valproate semisodium loading, valproate

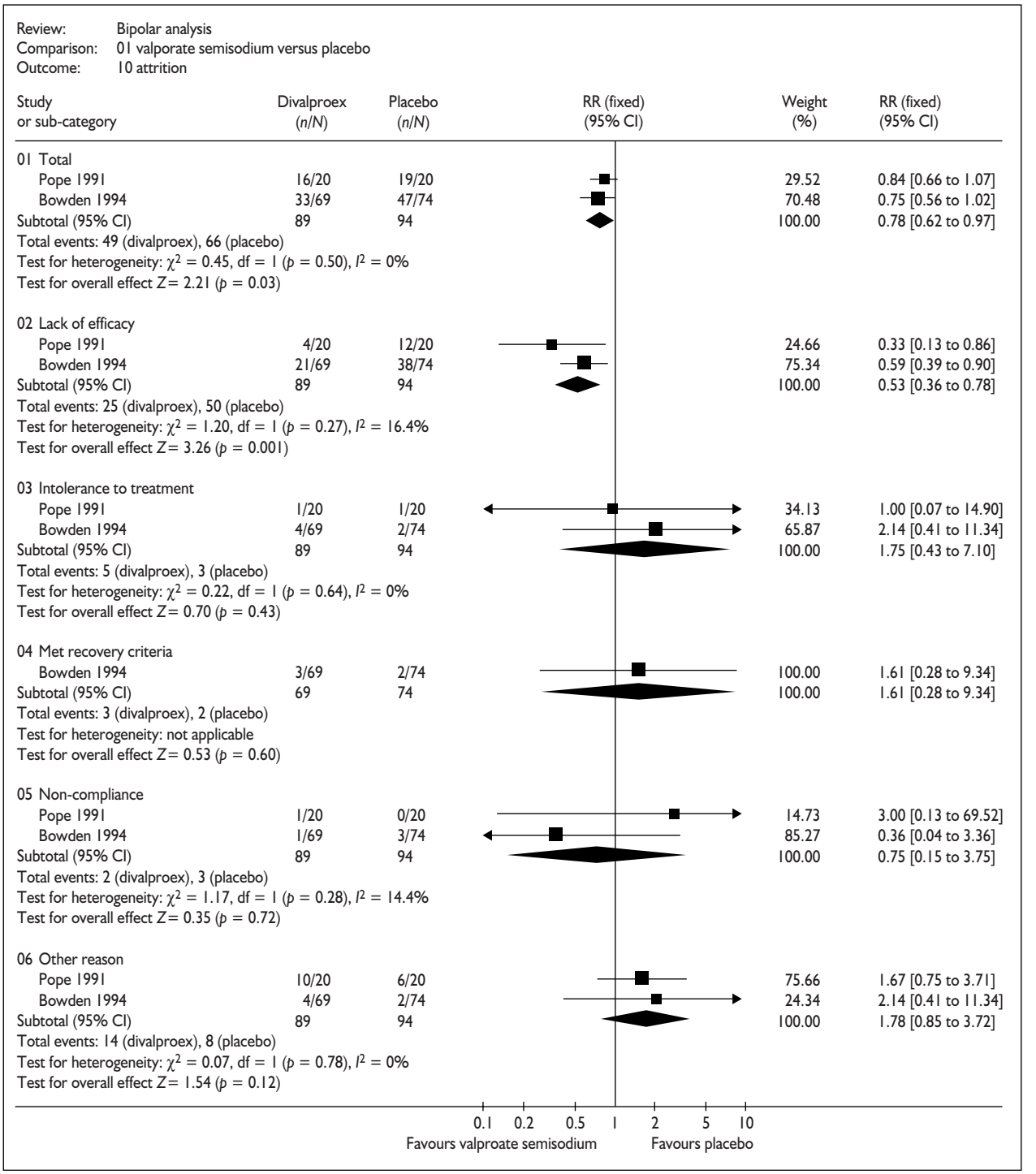

FIGURE 65 *Leaving the study early – valproate semisodium versus placebo*

semisodium non-loading and lithium carbonate ($p = 0.467$). In the Bowden 1994[49] trial, results were only reported for the valproate semisodium and the placebo groups and not for the lithium group.

Children

Kowatch 2000[54] reported 'response' using the weekly CGI-I. There was no significant difference between valproate semisodium and lithium (RR 0.93, 95% CI 0.39 to 2.22) (*Figure 68*).

Effects on mania

Adults

The Bowden 1994[49] study reported SADS-C MRS change scores separately for lithium responders (–7.4 in the valproate semisodium group and –15.3 in the lithium group) and lithium non-

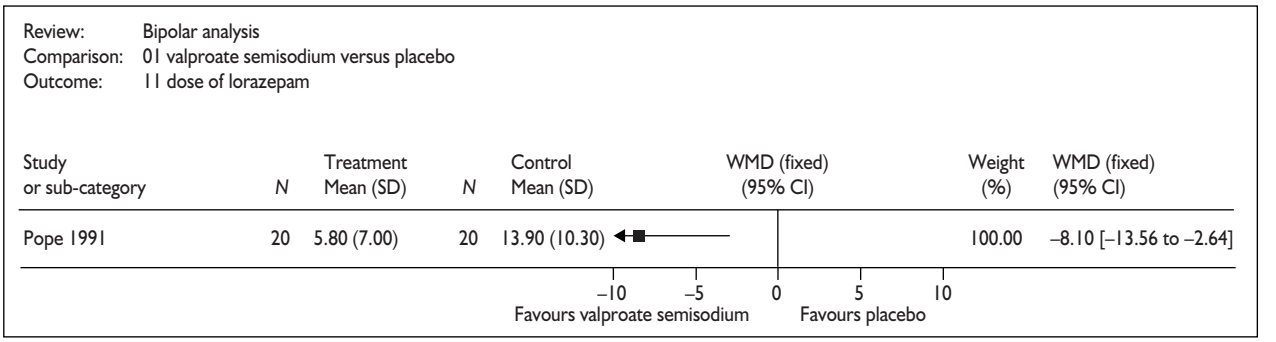

FIGURE 66 *Receipt of lorazepam – valproate semisodium versus placebo*

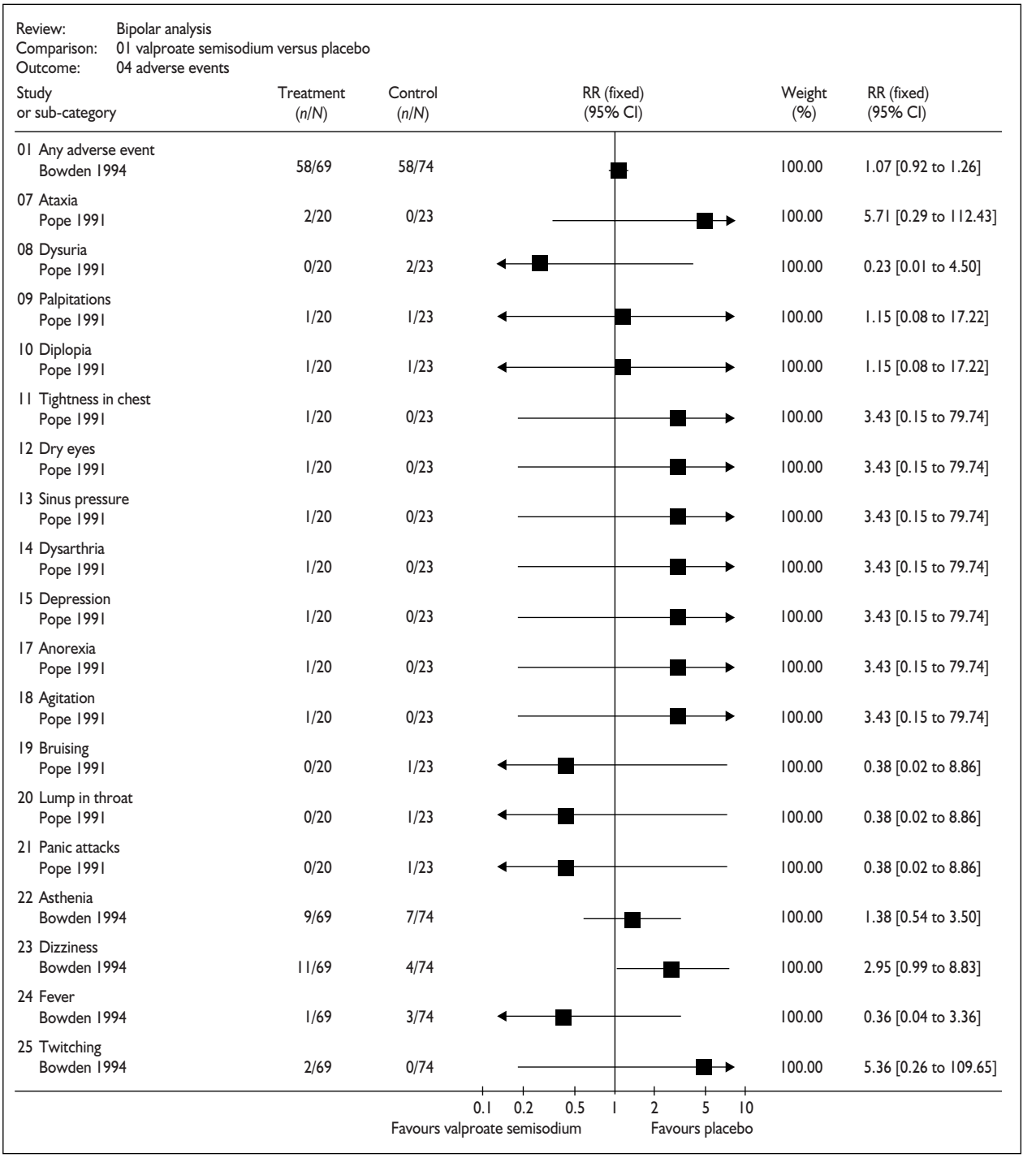

FIGURE 67 *Adverse effects – valproate semisodium versus placebo*

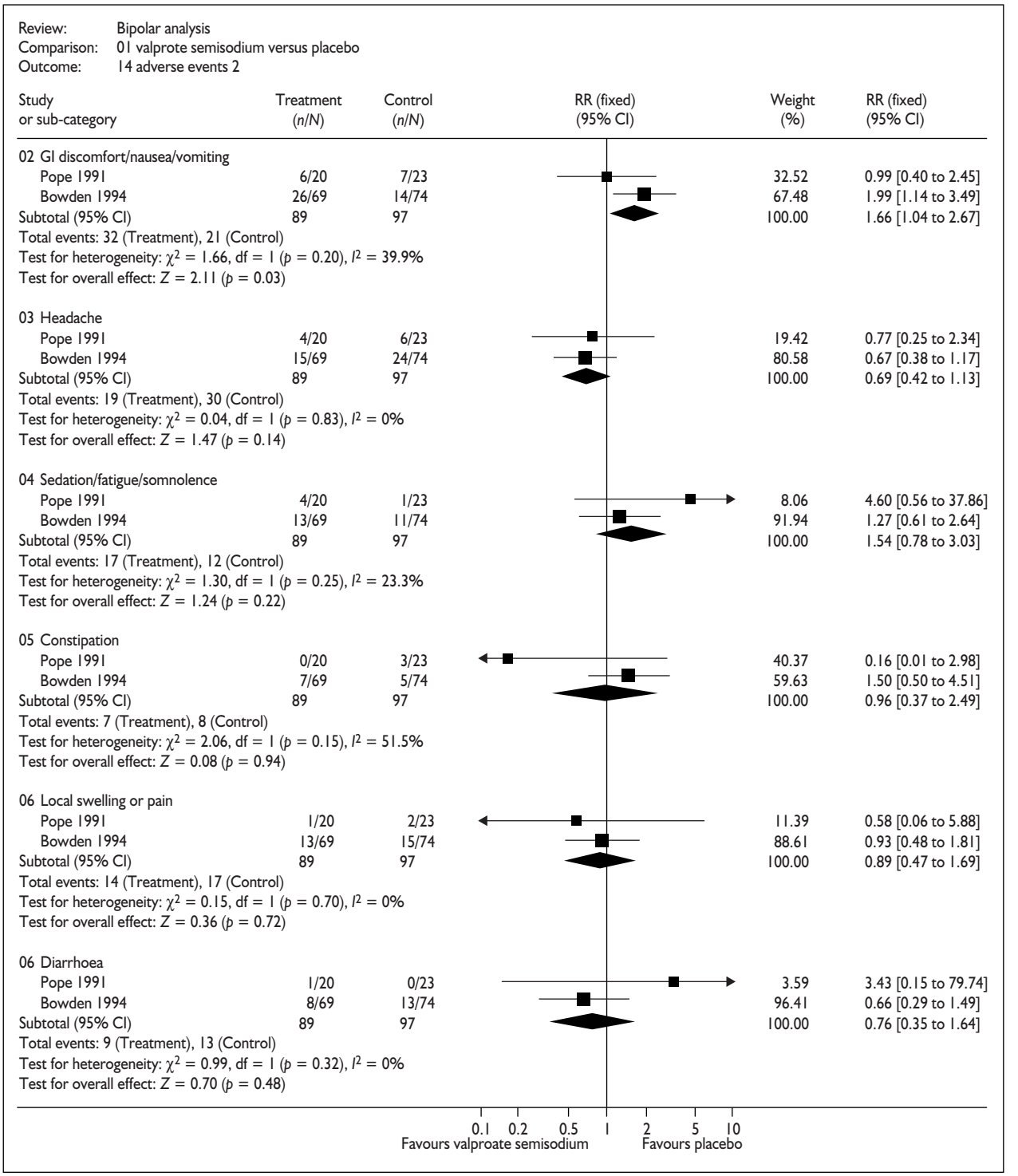

FIGURE 67 *Adverse effects – valproate semisodium versus placebo (cont'd)*

responders (–10.8 in the valproate semisodium group and –1.0 in the placebo group). No measure of variance was given so we cannot calculate a 95% CI around the MD in change scores of 7.9 in lithium responders and –9.8 in lithium non-responders. An effect size analysis of this trial[52] did report SD scores for the total MRS and subscales for the whole group. The total MD did not favour lithium or valproate semisodium (MD –0.20, 95% CI –6.40 to 6.00) but subscales of increased activity (MD 0.76, 95% CI 0.05 to 1.47) and less need for sleep (MD 1.36, 95% CI 0.62 to 2.10) favoured valproate semisodium (*Figure 69*).

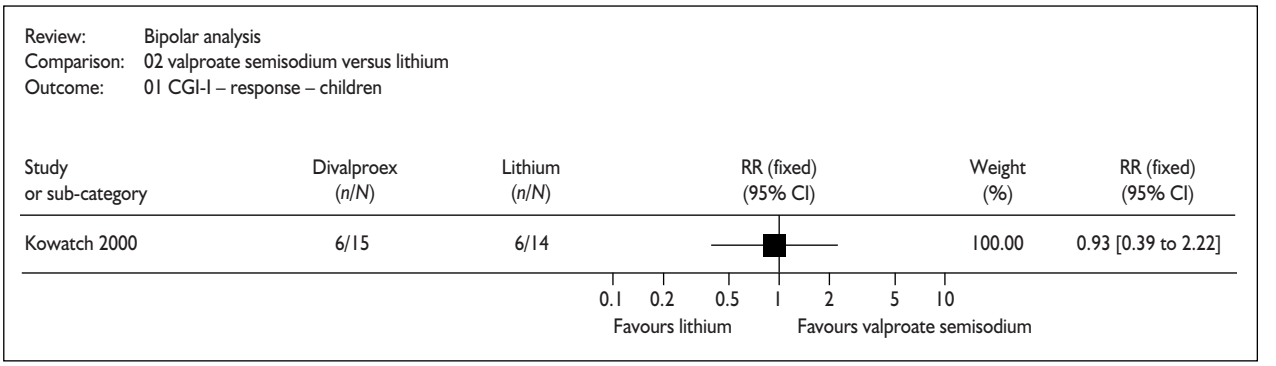

FIGURE 68 *CGI-I 'response' in children – valproate semisodium versus lithium*

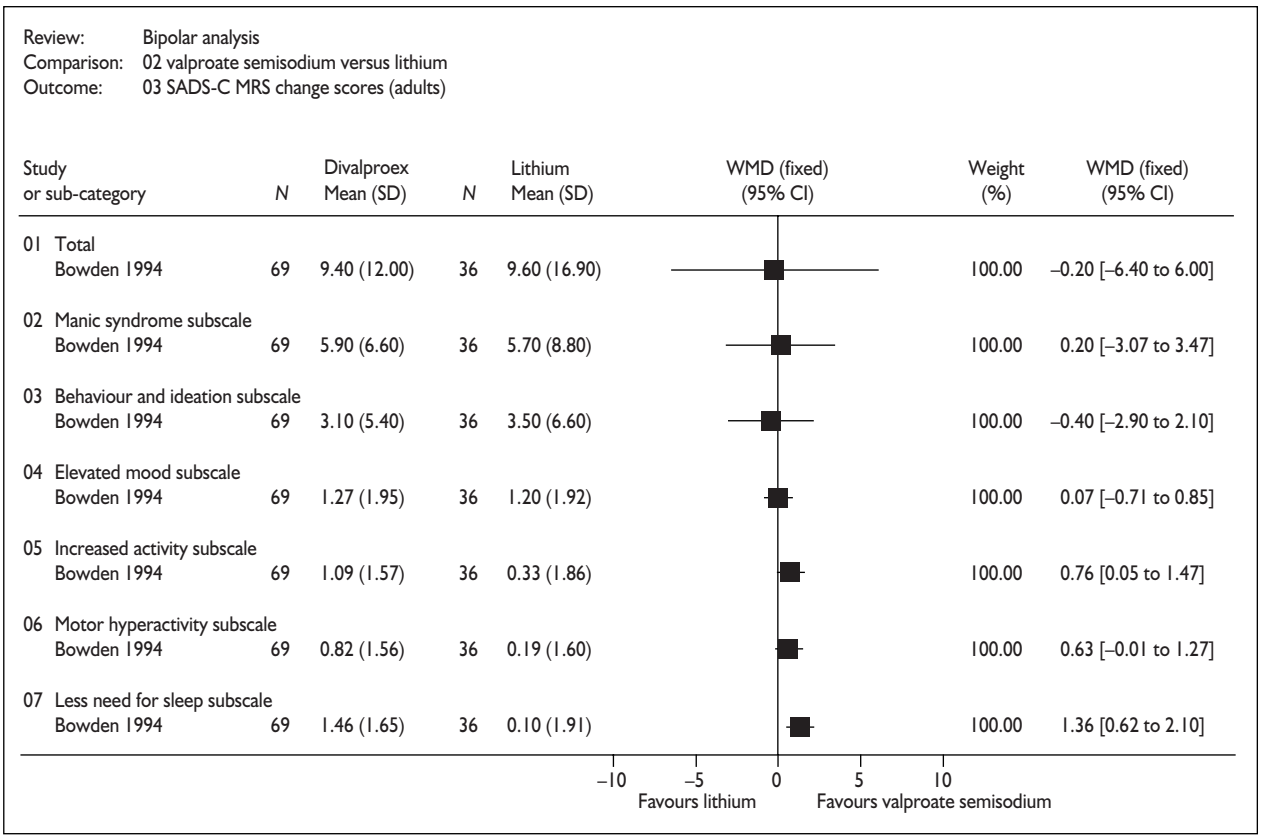

FIGURE 69 *SADS-C MRS scores in adults – valproate semisodium versus lithium*

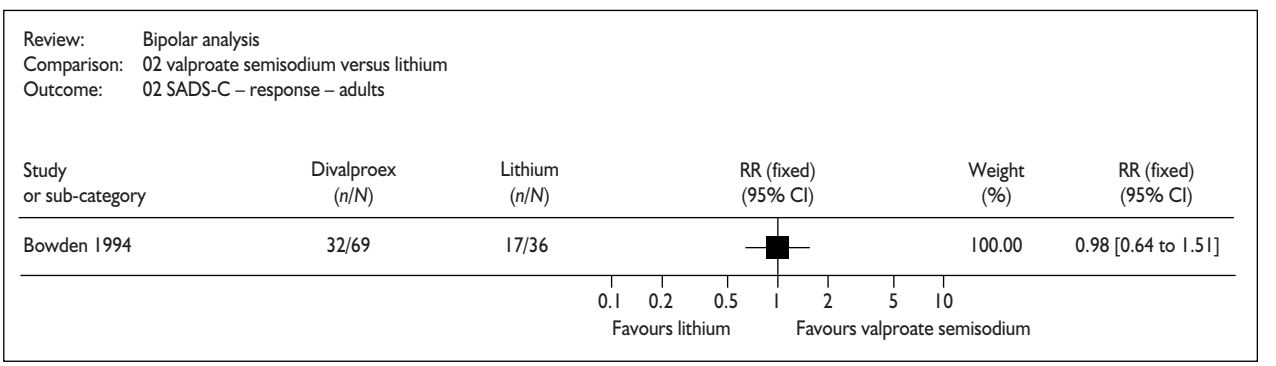

FIGURE 70 *SADS-C 'response' in adults – valproate semisodium versus lithium*

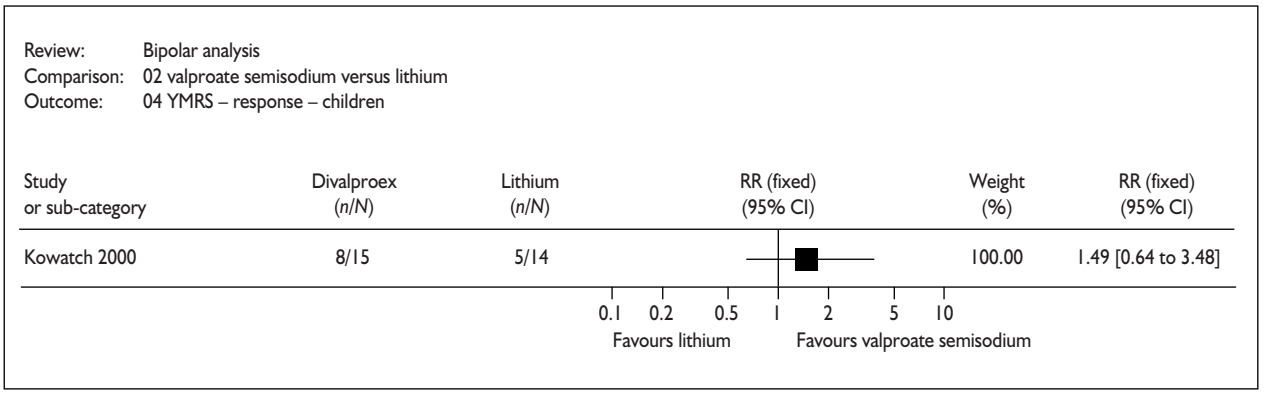

FIGURE 71 *YMRS 'response' in children – valproate semisodium versus lithium*

The Bowden 1994[49] trial also reported 'response' as being at least a 50% improvement on the SADS-C MRS score. No significant difference was seen between groups (RR 0.98, 95% CI 0.64 to 1.51) (*Figure 70*). Sensitivity analysis using positive assumptions for missing persons did not substantially affect this result (RR 0.98, 95% CI 0.64 to 1.50).

A subgroup analysis from this study[50] which compared three definitions of depressive mania, reported that depressive presentation was associated with a poorer response to lithium with less improvement (or even slight deterioration) in the SADS-C MRS compared with classic mania. Depressive symptoms had no significant effect on response to valproate semisodium. People experiencing depressive mania were reported to have better response to valproate semisodium than to lithium, but the reverse was true for classic mania.

Another subgroup analysis from this study[51] reported that antimanic response to treatment diverged sharply as the number of lifetime episodes of affective disorder increased. Values for improvement with a low number of episodes were 5.9 (SD 1.1) for valproate semisodium and 5.6 (SD 1.2) for lithium. There was no significant difference between valproate semisodium- and placebo-treated groups in transition between high and low response.

In the Hirschfeld 1999[53] study the results were presented graphically but means and SDs were not reported. In this study the authors reported that similar improvements were seen on YMRS (including subscales) in all three groups: valproate semisodium loading, valproate semisodium non-loading and lithium carbonate ($p = 0.152$).

Children

Kowatch 2000[54] trial reported mean change scores for the YMRS but SDs were not reported separately for each group; only a 'pooled' SD was reported so we could not calculate the 95% CI around the MD of 5.07 in favour of valproate semisodium. Also reported was 'response' (defined as at least a 50% improvement in YMRS score). There was no significant difference between valproate semisodium and lithium groups in terms of response (RR 1.49, 95% CI 0.64 to 3.48) (*Figure 71*).

Other psychiatric assessments

Adults

The Bowden 1994[49] study measured ADRS change scores and subsequently reported mean and SD for each group.[52] The mean difference between groups was not significant for the mania, psychosis or elated or grandiose subscales (*Figure 72*).

A subgroup analysis from this study,[50] which compared three definitions of depressive mania, reported that depressive presentation was associated with a poorer response to lithium with less improvement (or even slight deterioration) in the behaviour–ideation scale compared with classic mania. Depressive symptoms had no significant effect on response to valproate semisodium. People experiencing depressive mania were reported to have better response to valproate semisodium than to lithium, but the reverse was true for classic mania.

Leaving the study early

Adults

Both trials reported the number of people withdrawing early from the study. No significant differences were seen between people receiving valproate semisodium (loading or standard dose)

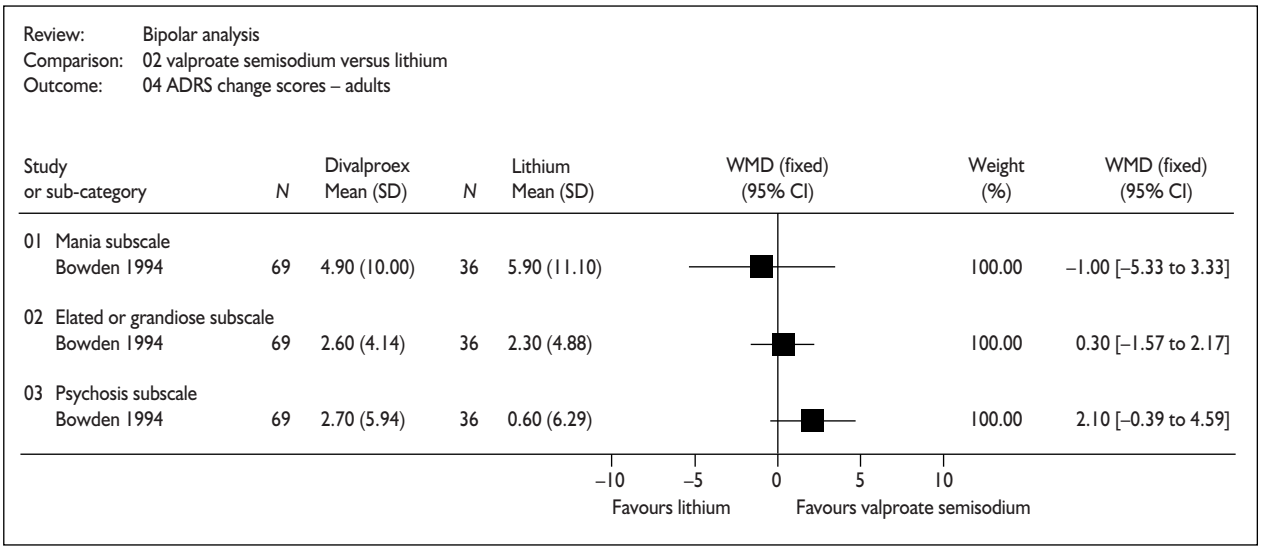

FIGURE 72 *ADRS scores in adults – valproate semisodium versus lithium*

and people receiving lithium for this outcome (RR 0.78, 95% CI 0.57 to 1.07) (*Figure 73*).

Children

No significant difference was seen in one small trial between lithium and valproate semisodium groups for the outcome of leaving the study early (RR 0.93, 95% CI 0.15 to 5.76) (*Figure 74*).

Length of stay

None of the three trials which compared lithium with valproate semisodium reported length of stay in hospital as an outcome.

Receipt of lorazepam

Adults

The Hirschfeld 1999[53] trial reported how many people in each group received lorazepam. The number was not significantly different in lithium and valproate semisodium groups (RR 0.91, 95% CI 0.68 to 1.21) (*Figure 75*).

Adverse effects

Adults

No significant differences were seen between valproate semisodium and lithium groups in the occurrence of any adverse events, asthenia, constipation, diarrhoea, dizziness, headache, pain, nausea, vomiting, somnolence or twitching. There was a higher risk of fever in the lithium group than the valproate semisodium group (RR 0.10, 95% CI 0.01 to 0.86) (*Figure 76*).

Children

The Kowatch 2000[54] trial reported numbers only for the adverse effect of nausea (no difference was found between groups: RR 0.93, 95% CI 0.22 to 3.88) (*Figure 77*). In this study, the authors reported that nausea was the most common side-effect and the majority of side-effects were mild to moderate and tolerated by most. There were no serious adverse events needing hospitalisation.

Valproate semisodium versus carbamazepine

One study (Kowatch 2000[54]) compared valproate semisodium (20 mg/kg/day, standard titration) with carbamazepine (15 mg/kg/day) for 4–8 weeks in children with DSM-IV bipolar I or II disorder, mixed or manic episodes.

Global effects

'Response' on the CGI-I scale, defined as at least a 50% decrease in score, was reported. There was no significant difference between valproate semisodium and carbamazepine groups in this outcome (RR 1.30, 95% CI 0.47 to 3.62) (*Figure 78*).

Effects on mania

The Kowatch 2000[54] trial reported mean change scores for the YMRS but the SD was not reported separately for each group; only a 'pooled' SD was reported so we could not calculate the 95% CI around the MD of 5.53 in favour of valproate semisodium. Also reported was 'response' (defined as at least a 50% improvement in YMRS score). There was no significant difference between valproate semisodium and carbamazepine groups in terms of response (RR 1.39, 95% CI 0.60 to 3.20) (*Figure 79*).

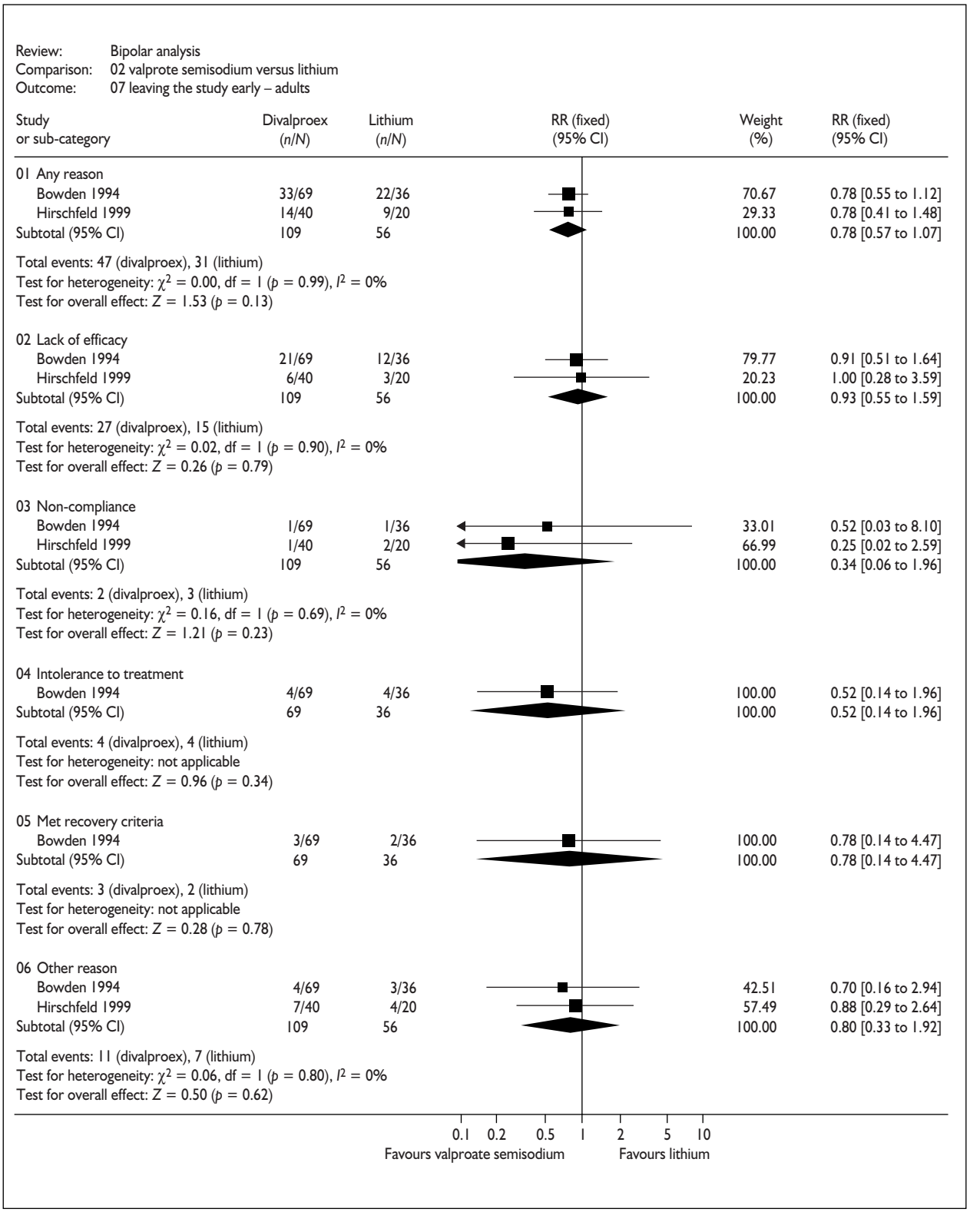

FIGURE 73 *Leaving the study early – adults – valproate semisodium versus lithium*

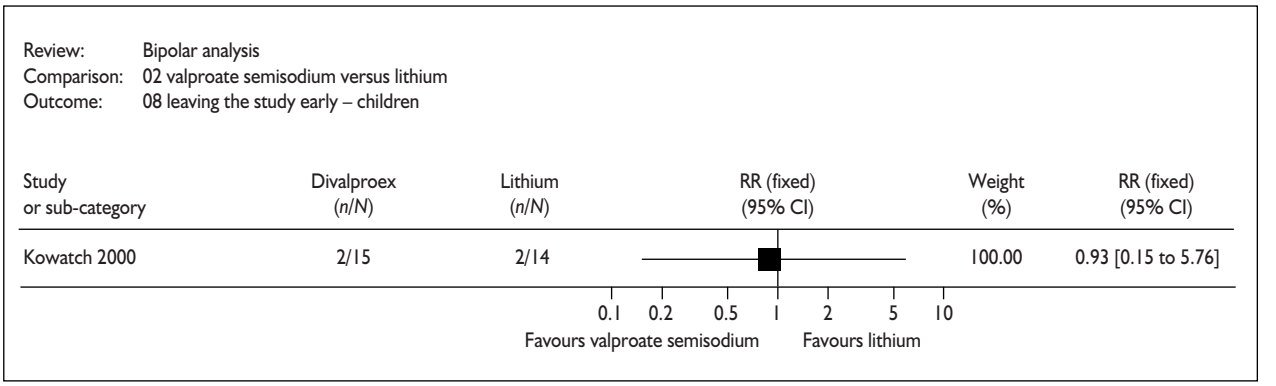

FIGURE 74 *Leaving the study early – children – valproate semisodium versus lithium*

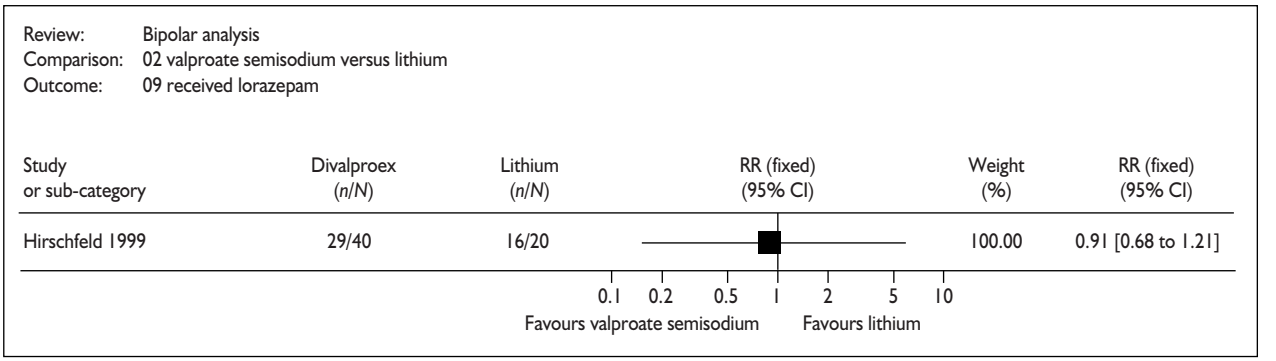

FIGURE 75 *Receipt of lorazepam – adults – valproate semisodium versus lithium*

Other psychiatric assessments

No other psychiatric assessments were reported in this study.

Leaving the study early

No significant difference was seen between valproate semisodium and carbamazepine groups in terms of leaving the study early (RR 0.87, 95% CI 0.14 to 5.32) (*Figure 80*).

Length of stay

Length of stay was not reported in this study.

Receipt of lorazepam

Receipt of lorazepam was not an outcome reported in this study.

Adverse effects

The only adverse effect that any numbers were reported for was nausea. This was reported to be the most common side-effect. There was no significant difference in risk of nausea between valproate semisodium and carbamazepine groups (RR 0.43, 95% CI 0.13 to 1.40) (*Figure 81*).

Valproate semisodium versus haloperidol

One study (McElroy 1996[55]) compared valproate semisodium (20 mg/kg/day) with haloperidol (20 mg/kg/day) for 6 days in bipolar mixed or manic patients with psychotic features.

Global effects

No global assessment seems to have been undertaken in this study.

Effects on mania

YMRS end-point scores are reported. There were no significant differences between groups in terms of mean end-point scores (MD –3.60, 95% CI –11.48 to 4.28) (*Figure 82*). Again, it may be worth noting that end-point YMRS scores in both groups were >14, which is the entry definition of mania in many of the included trials.

'Response' is also reported with reference to the YMRS scale. People in the valproate semisodium group were not significantly more likely to respond than people in the haloperidol group (RR 1.43, 95% CI 0.61 to 3.32) (*Figure 83*).

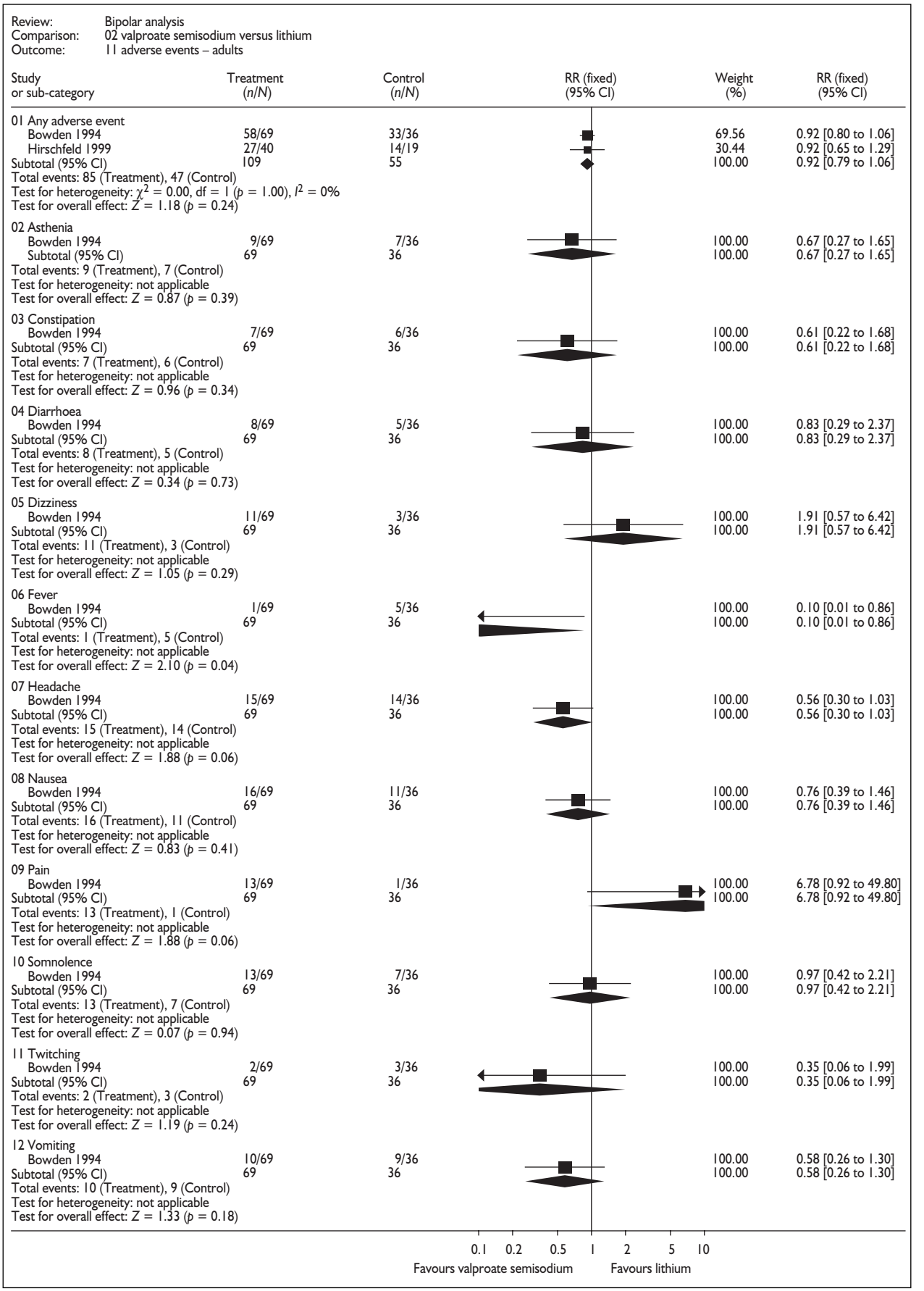

FIGURE 76 *Adverse events – adults – valproate semisodium versus lithium*

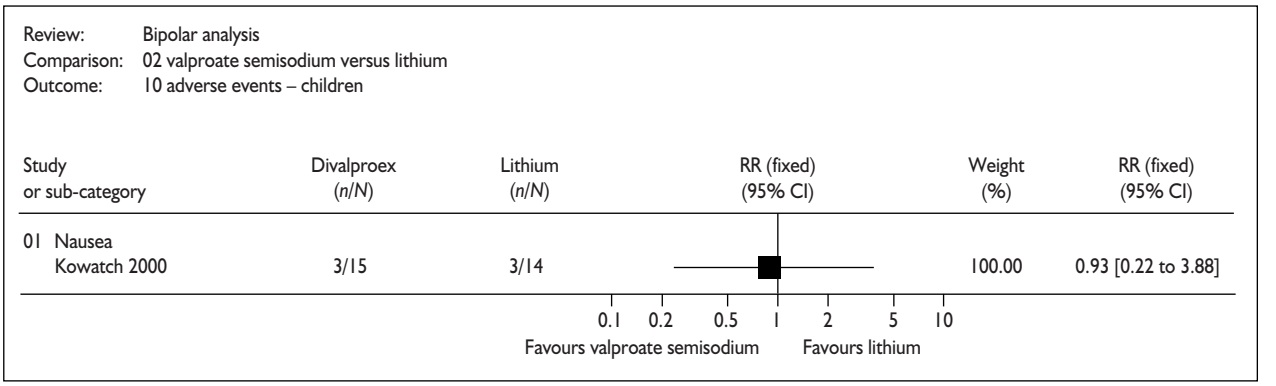

FIGURE 77 *Adverse effects – children – valproate semisodium versus lithium*

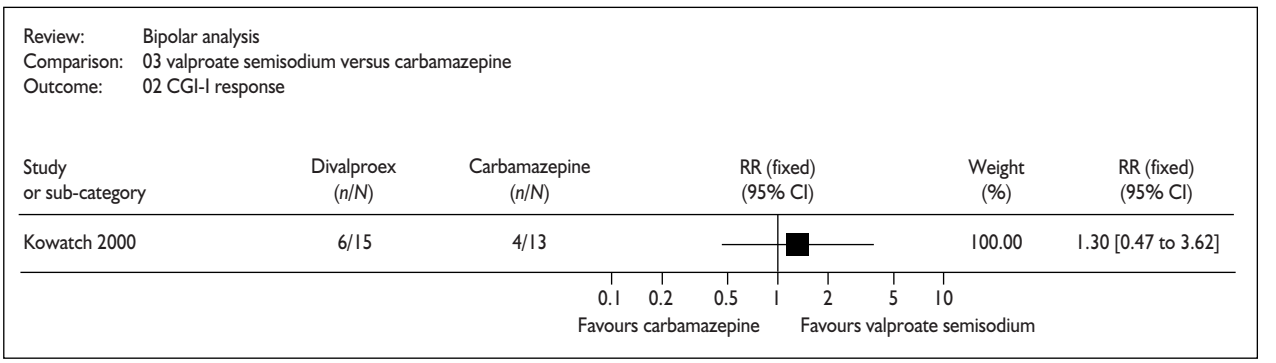

FIGURE 78 *CGI-I response – valproate semisodium versus carbamazepine – children*

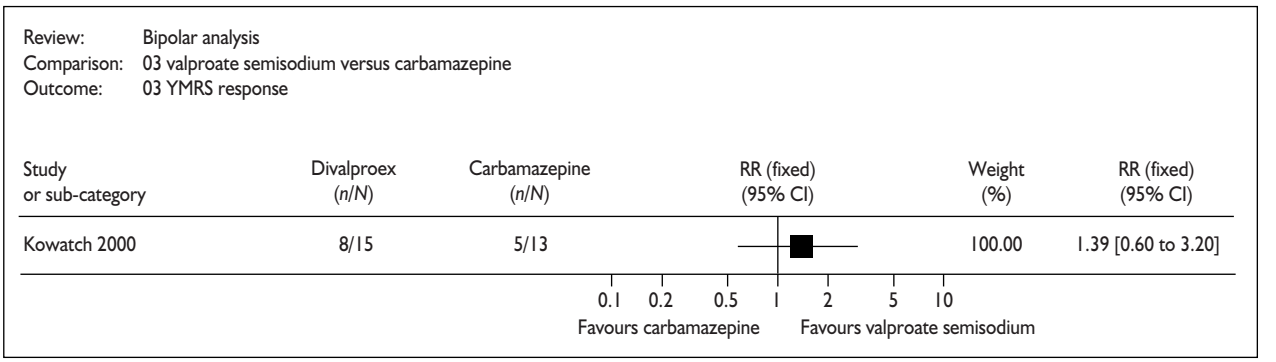

FIGURE 79 *YMRS response – valproate semisodium versus carbamazepine – children*

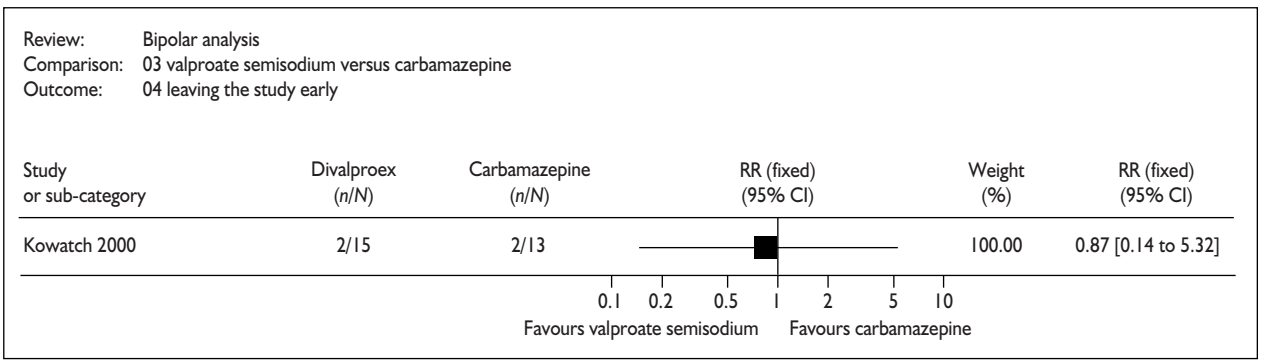

FIGURE 80 *Leaving the study early – valproate semisodium versus carbamazepine – children*

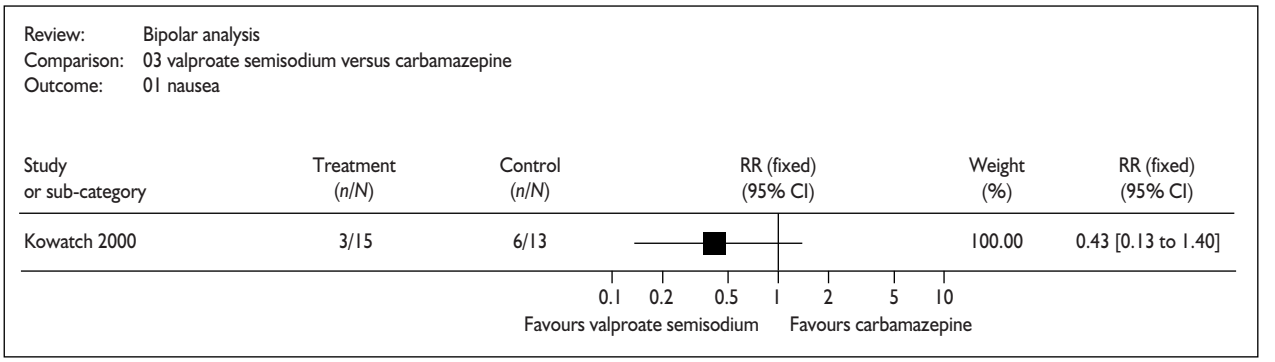

FIGURE 81 *Nausea – valproate semisodium versus carbamazepine – children*

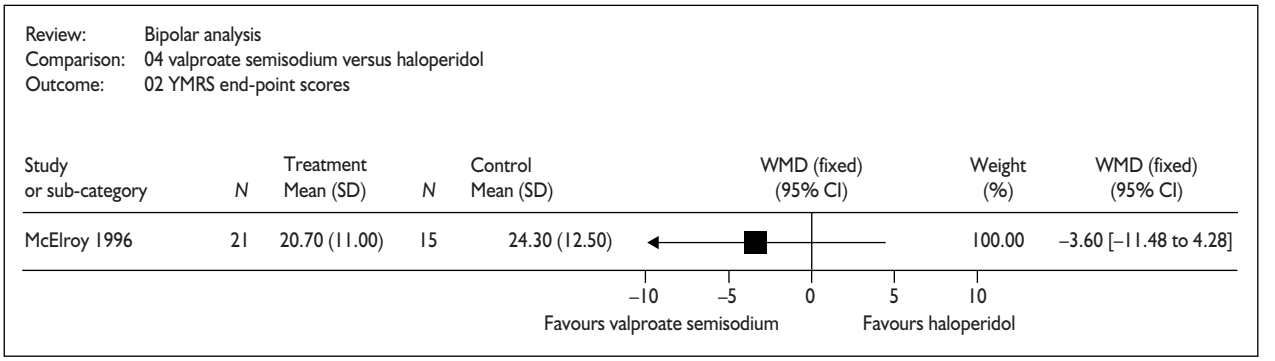

FIGURE 82 *YMRS scores – valproate semisodium versus haloperidol*

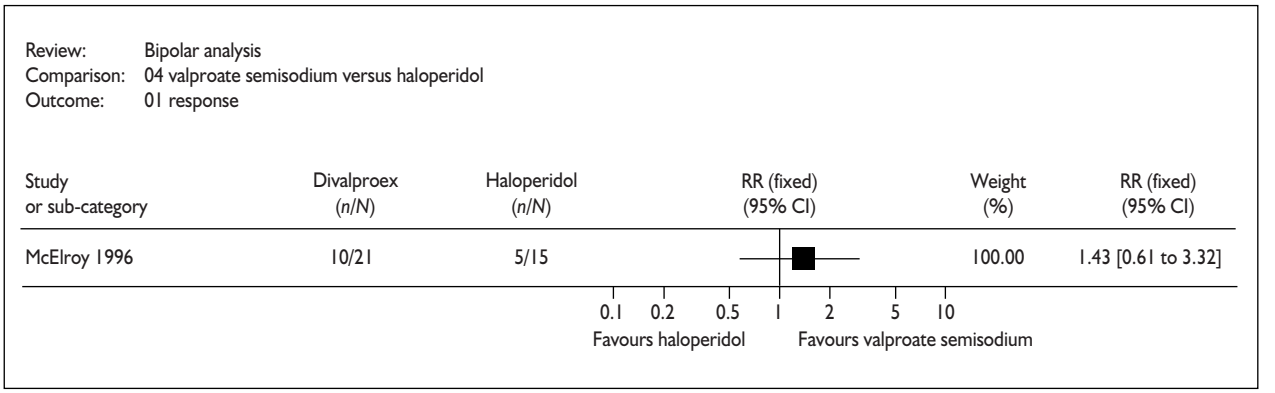

FIGURE 83 *Response – valproate semisodium versus haloperidol*

Other psychiatric assessments

SAPS subscale scores for hallucination, delusion, bizarre thinking and thought disorder are presented (*Figure 84*). No significant differences between groups were found for any of these subscales.

Leaving the study early

Attrition was not reported for either group in this study.

Length of stay

No significant difference was seen between groups in length of hospital stay (MD 3.30, 95% CI –2.66 to 9.26) (*Figure 85*).

Receipt of lorazepam

Receipt of lorazepam was not reported in this study.

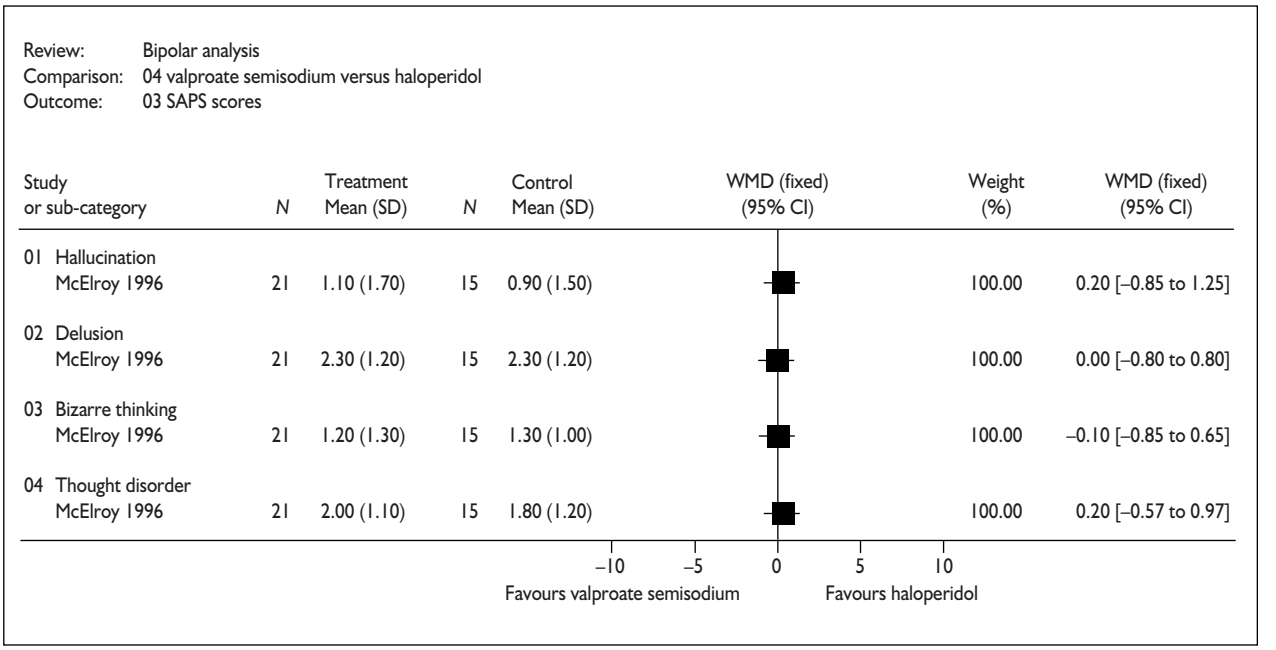

FIGURE 84 *SAPS scores – valproate semisodium versus haloperidol*

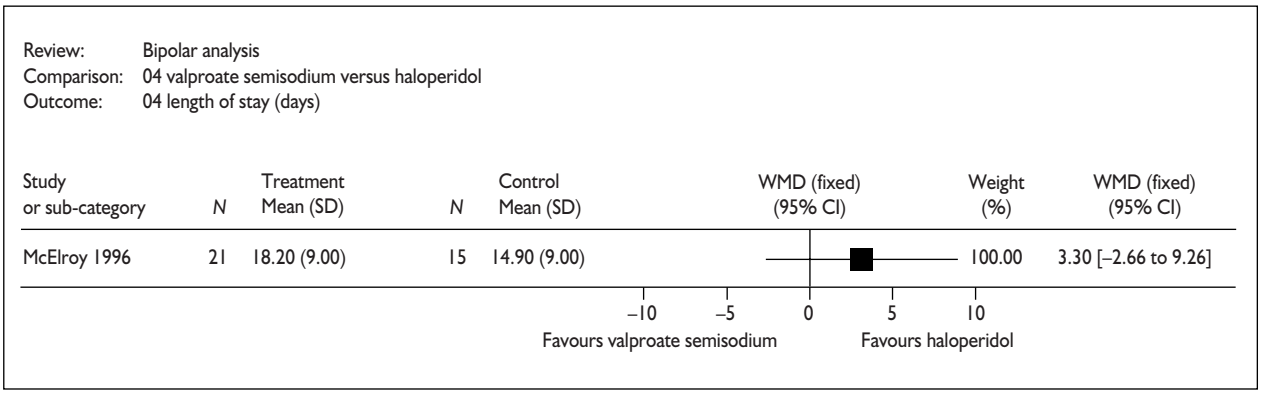

FIGURE 85 *Length of stay – valproate semisodium versus haloperidol*

Adverse effects

Apart from extrapyramidal side-effects, which were significantly less likely to occur in the valproate semisodium group (RR 0.04, 95% CI 0.00 to 0.69), no significant difference was seen between valproate semisodium and haloperidol in the following reported side-effects: sedation, indigestion, headache, dry mouth or insomnia (*Figure 86*).

Valproate semisodium versus olanzapine

Two RCTs (Tohen 2002[56] and Zajecka 2000[57]) compared valproate semisodium and olanzapine (*Table 4*).

Description of included trials

The Tohen 2002[56] trial gave valproate semisodium at a dose of 500–2500 mg/day and the Zajecka 2000[57] trial at a dose of 20 mg/kg/day. Olanzapine was given at a dose of 5–20 mg/day in the Tohen 2002[56] and 10–20 mg/day in the Zajecka 2000[57] trial. Results are given at 3 weeks of treatment for both trials. Zajecka 2000[57] also gives results at 12 weeks of treatment but these are not presented here (except for weight gain) as we do not feel this constitutes an 'acute' episode of mania.

Participants in the Tohen 2002[56] trial were diagnosed with DSM-IV bipolar I disorder, manic or mixed episode with or without psychotic

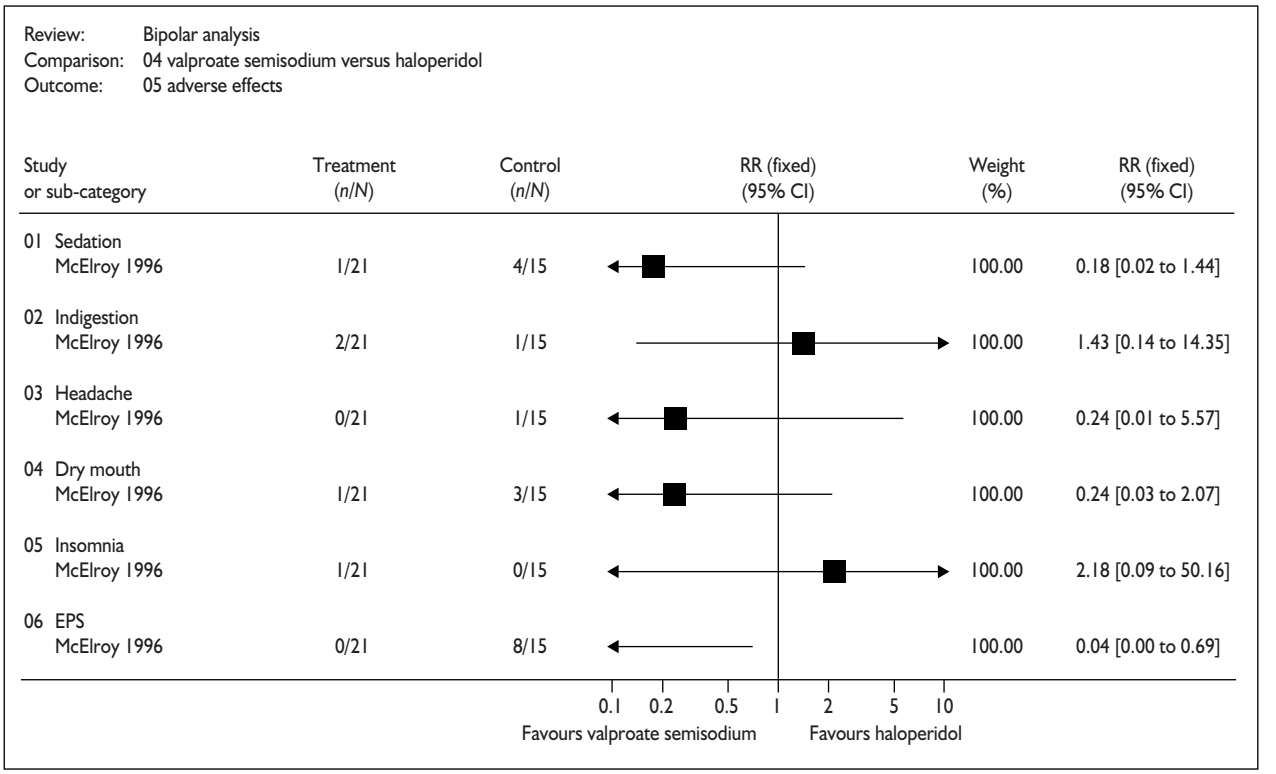

FIGURE 86 *Adverse effects – valproate semisodium versus haloperidol*

TABLE 4 *Valproate semisodium versus olanzapine – included studies*

Study	Participants	Interventions	Outcomes
Tohen 2002[56] (full paper)	*N* = 251 Diagnosis: DSM-IV bipolar I disorder manic or mixed episode with or without psychotic features. YMRS score ≥ 20 Duration of illness: not reported	3 weeks Valproate semisodium (*n* = 126) 5–20 mg/day (initial 15 mg/day) Olanzapine (*n* = 125) 5–20 mg/day (initial 15 mg/day)	Attrition Adverse events YMRS score; YMRS response rate; YMRS remission rate; GAS scores; BPRS-A scores; receipt of lorazepam
Zajecka 2000[57] (abstract)	*N* = 126 Diagnosis: bipolar disorder, acute mania (hospitalised)	3 weeks (also 12 weeks). Valproate semisodium (*n* = 63) 20 mg/kg/day Olanzapine (*n* = 57): 20 mg/kg/day	Adverse events MRS; CGI score; BPRS score; HAM-D score; Q-LES-Q score

Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

features and participants in the Zajecka 2000[57] trial were diagnosed with acute mania in bipolar disorder (further details not reported). Participants in Tohen 2002[56] had a mean age of 40.0–41.1 years and 57% were female. They were required to have a minimum score of 20 on the YMRS at baseline. People with serious and unstable medical illness, substance dependence, intolerance to olanzapine or valproate semisodium or who had received lithium, an anticonvulsant or an antipsychotic medication within 24 hours of randomisation were excluded from Tohen 2002.[56] Participants in Zajecka 2000[57] had a mean age of 38.1–38.9 years and 46% were female. Inclusion criteria were not stated for this study but mean baseline mania rating scores were reported as 30.8 in the valproate semisodium group and 32.2 in the olanzapine group.

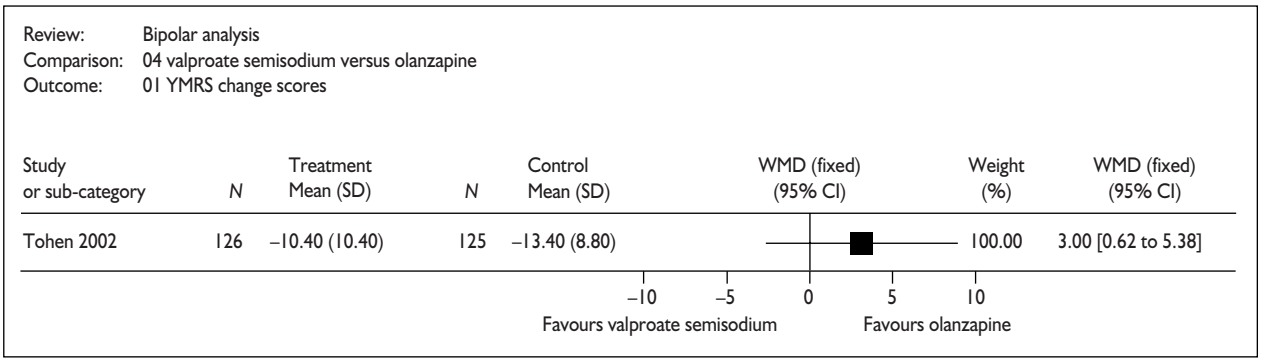

FIGURE 87 *YMRS change scores – valproate semisodium versus olanzapine*

Approximately 30% of the participants were 'rapid cyclers' and between 45 and 50% had mixed mania.

Validity

Neither trial reported their method of randomisation or allocation concealment. Tohen 2002[56] stated the number randomised, that the groups were comparable at baseline and that co-interventions were reported. Zajecka 2000[57] reported a significantly higher mania rating score for the olanzapine group at baseline (but significance tests are not an appropriate way of assessing baseline comparability). The difference of 1.4 points may not be clinically significant. The groups appear to be similar on other reported baseline characteristics. Both trials were reported to be double blind; however, in Zajecka 2000[57] it is unclear whether the outcome assessors were blind to treatment group. People who withdrew from treatment early are accounted for in Tohen 2002[56] but not in Zajecka 2000.[57] Both drugs seem to have been given in appropriate doses in both trials. Tohen 2002[56] used an ITT analysis but it was unclear whether Zajecka 2000[57] also did so.

Main results

Global effects

Zajecka 2000[57] measured global outcome using the CGI-I scale. Mean change from baseline was reported to be –0.8 for the valproate semisodium group and –1.0 for the olanzapine group. This difference was not statistically significant ($p = 0.439$). No SD was reported so we could not calculate a 95% CI around the MD of 0.2.

Effects on mania

Zajecka 2000[57] reported mean change scores on the MRS of –14.8 in the valproate semisodium group and –17.2 in the olanzapine group. This difference was not statistically significant ($p = 0.210$). No SD was reported so we could not calculate a 95% CI around the MD of 2.4. Tohen 2002[56] also reports mean change scores and SDs on the YMRS. The MD clearly favours olanzapine (MD 3.00, 95% CI 0.62 to 5.38) (*Figure 87*).

The trial authors report the results of a subgroup analysis of patients with psychotic features and patients without psychotic features. In the subgroup with psychotic features, there was no statistically significant difference in improvement between the olanzapine patients and the valproate semisodium patients (MD –0.20, 95% CI –2.88 to 2.48). In the subgroup without psychotic features, the improvement with olanzapine was significantly greater than the improvement with valproate semisodium (MD 5.40, 95% CI 3.28 to 7.52) (*Figure 88*).

Tohen 2002[56] also reported 'response' (defined as at least a 50% reduction in YMRS scores) and remission (defined as YMRS score ≤ 12). These results also marginally favour olanzapine (response RR 0.76, 95% CI 0.58 to 0.99; remission RR 0.71, 95% CI 0.52 to 0.96) (*Figures 89* and *90*). Sensitivity analysis using positive assumptions for missing persons did not substantially affect the result for remission (RR 0.72, 95% CI 0.53 to 0.98), but the result for response became non-significant (RR 0.78, 95% CI 0.60 to 1.01).

Other psychiatric assessments

The Tohen 2002[56] and Zajecka 2000[57] trials both report mean change scores on the HAM-D, but Zajecka 2000[57] did not report SDs so we could not calculate a 95% CI around the MD of 0.6. This difference was reported not to be statistically significant ($p = 0.593$). Tohen 2002[56] also found no significant difference between groups (MD 1.40, 95% CI –0.29 to 3.09) (*Figure 91*).

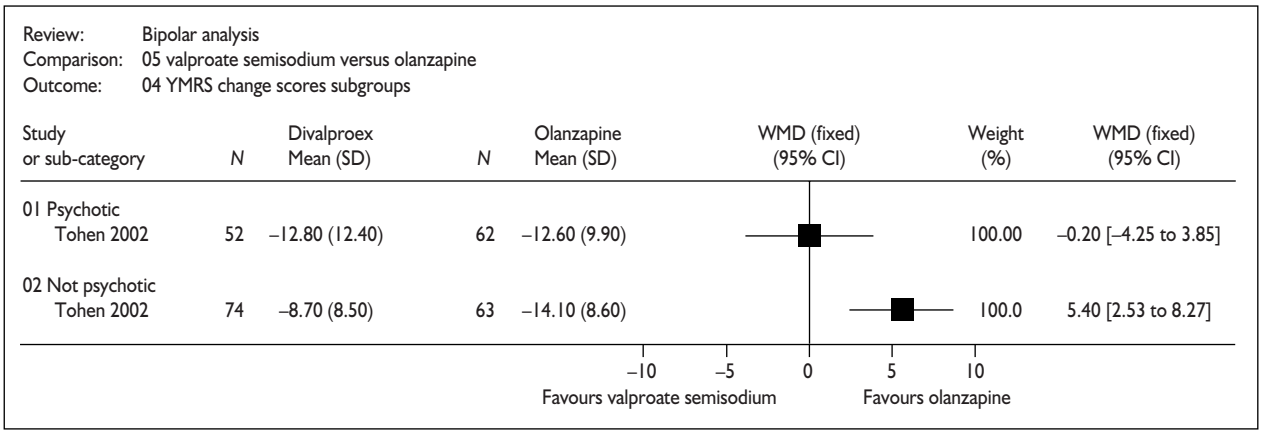

FIGURE 88 *YMRS change scores subgroup analysis*

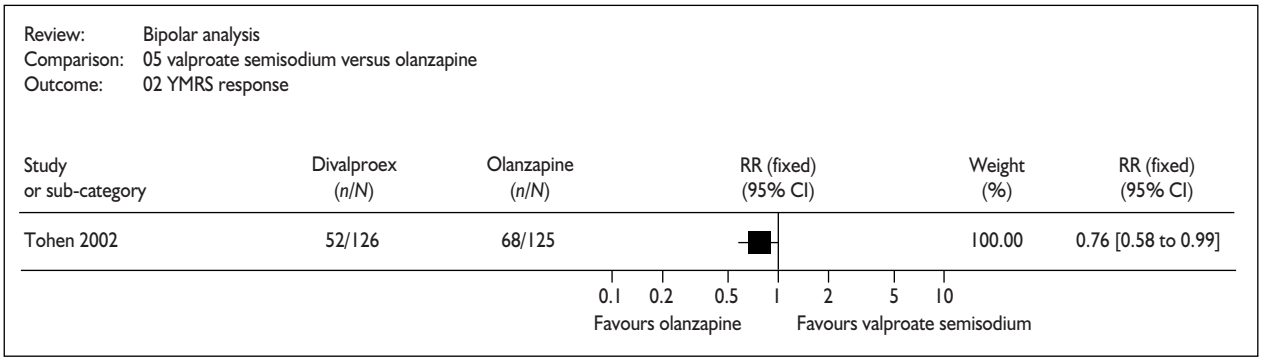

FIGURE 89 *YMRS response – valproate semisodium versus olanzapine*

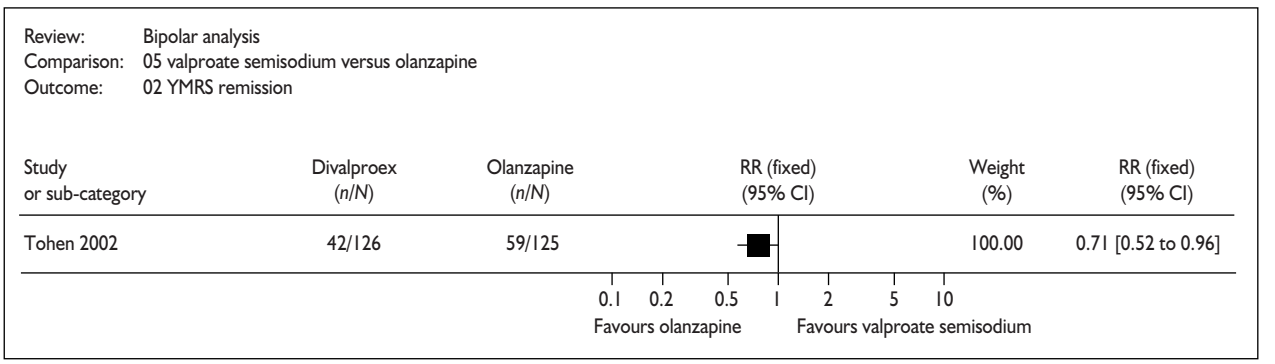

FIGURE 90 *YMRS remission – valproate semisodium versus olanzapine*

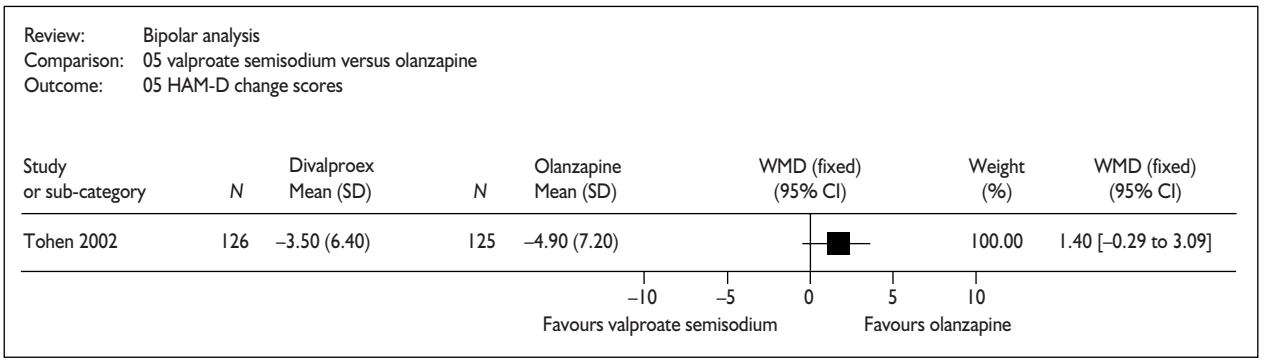

FIGURE 91 *HAM-D change scores – valproate semisodium versus olanzapine*

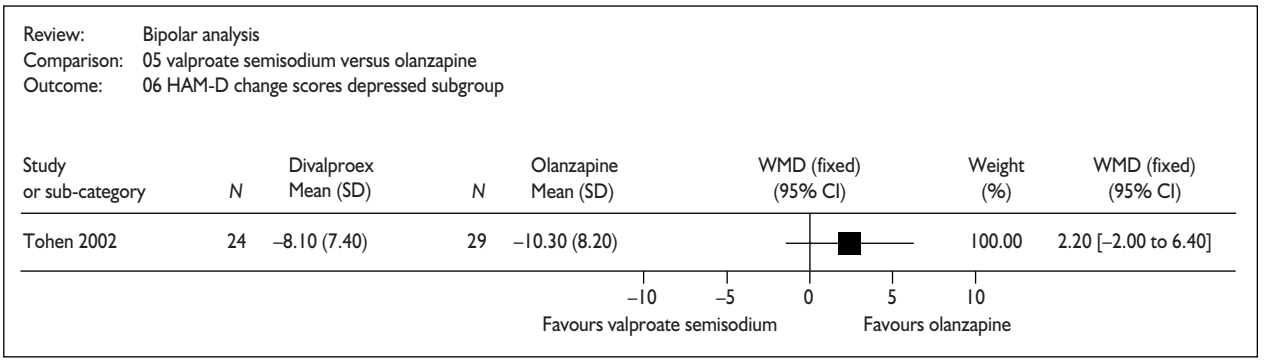

FIGURE 92 *HAM-D change scores, depressed subgroup – valproate semisodium versus olanzapine*

A subgroup analysis of patients with a HAM-D total score of ≥ 20 at baseline still showed no significant difference in mean HAM-D change scores between valproate semisodium- and olanzapine-treated groups (MD 2.20, 95% CI –2.00 to 6.40) (*Figure 92*).

Zajecka 2000[57] also assessed BPRS change scores and reported no significant difference between groups ($p = 0.302$). No SD was reported so we could not calculate a 95% CI around the MD of 2.1.

Leaving the study early

This outcome was reported by both trials. No significant differences were seen between treatment groups for people leaving the study early for any reason (*Figure 93*).

Length of stay

Neither study reported length of hospital stay.

Receipt of lorazepam

Neither study reported receipt of lorazepam as an outcome.

Adverse effects

Tohen 2002[56] reported a greater risk in the olanzapine group of dry mouth (RR 0.19, 95% CI 0.09 to 0.39) and increased appetite (RR 0.20, 95% CI 0.06 to 0.67) and an increased risk in the valproate semisodium group of nausea (RR 2.75, 95% CI 1.53 to 4.93). Zajecka 2000[57] reported an increased risk of oedema in the olanzapine group (RR 0.05, 95% CI 0.00 to 0.90). Pooled results from both trials indicate an increased risk of somnolence (RR 0.55, 95% CI 0.41 to 0.76), weight gain (RR 0.53, 95% CI 0.30 to 0.93) and speech disorder or slurred speech (RR 0.10, 95% CI 0.02 to 0.53) in the olanzapine group (*Figure 94*).

The Tohen 2002[56] also reported EPS ratings. No significant differences were seen between groups for change scores on the AIMS or the BAS, but the SAS change score was in favour of valproate semisodium (MD –0.72, 95% CI –1.33 to –0.11) (*Figure 95*).

Both studies also reported weight change. Zajecka 2000[57] reported significantly more weight gain at 12 weeks in the olanzapine than the valproate semisodium group ($p = 0.049$). No measure of variance was reported so we could not calculate a 95% CI around the MD of 3.3 lb (1.5 kg). Tohen 2002[56] reported weight change and SD in both groups. The olanzapine group gained significantly more weight than the valproate semisodium group at 12 weeks (MD –1.57, 95% CI –2.19 to –0.95) (*Figure 96*).

Quality of life

Zajecka 2000[57] assessed QoL using the Q-LES-Q after hospital discharge and at weeks 6 and 12. No statistically significant differences were noted between the two groups in change from baseline at 12 weeks.

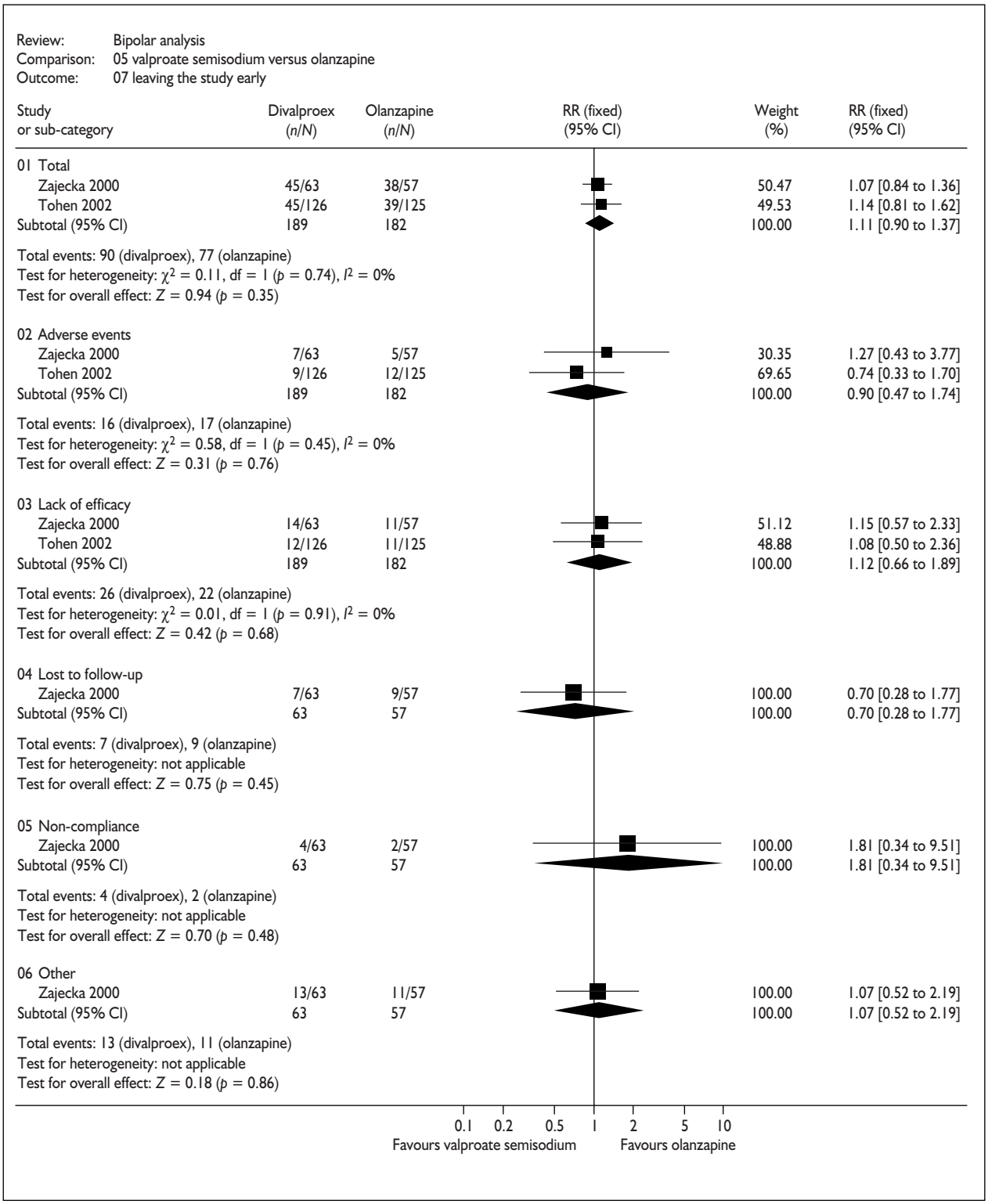

FIGURE 93 *Leaving the study early – valproate semisodium versus olanzapine*

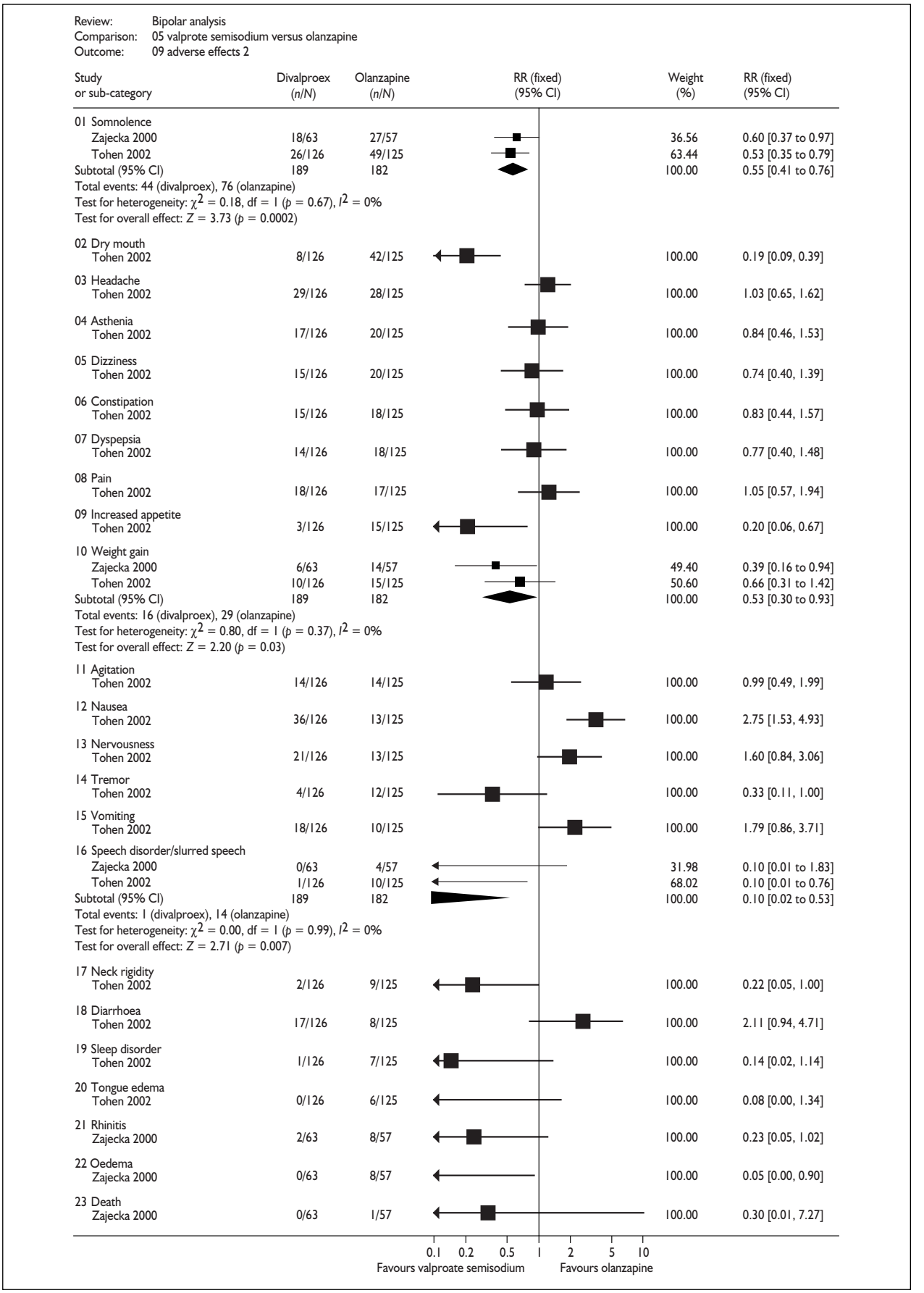

FIGURE 94 *Adverse events*

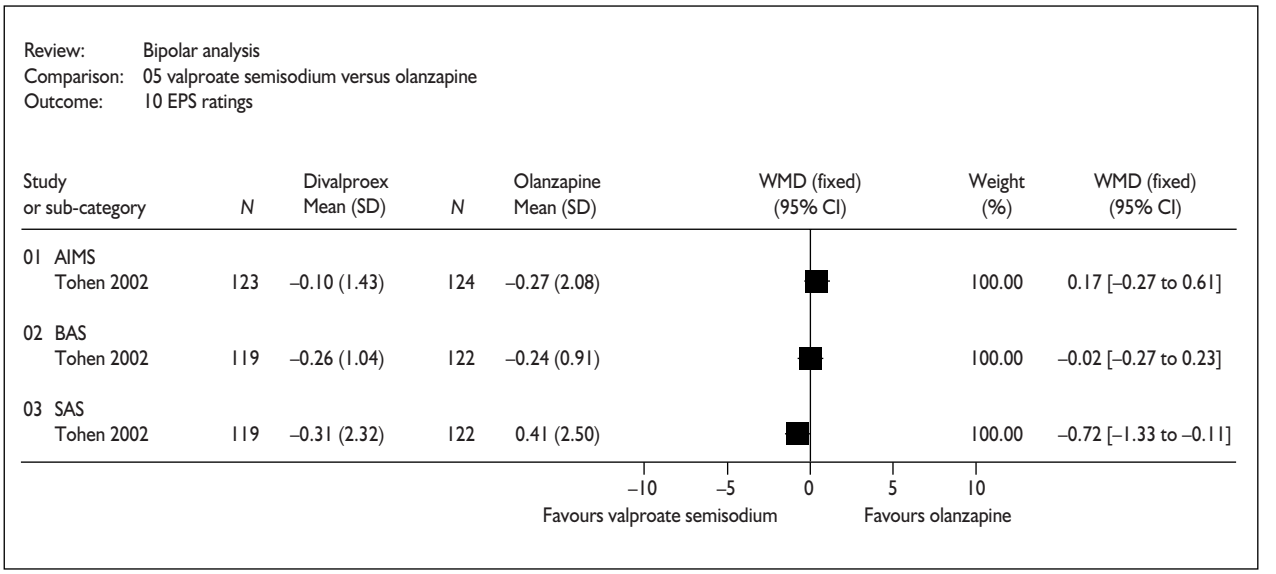

FIGURE 95 *EPS rating scale change scores – valproate semisodium versus olanzapine*

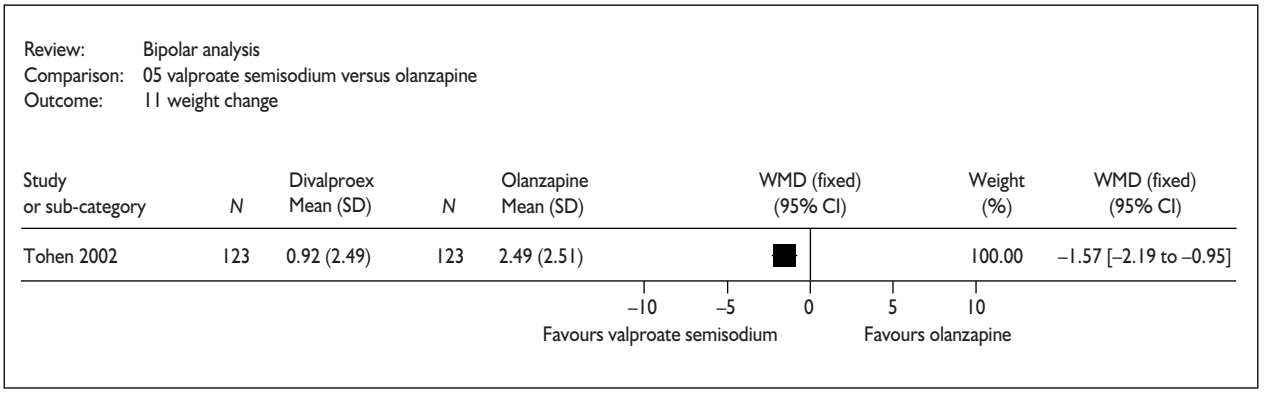

FIGURE 96 *Weight change – valproate semisodium versus olanzapine*

Chapter 4

Economic review

Summary of studies included in the cost-effectiveness review

The systematic literature search detailed in Chapter 2 identified two studies which met the criteria for inclusion in the cost-effectiveness review.[57,58] Economic evidence was also submitted by the stakeholders. Separate cost-effectiveness models and accompanying reports were submitted by Sanofi-Synthelabo and Eli Lilly. No economic data were provided by AstraZeneca for consideration in this review.

The following sections provide a detailed overview of the cost-effectiveness evidence from each of these sources and an assessment of the quality and relevance of the data from the perspective of the UK NHS. Data extraction tables and the quality checklist for each study are reported in Appendices 8 and 9, respectively. An overall summary of the cost-effectiveness evidence is provided at the end of the chapter.

Review of Keck and colleagues (1996). A pharmacoeconomic model of valproate semisodium vs lithium in the acute and prophylactic treatment of bipolar I disorder[58]

Overview

This study evaluated the costs of valproate semisodium versus lithium in the acute and prophylactic treatment of patients with bipolar I disorder in the USA over a 1-year period.[58] The study is based on a deterministic, decision-analytic model. The focus of the study relates to the evaluation of the costs associated with these alternative treatment strategies and does not make any direct statements concerning the relative cost-effectiveness of either strategy. However, since the model evaluates both costs and outcomes, it is possible to determine the relative cost-effectiveness of the two drugs from the information reported.

The model was used to estimate the response to initial 'mood-stabiliser' therapy, the mean length of stay during hospitalisation and the frequency of repeat hospitalisations, the rates of adverse events associated with either therapy and the overall costs of treating patients during a 1-year period. The perspective of the study is not explicitly stated, although it is possible to infer that the perspective is that of a third-party payer.

The model begins with an initial hospitalisation for mania. Treatment was modelled as resulting in either (1) response, in which the patient had a >50% symptomatic improvement with lithium or valproate semisodium with or without adjunctive medication, or (2) non-response, in which the patient had no or minimal improvement in manic symptoms (<50% symptomatic improvement). Those who were non-responders were assumed to have the alternative drug added, and then to have a pattern of relapse that did not differ by initial treatment. Those patients who initially responded were separated into those who did and did not have subsequent hospitalisations. Finally, the relapses were separated by whether or not they required hospitalisation. Data used in the model were sourced from published studies, the University of Cincinnati Mania Project database,[59,60] a five-member consensus panel and published pricing lists.

A brief summary of the evaluation is provided in the data extraction tables reported in Appendix 8. The key features are described in more detail below.

Summary of effectiveness data

The probabilities of response to treatment with lithium or valproate semisodium were derived from calculating the weighted mean of response rates reported in the studies identified in their literature search and from response rates reported in the University of Cincinnati Mania Project. The combined response rate was higher with valproate semisodium than lithium in the base-case analysis (0.59 versus 0.49). Data on subsequent events (e.g. the probability of relapse, time to relapse, number of relapses and probability of hospitalisation given relapse) were assumed to be equivalent in both treatment groups. A summary of the base-case parameter values is reported in *Table 5*.

TABLE 5 *Base-case parameters applied in the Keck[58] decision-analytic model*

Parameter	Lithium	Valproate semisodium
Initial hospital length of stay (days)	18.4	14.3
Initial response rate	0.49	0.59
Relapse rate	0.56	0.56
Time to first relapse (months) (for those who relapse)	4.2	4.2
Number of relapses (for those who relapse)	1.7	1.7
Probability of hospitalisation given relapse	0.43	0.43
Rate of reported side-effects	1.7	0.85
Rate of treated reported side-effects	1.1	0.55
Mean drug dose during prophylaxis (mg)	1412	1674

Summary of resource utilisation and cost data

Data for the mean length of stay for the initial hospitalisation were obtained from the University of Cincinnati Mania Project database. The database reported mean lengths of stay for the initial hospitalisation and subsequent hospitalisations separately by drug. The initial length of stay reported for valproate semisodium was 14.3 days compared with 18.4 days for lithium. No information was reported on the length of stay for subsequent hospitalisations and whether this was assumed to vary between the treatments. Data on resource use associated with outpatient visits and laboratory tests were obtained from the expert panel. Unit costs were derived from national sources.

Mean total costs were estimated to be US$43 400 and US$39 643, respectively, for patients initially treated with lithium and valproate semisodium. The bulk of the cost reduction with valproate semisodium was attributed to the shorter length of stay for the initial hospitalisation. The results indicated that valproate semisodium is a less costly treatment than lithium in the acute and prophylactic treatment of patients with bipolar I disorder. A series of univariate sensitivity analyses were performed to test the robustness of the main conclusions of the study. Although the majority of these variations made only a small change in overall costs, the results were most sensitive to changes in the length of stay estimates for the initial hospitalisation.

Summary of cost-effectiveness analysis

The focus of the study was on the 1-year treatment costs associated with initial treatment with either lithium or valproate semisodium. No direct statements were made concerning the cost-effectiveness of these drugs. However, since relapse rates were considered equivalent in the base-case analysis, the higher response rate (0.59 versus 0.49) applied in the acute period for valproate semisodium implies that this regimen is more effective than lithium. Hence, it is possible to infer that valproate semisodium is cost-effective in comparison with lithium in the base-case analysis (i.e. is less costly and more effective).

Comments

This study is the only reliable published study found in the review process that could be considered a full economic evaluation. This study appears to be comprehensive, well conducted and clearly presented. However, from a NHS perspective, the study has a number of important limitations. First, the effectiveness data were sourced from a combination of published studies and the University of Cincinnati Mania Project database, and insufficient details are provided regarding the generalisability and transferability of this database to other settings. The 10% difference in response rates in favour of valproate semisodium over lithium is thus derived from a mean of several potentially heterogeneous sources and the validity of this difference is difficult to establish, particularly in a UK context. Second, the study does not adequately justify the choice of alternatives under evaluation and considers only a limited range of potential treatment options. However, given that the study was published in 1996, the range of options may have been appropriate at that time. Finally, the majority of the cost savings associated with valproate semisodium are accrued as a result of the shorter length of stay for the initial hospitalisation. Although the data used in the model reflect the

standard clinical care at a single centre in the USA, the generalisability of these findings to other centres and, most importantly, to a UK setting, is unknown. Furthermore, the authors acknowledge that the reduction in the mean length of stay reported for valproate semisodium probably reflects the use of a rapid oral loading strategy (20 mg/kg/day), which is likely to produce a more rapid reduction of manic symptoms. It is not clear whether these results would still hold using conventional administration of valproate semisodium.

Review of Zajecka and colleagues (2000). Valproate semisodium vs olanzapine for the treatment of mania in bipolar disorder[57]

Overview

This study was based on the results of a randomised trial of valproate semisodium and olanzapine for the treatment of mania in bipolar disorder.[57] Given that the results were published as an abstract from a conference presentation, only limited information is reported. The economic analysis included only those patients who met the improvement criteria (not defined) at or before day 21 and were discharged from hospital. The results for the economic analysis excluded those patients who did not meet the improvement criteria. Economic data, including direct costs such as drug costs, hospitalisation costs and outpatient appointments, were evaluated at two time points (6 and 12 weeks). Only the costs of outpatient treatment were reported in the abstract. The 12-week outpatient costs were significantly lower in the valproate semisodium group (US$554) than the olanzapine group ($1109); $p = 0.0028$. No attempt was made formally to combine the cost and outcome data reported in the study. Consequently, no conclusions can be drawn on the relative cost-effectiveness of valproate semisodium and olanzapine from this source.

A brief summary of the evaluation is provided in the data extraction tables reported in Appendix 8 and the results of the quality checklist are reported in Appendix 9.

Comments

Given the limited data reported in the published abstract, it has not been possible to assess most of the points related to its overall quality. In addition, the cost analysis considers the costs only for the subgroup of patients who met the reported improvement criteria at 3 weeks. No economic data are reported on those patients who did not meet this criteria. Furthermore, the cost data reported in the paper represent only comparative data on outpatient costs, and no data are presented on any other costs included in the study. As a result, it is not possible to make any direct comparisons of the overall differences in costs between valproate semisodium and olanzapine. Hence it is not possible to establish the relative cost-effectiveness of these drugs from this article.

Review of the AstraZeneca submission

No economic submission was made.

Review of the Eli Lilly submission

Overview

The Eli Lilly submission assessed the cost-effectiveness of olanzapine as monotherapy and as part of combination therapy, using three separate scenarios. The first scenario was used to evaluate the cost-effectiveness of olanzapine as part of a combination therapy regimen with lithium or valproate semisodium in comparison with a mixed group of patients treated with either lithium or valproate semisodium alone. The second scenario was used to estimate the cost-effectiveness of olanzapine monotherapy in comparison with valproate semisodium. A third scenario was considered in which an olanzapine monotherapy strategy was compared with haloperidol. No direct comparison was made between the strategies across each of the various scenarios. The model was based on a 1-year period, which included the use of drugs in both the acute treatment period and as part of maintenance therapy. The model was based on the structure and methods used in the Keck study.[58] The primary measure of effectiveness was the number of days in remission (i.e. free of acute symptoms).

The model assumed that during an acute episode patients were treated with a first-line medication and, conditional upon the patient responding, patients then entered a maintenance phase until another episode occurred. For patients who did not respond to first-line treatment, the model assumed that they would be given a second-line medication. In a similar manner to the first-line treatment, patients who responded to second-line

TABLE 6 *Overview of the treatment strategies considered in the Eli-Lilly submission*

Scenario 1	**Strategy 1**	**Strategy 2**
First line	Olanzapine + lithium/valproate semisodium	Lithium/valproate semisodium
Second line	Olanzapine + lithium/valproate semisodium (increased dose)	Olanzapine + lithium/valproate semisodium
Third line	Olanzapine + lithium/valproate semisodium (increased dose)	Olanzapine + lithium/valproate semisodium (increased dose)
Scenario 2	**Strategy 3**	**Strategy 4**
First line	Olanzapine	Valproate semisodium
Second line	Olanzapine + lithium/valproate semisodium	Olanzapine + lithium/valproate semisodium
Third line	Olanzapine + lithium/valproate semisodium (increased dose)	Olanzapine + lithium/valproate semisodium (increased dose)
Scenario 3	**Strategy 5**	**Strategy 6**
First line	Olanzapine	Haloperidol
Second line	Olanzapine + lithium/valproate semisodium	Lithium/valproate semisodium
Third line	Olanzapine + lithium/valproate semisodium (increased dose)	Lithium/valproate semisodium (increased dose)

treatment then entered a maintenance phase, where the regimen was continued until the onset of another episode. Patients who did not respond to second-line treatment were then given a third-line treatment option. All patients were assumed to respond to third-line treatment. The full range of treatment options for first-, second- and third-line treatments are summarised in *Table 6* for each of the three scenarios considered in the model.

The study assessed the direct costs of treating patients with bipolar disorder from the NHS perspective. Costs and outcomes were calculated according to six episode types: classic mania; classic depression; rapid cycling mania; rapid cycling depression; mixed and no episode. Mean total annual costs and outcomes were calculated by weighting episode types for each of the following patient subgroups: newly diagnosed (0.9%); no episodes (76%); classic bipolar disorder (8.5%); rapid cycling (3.5%) and mixed episodes (11.1%). Separate data on costs and outcomes were also reported for each of these subgroups. Given the scope of this review, only the data relating to the entire group and the subgroup of classic mania patients are considered. The classic mania group was selected as the group which most closely reflects the relevant patient population considered in this review.

Summary of effectiveness data

The criteria used to determine remission of the current episode was defined as a score on the YMRS of ≤ 12 for remission of mania. In the model, the end-point of remission was used to signify the end of the acute phase of the episode and the start of the maintenance phase. Recurrence of mania was defined as a score on the YMRS of ≥ 15. The model calculated the following outcomes over the course of 1 year: the number of episodes, the number of days of acute symptoms and the number of days in remission.

Data on remission and recurrence rates were derived from the clinical trials included in the accompanying systematic review. For the purposes of the model, a number of assumptions were made. First, the model assumed that each drug was equally effective regardless of in which line the drug was used. Consequently, the remission and recurrence rates reported for a drug at first line were assumed to be the same at second and third line for each individual drug. This assumption was made despite the lack of evidence, for the majority of these drugs, regarding their effectiveness in patients who had previously failed to respond to an earlier drug. Second, a similar assumption was made in relation to the effectiveness of olanzapine cotherapy. The only source of evidence for the olanzapine cotherapy treatment was derived from a single study,[41] which evaluated the effectiveness of this drug in patients who had previously not responded to lithium or valproate semisodium monotherapy (e.g. as second-line treatment). The model thus assumed that the olanzapine cotherapy treatment would be equally effective in first-line (and third-line) treatment as demonstrated at second line.

TABLE 7 *Annual costs and outcomes for total population*

	Scenario 1		Scenario 2		Scenario 3	
	Olanzapine + lithium/ valproate semisodium	**Lithium/ valproate semisodium**	**Olanzapine**	**Valproate semisodium**	**Haloperidol**	**Olanzapine**
Total costs (£)	5908	6752	6427	6465	6873	6198
Inpatient (£)	3648	4506	4033	4134	4618	3888
Outpatient (£)	1657	1687	1723	1723	1763	1705
Drug use (£)	209	118	272	179	54	214
Home visits (£)	230	116	253	260	294	245
Laboratory/ diagnostics (£)	164	278	148	170	143	146
Episodes per year	0.33	0.41	0.37	0.38	0.42	0.35
Acute symptom days	4.63	8.20	6.49	6.38	12.65	10.38
Remission days	360.37	356.80	358.51	358.62	352.35	354.62
Incremental cost-effectiveness (per symptom-free day)	Dominant			£320.62		Dominant

TABLE 8 *Annual costs and outcomes in classic bipolar patients*

	Scenario 1		Scenario 2		Scenario 3	
	Olanzapine + lithium/ valproate semisodium	**Lithium/ valproate semisodium**	**Olanzapine**	**Valproate semisodium**	**Haloperidol**	**Olanzapine**
Total costs (£)	15365	17661	16789	17039	18316	16187
Inpatient (£)	11337	13679	12409	12724	14236	12037
Outpatient (£)	2230	2310	2459	2469	2639	2412
Drug use (£)	671	412	790	593	192	630
Home visits (£)	921	1072	995	1025	1167	976
Laboratory/ diagnostics (£)	206	187	135	228	82	132
Episode per year	1.34	1.66	1.48	1.51	1.67	1.43
Acute symptom days	18.78	32.77	26.13	25.61	50.68	41.88
Remission days	346.22	332.23	338.87	339.39	314.32	323.12
Incremental cost-effectiveness (per symptom-free day)	Dominant			£467.33		Dominant

In addition, no attempt was made formally to synthesise data from all the available studies. In the absence of a common comparator against which to evaluate the relative effectiveness of each strategy, the submission uses separate scenarios to make a series of pairwise comparisons between strategies for which direct comparisons existed. Hence, although scenarios 2 and 3 evaluated olanzapine as a monotherapy, the initial remission rate was different in each scenario because the information was derived from two separate trials. Given the different data sources applied to each scenario, it is not possible to make any direct comparisons across the full range of strategies considered in the three scenarios.

A summary of the average symptom-free days for each scenario is presented in *Tables 7* and *8* for all bipolar patients and for patients with classic mania only. For scenario 1, the average number of

symptom-free days was higher for patients treated initially with olanzapine co-therapy than for patients treated with lithium/valproate semisodium monotherapy. These outcomes were higher across both the entire group and for the separate analysis of classic bipolar patients only.

In scenario 2, the average symptom-free days per patient were slightly lower amongst patients initially treated with olanzapine monotherapy than those initially treated with valproate semisodium. This seems potentially counter-intuitive since patients receiving olanzapine had higher compliance and remission rates and a longer time to recurrence than patients treated with valproate semisodium. However, this result was attributed to a higher proportion of patients failing first-line therapy with valproate semisodium who were subsequently switched at second line to treatment with olanzapine cotherapy. Since olanzapine cotherapy was assumed to be more effective in preventing recurrent episodes than either of the monotherapies alone, the overall impact was to reduce the number of recurrences (and hence increase the number of symptom-free days) in patients initially treated with valproate semisodium. The average number of symptom-free days in patients treated with olanzapine was lower in both the entire group of bipolar patients and in classic bipolar patients only. This scenario highlights the problems associated with making pairwise comparisons in this manner and not considering the full range of potential strategies as part of first-line therapy. It is clear (given the assumptions in the model) that the use of olanzapine co-therapy as part of first-line treatment could potentially have been more effective and cost-effective than either of the strategies considered in scenario 2.

In scenario 3, the average number of remission-free days per patient (for the entire group and for classic bipolar patients only) was higher in patients initially treated with olanzapine monotherapy in comparison with patients treated with haloperidol.

Summary of resource utilisation and cost data

The primary source for resource use data (inpatient, outpatient and home-care) was a retrospective UK chart review of patients with bipolar disorder. This source was used in preference to resource use data from the clinical trials since it was specific to UK practice and reflected current care. Since the chart review did not allow the distinction to be made between the resource use associated with each of the alternative treatment strategies, an assumption was made that resource use (excluding laboratory and diagnostic tests) was the same for all treatment strategies. No supporting information is provided to determine how representative the patients were who were included in the UK chart review data. Resource use over the 1-year period was estimated as the average resource use during the acute and maintenance phases of an episode.

The dosage for all drugs was obtained from the clinical trial data and, where data were not reported, the BNF was used to provide information of the recommended daily dosing. The duration of drug use on the acute episode was assumed to be the length of time to remission. For maintenance therapy, the duration of drug use was assumed to be the time from remission until the time to relapse. Compliance rates were assumed to be 100% during the acute period and data from the clinical trials were used for compliance during the maintenance phase. Laboratory and diagnostic tests were also included in the estimates of resource utilisations. Data from several national sources were used to estimate the monitoring requirements for each drug therapy. The costs of adverse events were not considered in the model.

A summary of the average costs for each scenario is presented in *Tables 7* and *8*. For scenario 1, the mean total costs were lower for patients treated initially with olanzapine co-therapy than with patients treated with lithium/valproate semisodium monotherapy. These costs were lower across the entire group considered and in the separate analysis of classic bipolar patients only.

In scenario 2, the average cost per patient was slightly lower amongst patients treated with olanzapine monotherapy than those treated with valproate semisodium. As in scenario 1, these costs were lower in both the entire group of bipolar patients and in classic bipolar patients only.

In scenario 3, the average costs per patient (for the entire group and for classic bipolar patients only) were lower in patients initially treated with olanzapine monotherapy than patients treated with haloperidol.

Summary of cost-effectiveness

A summary of the incremental cost-effectiveness ratio for each scenario is reported in *Tables 7* and *8*. In scenario 1, olanzapine co-therapy dominated the lithium/valproate semisodium strategy for all patients and for the classic mania group only. In scenario 2, olanzapine monotherapy was

associated with a lower number of mean symptom-free days and a slightly lower mean cost per patient. The ICER for olanzapine versus valproate semisodium was estimated to be £321 per additional symptom-free day across all patient groups and £467 per additional symptom-free day in classic mania patients. In scenario 3, olanzapine monotherapy dominated haloperidol.

Comments

The model presented in the Eli Lilly submission makes a number of assumptions which make it difficult to assess the validity of the study results to the NHS. Perhaps most importantly, the model assumes that the effectiveness evidence from trials reporting at first line would be the same as when a drug is used in second- or third-line treatments, in patients who do not respond to previous treatment. There does not appear to be any evidence to support this assumption. A more realistic assumption would have been to consider a reduction in effectiveness at second or third line. In addition, the model is based on the use of these drugs as part of both the acute treatment period and their continued use as part of maintenance therapy. Given that the higher acquisition costs associated with olanzapine are subsequently recouped by a lower repeat hospitalisation for recurrent episodes, the cost-effectiveness results reported for olanzapine are likely to be more conservative when considered in relation to the acute manic episode only.

Finally, it is not possible to make any direct comparison across the strategies assessed in the three scenarios considered in the model owing to the different sources of data used to populate the model. It is not clear how a decision-maker should interpret the separate pairwise comparisons presented in the model. Without a direct comparison, it is not possible to determine whether olanzapine co-therapy is a cost-effective first-line treatment because no direct comparison has been made between this strategy and either haloperidol or olanzapine monotherapy (and an indirect comparison is not valid given the different source of data used in each scenario).

Review of the Sanofi-Synthelabo submission

Overview

The economic analysis in the Sanofi-Synthelabo submission evaluated the cost-effectiveness of valproate semisodium compared with lithium. In addition, a separate comparison of the cost-effectiveness of valproate semisodium compared with olanzapine is presented as part of the sensitivity analysis. The analysis was based on a deterministic decision-analytic model which estimated the costs and benefits of treating 1000 patients presenting to hospital with an acute manic episode. The analytic structure was adapted from the decision model outlined in the Keck study.[58] The evaluation covered a 90-day time horizon and estimated costs from the NHS perspective. The 90-day period included an initial 21-day period based on the timescale of the effectiveness data and a continuation period of 69 days. The model assumed that the maintenance phase would begin after 90 days and hence the analysis of costs and effects beyond this time point is not considered in the analysis.

The primary outcome used in the model was treatment response at 3 weeks. The response rate was defined as a ≥ 50% reduction in a patient's baseline score derived from an interview-based assessment scale reported in the Keck study.[58] Responders were assumed to continue on their initial medication and dosage, without the need for adjunctive medication, between days 22 and 90 of the model. Patients who did not respond to their initial medication received additional or substitute medications dependent upon their initial medication. The model assumed that patients who did not respond at 3 weeks remained non-responders despite receiving these alternative medications. A brief summary of the evaluation is provided in the data extraction tables reported in Appendix 8. The key features are described in more detail below.

Summary of effectiveness data

The model used the clinical data from the published economic study by Keck and colleagues[58] to determine the base-case response rate for valproate semisodium and lithium. Given that the submission relies entirely on the data reported in the Keck study[58] to estimate the response rate applied in the model, the same limitations discussed in relation to the Keck study apply here. The study assumes equivalent response rates for valproate semisodium and olanzapine. The base-case response rates applied in the model were 0.49 for lithium and 0.59 for both valproate semisodium and olanzapine.

Summary of resource utilisation and cost data

A summary of the drug doses and treatment algorithms applied in the model is given in *Table 9*. The relevant drug doses and treatment

TABLE 9 *Summary of treatment options and doses applied in the Sanofi-Synthelabo model*

Initial therapy	Treatment pathway
Valproate semisodium	**Initial treatment and continuation treatment for responders**: Days 0 to 21 (3 weeks) Valproate semisodium 1500 mg/day
	Continuation treatment for non-responders: Days 21 to 42 (3 weeks) Increase dose of valproate semisodium to 200 mg/day
	Days 42 to 90 (7 weeks) Switch medication; 30% of patients to lithium (900 mg/day), 70% of patients to olanzapine (15 mg/day)
Lithium	**Initial treatment and continuation treatment for responders**: Days 0 to 21 (3 weeks) Lithium 900 mg/day
	Continuation treatment for non-responders: Days 21 to 42 (3 weeks) Switch to olanzapine (15 mg/day)
	Day 42 to 90 (7 weeks) Continue olanzapine (15 mg/day) plus a short-acting intramuscular antipsychotic in 50% of patients
Olanzapine	**Initial treatment and continuation treatment for responders**: Days 0 to 21 (3 weeks) Olanzapine 15 mg/day
	Continuation treatment for non-responders: Days 21 to 42 (3 weeks) Increase dose of olanzapine to 20 mg/day
	Days 42 to 90 (7 weeks) Switch medication; 50% of patients to lithium (900 mg/day), 50% of patients to valproate semisodium (1500 mg/day)

pathways were obtained in consultation with a single clinical expert.

Average drug costs were calculated by multiplying the average daily dose by the cost per milligram of each drug, using the average costs reported across available presentations and pack sizes. The use of adjunctive medications during the first 14 days of treatment was also included in the model. Adjunctive medications included the use of lorazepam and olanzapine in 50% of patients receiving lithium or valproate semisodium as primary medication, and lorazepam and valproate semisodium in 50% of patients receiving olanzapine as primary medication.

The most significant resource component included in the model related to the index hospitalisation. The model assumed that all patients started the model as hospital inpatients. Separate lengths of stay were calculated for responders and non-responders. The length of stay for responders treated with lithium was obtained from the median length of stay for manic or mixed patients reported in the 2000–01 Hospital Episode Statistics (33.64 days). The length of stay for responders treated with valproate semisodium was adjusted using data taken from the Keck study,[58] which reported a lower initial length of stay for the initial hospitalisation in comparison with lithium. The Keck study was therefore used to adjust the median length of stay for valproate semisodium by applying the ratio reported (0.78) of the proportion of time valproate semisodium patients were hospitalised compared with lithium patients. The length of stay for responders treated with valproate semisodium was thus assumed to be 26.18 days (33.64×0.78). Patients considered as non-responders were assumed to remain in hospital for 60 days. The submission assumed that responders in the olanzapine group would have the same length of stay as those treated with valproate semisodium. Unit per diem costs for hospitalisations were calculated as a weighted mean of the costs of all hospitalisations for bipolar disorder presented in a recent UK cost-of-illness study.[16]

TABLE 10 *Summary of costs for 1000 patients for each drug from the Sanofi-Synthelabo model*

	Valproate semisodium	Lithium	Olanzapine
Number of responders	590	490	590
Total days in hospital for responders	15446.20	16483.60	15446.20
Total days in hospital for non-responders	24600	30600	24600
Number of ambulance trips	300	300	300
Medication costs (£)			
Initial phase (21 days)			
Primary medication costs	55440	1890	116340
Adjunctive medication costs	11680	11680	7310
Continuation phase (69 days)			
Primary medication costs	137744.70	3042.90	289185.90
Switch medication costs	76948.80	199527.30	26875.50
Total medication costs	281813.50	216140.20	439711.40
Resource costs			
Hospitalisation costs	5850601.60	6869477	5850601.60
Outpatient appointments	1090912	1004738.60	1090912
Total resource costs	6941513.60	7874215.60	6941513.60
Total costs	7223327.10	8090355.80	7381225

The model also incorporated the costs of outpatient resource use following discharge derived from consultation with a single clinical expert. Patients were assumed to receive visits from two members of a community mental health team, which declined in frequency over the weeks following discharge (five visits in week 1, two visits in week 2 and one visit per week thereafter). In addition, patients were assumed to have a consultant outpatient appointment every 2 weeks.

Table 10 provides a summary of the total costs for 1000 patients treated with each drug based on the Sanofi-Synthelabo model. The mean total costs were £7233, £8090 and £7381 for patients treated with valproate semisodium, lithium and olanzapine, respectively.

Summary of cost-effectiveness analysis

Based on a comparison of mean total costs and response rates, the results of the Sanofi-Synthelabo submission suggest that valproate semisodium appears cost-effective in comparison with lithium and olanzapine. Valproate semisodium dominates lithium by being more effective and less costly. Assuming equivalent response rates with olanzapine, valproate semisodium also dominates olanzapine by incurring lower mean total costs. A univariate sensitivity analysis was performed in order to test the robustness of the model. The results suggest that the model is relatively insensitive to changes in the majority of the inputs, but appears to be highly sensitive to the assumptions concerning the differences in the length of stay for the alternative drugs.

Comments

This economic evaluation satisfies almost all the points listed used to assess its overall quality reported in Appendix 5. However, there are several key assumptions which are not adequately justified and which reduce the validity of the model's results. First, the response rates used in the model have not been derived systematically and are based on estimates which were reported in 1996 in the Keck study.[58] No attempt has been made to update this evidence using studies published after 1996. The 10% difference in response rates in favour of valproate semisodium over lithium is derived from a mean of several potentially heterogeneous sources and the validity of this difference is difficult to establish. This difference is critical to the model since the cost-effectiveness of valproate semisodium, in comparison with lithium, is dependent not only on the additional response rate, but also on the impact that this has on reducing inpatient costs and subsequent medication costs.

Similarly, by assuming equivalent response rates with olanzapine, the lower acquisition costs associated with valproate semisodium result in this becoming the dominant strategy. The assumption of equivalent response rates with olanzapine,

however, is not adequately justified and appears to contradict the results reported in the Tohen 2002[56] trial. In the absence of a formal meta-analysis and a systematic approach to study inclusion, the results from the cost-effectiveness model are potentially biased.

Furthermore, the assumptions used to derive the inpatient hospitalisation costs are not adequately supported by the available evidence. These costs are key input parameters since the cost implications of the assumed shorter length of stay for valproate semisodium, in comparison with lithium, more than offset the higher acquisition costs of valproate semisodium. It is not clear why the median length of stay was used to estimate the length of stay of responsive patients, and no data are used to support this assumption. In addition, patients who respond with valproate semisodium (and olanzapine) also have an additional reduction in their assumed length of stay based on the findings from the Keck study.[58] Given that this reduction was based on the finding of a single US centre from 1996, it is not clear whether this estimate is generalisable to a UK setting. Finally, the length of stay for non-responders of 60 days appears entirely arbitrary, and is actually lower than the mean length of stay reported in the NHS Hospital Episode Statistics.[61]

Summary of findings from the cost-effectiveness review

The review of economic evidence from the literature and stakeholder submissions has highlighted a number of significant limitations in existing studies assessing the cost-effectiveness of alternative drugs for the acute manic episode in bipolar disorder. First, no single study has directly compared the full range of possible strategies that would appear to be relevant to the NHS. Consequently, it is not possible to make any direct comparison of the relative cost-effectiveness of these alternative treatments from the existing evidence.

Second, the existing studies are based on a range of alternative analytic structures and assumptions concerning the estimates of effectiveness, costs and appropriate time horizon. It would therefore be inappropriate to attempt to make any comparisons across the different studies. Third, both the Keck study and the Eli Lilly submission estimates of cost-effectiveness are based on the use of drugs for both the acute treatment for the manic episode and for maintenance therapy. The cost-effectiveness of these drugs as part of maintenance therapy is beyond the scope of this review. As such, it is not clear whether the conclusions for these studies would alter significantly based on an evaluation of treatment for the acute episode only.

Finally, the two studies identified in the systematic literature search used data from the USA to derive estimates of resource utilisation and cost, and the generalisability of these findings to the NHS is thus unknown. This also has significant implications for the generalisability of the results presented in the Sanofi-Synthelabo submission, since the majority of the cost savings reported for valproate semisodium accrue through a lower length of hospitalisation derived from assumptions from a US study.[58] The impact on the initial length of stay in a UK context has not been adequately demonstrated and hence the validity of these findings is unclear.

The cost-effectiveness of alternative drugs for the acute manic episode for bipolar disorder has, therefore, not been adequately addressed in the existing studies. The next chapter of this report details the results of a new decision analytic model that has been developed to address this issue more formally.

Chapter 5
Economic model

Introduction

The review of cost-effectiveness studies in Chapter 4 outlined a number of important 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. To overcome these limitations and to assist the decision-making process in the context of the NHS, a new model was developed. The following sections outline the structure of the model in detail and provide an overview of the key assumptions and data sources used to populate the model.

Methods

Model structure

The model has been 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 evaluates the cost-effectiveness of the alternative drugs when used as part of treatment for the acute manic episode only. The cost-effectiveness of these drugs as part of maintenance treatment is outside the scope of this review and therefore not considered in the model. For the base-case analysis, a 3-week time horizon has been 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 model is probabilistic in that response rates are entered into the model as probability distributions to reflect second-order uncertainty, that is, uncertainty in the mean response rates.[62] Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis can also be presented with their uncertainty. A 2001–02 price base is used, and no discounting is applied given the short time-frame of the model.

Choice of outcome measures for the model

The decision-analytic model builds on the trial-based evidence summarised in the accompanying systematic review of the effectiveness data (see Chapter 3). *Table 11* provides an overview of relevant studies included for consideration in the model. The studies reviewed in Chapter 3 were only included if they reported an overall summary measure of outcome based on either response or remission. These composite measures were chosen on the basis that they have the most clinical relevance during the manic episode.[1] A total of 14 studies reported data on either response and/or remission. All 14 of the studies reported data on response, typically defined as a ≥ 50% improvement in a patient's baseline mania score assessed using the YMRS. Of these 14 studies, only four reported data on remission. The use of response rates (as opposed to remission rates) in the model allows a broader range of comparisons to be made and ensures a more systematic approach to study inclusion. On this basis, response was chosen as the primary measure of effectiveness for the model.

The majority of trials evaluated the effectiveness of these drugs as part of first-line therapy during the acute manic episode. However, two of the 14 studies[48,56] reported on the use of drugs as part of second-line treatment for patients who had previously failed to respond to first-line treatment. Since the patient groups for first- and second-line trials are unlikely to be comparable, the two second-line studies were excluded from consideration in the model. Furthermore, owing to the limited data available on the effectiveness of drugs as part of second-line therapy (e.g. data are only available for olanzapine co-therapy and valproate semisodium), the model is restricted to an analysis of the cost-effectiveness of drugs used as part of first-line therapy only. Hence olanzapine co-therapy could not be considered in the economic model because no trial had reported on its use in first-line treatment.

One of the primary limitations of the existing evidence from the remaining 12 RCTs is that there are no direct data which can be used to evaluate the full range of possible treatment strategies. Owing to various sources of between-study heterogeneity and a lack of direct comparative trial data, no formal attempt is made in the effectiveness review section in Chapter 3 either formally to synthesise the results for each drug across the trials or to make indirect comparisons concerning the relative effectiveness, owing to the potential bias that this may induce. Although such an approach is entirely justified in the context of the review, it is equally important to recognise that, for the purposes of decision-making, this is a potentially significant limitation (particularly if individual studies give conflicting results). The model has been designed to overcome this limitation by addressing the specific issues faced by a decision-maker in assessing the potential cost-effectiveness of alternative drugs in the acute manic episode. The model is valuable as it can be used to provide an explicit analytical framework to identify the most cost-effective of all the alternative drug treatments given the combined weight of evidence from all relevant studies. The next section reports on the approach used to synthesise the effectiveness data.

Approaches to synthesising the effectiveness data

The 12 RCTs present a number of separate comparisons for eight different drug treatments, including placebo. These comparisons include direct head-to-head evidence for several of the drugs, whereas for others evidence is only available against placebo. In this situation, there are several conventional approaches which could be adopted. The potential limitations of these are discussed below.

One potential approach would be to make a series of separate pairwise comparisons between treatments using the same comparisons reported in the trials. Clearly, it will not be possible to base a single, coherent, comparative cost-effectiveness assessment of **all** treatments on separate pairwise comparisons, especially as not all of the possible comparisons would be informed by direct trial data.

An alternative approach would be to estimate the relative treatment effect of each intervention against a common comparator (e.g. against placebo or conventional care), and to use these estimates within a decision model to facilitate a direct comparison. The relative treatment effects could then be incorporated in the model by applying the RRs or odds ratios (ORs) associated with each intervention relative to the common baseline. In the studies included for consideration in the model, placebo comparisons were reported in five of the studies. These data could be used to provide a common baseline to estimate the relative treatment effect for the each of following drugs: olanzapine monotherapy, quetiapine monotherapy, valproate semisodium, lithium and haloperidol.

This approach was explored further, but its limitations and potential inconsistencies, given the available data, were revealed. The relative treatment effect was estimated for each of the five drugs using a random-effects meta analysis in STATA to estimate the OR for treatment response. [The response rates reported in the Tohen 2000[56] study for olanzapine and placebo were much higher than those in the other studies owing to the longer follow-up (4 versus 3 weeks for the majority of the other studies). To minimise the potential bias of including this study, the response rates were adjusted downwards using an exponential function to predict the response rates at 3 weeks.] The results of this are presented in *Table 12*. Based on a comparison of the relative treatment effects, valproate semisodium (OR = 2.74) and lithium (OR = 2.82) were associated with a higher mean response rate than olanzapine (OR = 2.69), quetiapine (OR = 2.01) and haloperidol (OR = 2.48). Although this approach would enable a broader comparison of strategies to be made than that reported in any individual trial, the results appear inconsistent when considered in conjunction with the evidence from trials which had to be excluded because of the absence of a common comparator. In particular, the direct head-to-head comparison of olanzapine and valproate semisodium reported in the Tohen 2002[56] trial appears to contradict these results as this study provides evidence of an improved treatment response in favour of olanzapine (OR 1.63, 95% CI 0.99 to 2.69).

It is evident that both of these approaches suffer from a number of potential limitations. Most problematic is that both approaches make selective use of the available data, whereas what is required is a characterisation of the joint distribution of the efficacy of the treatments, based on the complete evidence base. An alternative approach developed to address these limitations is outlined below.

Methods of evidence synthesis to allow mixed comparisons

It is recognised that statistical inference concerning a comparison of two treatments, say

TABLE 11 *Summary of studies reporting data on response or remission*

Study	Comparison	1st or 2nd line	Interventions	Study duration (weeks)	Mean doses (mg/day)	Total *N*	Response measure	Response	Remission measure	Remission
Tohen 1999[35]	Monotherapy	1st	Olanzapine	3	14.9	70	YMRS ≥ 50% improvement	34/70 (48.6%)	NR	NR
			Placebo		NA	69		16/66 (24.2%)		NR
Tohen 2000[36]	Monotherapy	1st	Olanzapine	4	16.4	55	YMRS ≥ 50% improvement	35/54 (64.8%)	YMRS ≤ 12	33/54 (61.1%)
			Placebo			60		24/56 (42.9%)		20/56 (35.7%)
Tohen 2002[41]	Combination vs monotherapy	2nd	Olanzapine co-therapy	6	10.4	229	YMRS ≥ 50% improvement	149/220 (67.7%)	YMRS ≤ 12	173/220 (78.6%)
			Lithium or valproate-semisodium		NR	115		51/114 (44.7%)		75/114 (65.8%)
Bowden 1994[49]	Monotherapy	1st	Valproate semisodium	3	NR	69	SADS-C MRS ≥ 50% improvement	32/67 (48%)	NR	NR
			Lithium		NR	36		17/35 (49%)		NR
			Placebo		NA	74		18/72 (25%)		NR
Kowatch 2000[54]	Monotherapy	1st	Valproate semisodium	1–8	NR	15	YMRS ≥ 50% improvement	8/15 (53.3%)	NR	NR
			Lithium		NR	14		5/13 (38.5%)		NR
			Carbamazepine		NR	13		5/13 (38.5%)		NR
McElroy 1996[55]	Monotherapy	1st	Valproate semisodium	1	1625.8	21	YMRS ≥ 50% improvement	10/21 (47.6%)	NR	NR
			Haloperidol		15.5	15		5/15 (33.3%)		NR
Pope 1991[48]	Monotherapy	2nd	Valproate semisodium	1–3	NR	20	YMRS ≥ 50% improvement	9/17 (52.9%)	NR	NR
			Placebo		NR	23		2/19 (10.5%)		NR
Tohen 2002[56]	Monotherapy	1st	Olanzapine	3	17.4	125	YMRS ≥ 50% improvement	68/125 (54.4%)	YMRS ≤ 12	59/125 (47.2%)
			Valproate semisodium		1401.2	126		52/123 (42.3%)		42/123 (34.1%)
Tohen 2001[37]	Monotherapy	1st	Olanzapine	6 (acute)	NR	234	YMRS ≥ 50% improvement	167/231 (72.3%)	YMRS ≤ 12	122/234 (52.1%)
			Haloperidol		NR	219		158/213 (74.2%)		101/219 (46.1%)
DelBello 2002[33]	Combination vs monotherapy	1st	Quetiapine co-therapy	6	432 (quetiapine)	15	YMRS ≥ 50% improvement	13/15 (87%)	NR	NR
			Valproate semisodium		NR	15		8/15 (53%)		NR

continued

TABLE 11 *Summary of studies reporting data on response or remission (cont'd)*

Study	Comparison	1st or 2nd line	Interventions	Study duration (weeks)	Mean doses (mg/day)	Total *N*	Response measure	Response	Remission measure	Remission
AZ Study 99[28]	Combination vs monotherapy	1st	Quetiapine co-therapy	3	NR	91	YMRS ≥ 50% improvement	44/81 (54.3%)	YMRS ≤ 12	37/81 (45.7%)
			Lithium or valproate-semisodium		NR	100		29/89 (32.6%)		23/89 (25.8%)
AZ Study 100[26,27]	Combination vs monotherapy	1st	Quetiapine cotherapy		CIC					
			Lithium or valproate-semisodium							
AZ Study 104[30]	Monotherapy	1st	Quetiapine	3 (acute)	NR	102	YMRS ≥ 50% improvement	43/101 (42.6%)	YMRS ≤ 12	NR
			Haloperidol		NR	99		55/98 (56.1%)		NR
			Lithium		NR	101		35/100 (35%)		
AZ Study 105[26,27]	Monotherapy	1st	Quetiapine	3 (acute)	NR	107	YMRS ≥ 50% improvement	57/107 (53.3%)	YMRS ≤ 12	NR
			Lithium		NR	98		51/98 (53%)		NR
			Placebo		NR	97		27/97 (27.4%)		

NA, not applicable; NR, not reported.

TABLE 12 *Odds ratio of response in comparison with placebo*

Drug	Mean OR and 95% CI
Lithium	2.82 (1.73 to 4.59)
Valproate semisodium	2.74 (1.34 to 5.62)
Quetiapine	2.01 (0.95 to 4.25)
Olanzapine	2.69 (1.58 to 4.58)
Haloperidol	2.48 (1.40 to 4.39)

A and B, would ideally be based on a direct 'head-to-head' RCT. Indirect comparisons of A and B based, for example, on A–C and B–C comparisons, are said to represent a lower level of evidence.[63] However, it is evident that, based on the principle of transitivity, if the true differences between AB, AC and BC are d_{AB}, d_{AC} and d_{BC}, then we expect

$$d_{AB} = d_{AC} - d_{BC}$$

Hence, reasonable inferences can be made about the AB comparison with few additional assumptions over those which are routinely made in simple meta-analyses. These assumptions are, first, the simple transitivity assumption outlined above, and second, that the differences are taken on an appropriate scale, for example, the log odds scale. Several authors have developed statistical models for combining mixed comparison evidence to provide a consistent set of log OR estimates, relative to a common baseline.[64–66] Higgins and Whitehead,[65] in particular, have shown how the use of 'external' AC and BC evidence can substantially reduce uncertainty about the AB comparison of primary interest.

Based on these general principles, the meta-analysis of response rates consisted of a hierarchical Bayesian model incorporating random study effects and fixed treatment effect and was conducted using Markov Chain Monte Carlo (MCMC) implemented in WinBUGS. The AstraZeneca co-therapy trials (Studies 99 and 100) were excluded from the model because the comparator group (a mixture of patients using lithium or valproate semisodium) provided no evidence on the relationship between quetiapine co-therapy and any of the other drug treatments under consideration. In addition, the Kowatch study[54] was also excluded on the grounds that the length of follow-up was variable (between 1 and 8 weeks) and also that it recruited only adolescent patients (all but one[33] of the other studies were based on an adult population). The DelBello[33] and Tohen[37] studies were also excluded since the length of follow-up (6 weeks) reported in these studies was significantly longer than that in the remaining studies. It was decided that the inclusion of these studies would introduce potential bias in the evidence synthesis model. On this basis, the meta-analysis incorporated seven studies, including evidence on six treatments (including placebo). The treatment effects of the following five drug treatments were thus analysed: lithium, valproate semisodium and quetiapine monotherapy, olanzapine monotherapy and haloperidol. A summary of the evidence used in the meta-analysis is provided in *Table 13*. Each individual study, drug treatment and response rate is indexed numerically for use in the WinBUGS model.

The model used here is based on that detailed by Ades[67] and is similar to that of Hasselblad[64] The model assumes a regression-like structure, with the logit of the probability of success on any treatment k, $k = 2, 3, \ldots, 6$, depending on a 'baseline' placebo term μ_i in trial i, $i = 1, 2, \ldots, 7$, and a fixed treatment effect δ^k. The trial-specific baselines are drawn from a common random

TABLE 13 *Response rates included for each drug*

		Treatment strategy number					
Study	Study number	6 Haloperidol	5 Olanzapine	4 Quetiapine	3 Valproate semisodium	2 Lithium	1 Placebo
Tohen 1999[35]	1		34/70 (1)				16/66(2)
Tohen 2000[36]	2		30/54 (3)				19/56(4)
Bowden 1994[49]	3				32/67 (5)	17/35 (6)	18/72(7)
Tohen 2002[56]	4		68/125 (8)		52/123 (9)		
AZ 104[30]	5	55/98 (10)		43/101 (11)			35/100(12)
AZ 105[26,27]	6			57/107 (13)		51/98 (14)	27/97(15)
McElroy 1996[55]	7	5/15 (16)			10/21 (17)		

normal distribution, whose parameters must be estimated from the data, given vague priors. Formally, this can be expressed as

$$\text{logit}(p_i^k) = \mu_i + \delta^k$$
$$\mu_i \sim N(\mu b, \tau b);$$

where

$\mu b \sim N(0,0.0001)$; $\tau b \sim \gamma(0.01,0.01)$

The treatment effects δ^k are also given independent vague priors, $N(0,0.0001)$. A binomial likelihood is assumed from the 17 available data points (or 'arms'):

$$r_i^k \sim \text{Bin}(p_i^k, n_i^k),$$

where k denotes all treatment indices in study i including placebo.

The WinBUGS code used to estimate the response rate is reported in Appendix 10. When undertaking MCMC, it is necessary to discard the initial simulations (termed the 'burn-in') because the distributions are not stationary. Hence, the first 100,000 iterations were discarded, and posterior summaries were based on the subsequent 10,000 iterations. To maintain correlation between the posterior estimates, the posterior simulations were exported directly into the Excel decision model described below. A summary of the response rates obtained from the meta-analysis is presented in *Table 14*. These response rates have been back transformed from the original logistic scale to enable interpretation on a probability scale.

A comparison of the **mean** response rates indicates that olanzapine (0.54) and haloperidol (0.52) appear to have higher response rates than either lithium (0.50), valproate semisodium (0.45) or quetiapine (0.47).

Adjustment for quality of life

The use of response rates as the primary effectiveness measure used in the model has potential limitations in assisting decisions about resource allocation. The use of response rates based on an improvement in a patient's manic symptoms is specific to the treatment of mania in bipolar patients. Comparisons are therefore restricted to other interventions which report using a similar outcome (i.e. other interventions aimed at alleviating a patient's manic symptoms). Ideally, a generic measure of outcome [e.g. quality-adjusted life-years (QALYs)] should be used to enable a broad range of comparisons to be made across different disease areas. However, in order to estimate QALYs, it is necessary to quality-adjust the period of time during which the average patient is either a responder or a non-responder within the model using an appropriate utility or preference score.

TABLE 14 *Mean response rates for each strategy from multiparameter synthesis model (base-case analysis)*

Strategy	Pooled response rates	
	Mean	**95% CI**
Lithium	0.4993	0.3945 to 0.5972
Valproate semisodium	0.4519	0.3722 to 0.538
Quetiapine	0.465	0.3783 to 0.5492
Olanzapine	0.5371	0.4614 to 0.6168
Haloperidol	0.5212	0.4116 to 0.6268

Ideally, utility data are required which differentiate between the health status of patients who respond and do not respond to first-line treatments. However, the interpretation of utility data in this population is potentially problematic owing to the nature of the manic episode. Consequently, the validity of using preference-based measures of health status in this patient group is not clear. This view is supported by a preliminary analysis of patient-level utility data obtained using the EQ-5D in a randomised trial of cognitive therapies for bipolar disorder (Hayhurst H, Department of Psychiatry, University of Cambridge: personal communication, 2003). In that study, an analysis of the relationship between the utility data and the severity of manic symptoms demonstrated that patients with more severe symptoms reported a higher QoL than patients with less severe symptoms. No other suitable data were reported in any of the studies reviewed. Consequently, it was not possible to quality-weight the response data using a generic measure of outcome.

Cost analysis

The costs included in the model are those considered to be the key components of treatment costs associated with bipolar disorder, and which are likely to differ by the various drug treatments. These include the cost of the initial hospitalisation, the drug acquisition costs and the specific laboratory and diagnostic costs required for monitoring purposes. The costs of adverse events are not formally considered in the model owing to the lack of suitable cost data reported in the literature. Although the exclusion of adverse events is a potential limitation, the majority of the adverse events summarised in Chapter 3 are unlikely to have significant resource implications in the short time horizon considered in the model.

TABLE 15 *Unit costs of drugs*

Initial drug	Average dose per day (mg)	Cost per mg (£)	Cost per day (£)
Valproate semisodium	1513.5	0.0016	2.43
Lithium	1417.4	0.00008	0.11
Olanzapine	16.2	0.34841	5.66
Quetiapine	619.2	0.00943	5.84
Haloperidol	10.4	0.02118	0.22

TABLE 16 *Laboratory and diagnostic tests used during the acute phase*[a]

Test	Unit cost (£)	No. of units during acute phase (3 weeks)		
		Olanzapine/quetiapine/ haloperidol	Lithium	Valproate semisodium
Complete blood count	2.23	1	1	1
Liver panel	15.13	0	0	2
Blood urea nitrogen	7.06	0	1	0
Creatinine	2.31	0	1	1
Thyroid function	51.23	0	1	0
Serum lithium concentration	8.23	0	3	0
ECG	32	0	1	0
Electrolytes	11.10	0	0	1
Complete blood count with differential	2.23	0	0	1

[a] Estimates for unit cost and number of units used are derived from the Eli Lilly submission.

The daily acquisition costs of the five drugs considered in the model are shown in *Table 15*. These are based on undiscounted prices from the BNF. For each drug, the lowest cost per milligram reported across the various presentations and pack sizes reported in the BNF were applied to the average daily dose reported in the trials. The overall daily costs (including VAT) for the drugs are £2.43 for valproate semisodium, £0.11 for lithium, £0.22 for haloperidol, £5.66 for olanzapine and £5.84 for quetiapine. The additional costs associated with adjunctive drug treatments used during the acute manic episode were not considered in the model.

Although lithium and valproate semisodium have lower acquisition costs than the atypical antipsychotics, it is important to incorporate the costs of laboratory and diagnostic tests required during the monitoring process. In the absence of any other relevant data, the model used information reported in the Eli Lilly submission to estimate the costs of laboratory and diagnostic tests for each drug treatment. Sensitivity analyses were undertaken to determine the robustness of the base-case results to alternative assumptions concerning these costs. A summary of the resource use and unit cost data applied to each drug is reported in *Table 16*. The total daily costs including both the drug acquisition costs and the costs for the laboratory and diagnostic tests are £4.72 for valproate semisodium, £5.80 for lithium, £0.33 for haloperidol, £5.76 for olanzapine and £5.94 for quetiapine. The additional laboratory and diagnostic tests required with lithium appear to offset the lower acquisition costs. This results in an overall daily cost for lithium which is comparable to those of the atypical antipsychotic drugs. Haloperidol had the lowest mean total drug costs in comparison with the four other drugs considered.

All patients were assumed to be hospitalised at the start of the model. The review of economic evidence highlighted the lack of reliable evidence, relevant to the UK, regarding whether individual drug treatments or response to treatment was associated with any impact on the length of the initial hospitalisation. In the absence of evidence to the contrary, the base-case analysis assumed that the length of the initial hospitalisation would be the same for each drug treatment and that patients would not be discharged before the end of the 3-week period (i.e. hospitalisation costs were equivalent for responders and non-responders). The unit costs per diem for the initial

TABLE 17 *Base-case costs for responders and non-responders*

Drug	Parameter	Cost for responders	Cost for non-responders
Olanzapine	Inpatient days	21	21
	Inpatient costs (£)	3040.13	3040.13
	Drug cost (£)	118.75	118.75
	Diagnostic cost (£)	2.23	2.23
	Total (£)	3161.11	3161.11
Valproate semisodium	Inpatient days	21	21
	Inpatient costs (£)	3040.13	3040.13
	Drug cost (£)	50.99	50.99
	Diagnostic cost (£)	48.13	48.13
	Total (£)	3139.24	3139.24
Quetiapine	Inpatient days	21	21
	Inpatient costs (£)	3040.13	3040.13
	Drug cost (£)	122.55	122.55
	Diagnostic cost (£)	2.23	2.23
	Total (£)	3164.91	3164.91
Lithium	Inpatient days	21	21
	Inpatient costs (£)	3040.13	3040.13
	Drug cost (£)	2.35	2.35
	Diagnostic cost (£)	119.52	119.52
	Total (£)	3161.99	3161.99
Haloperidol	Inpatient days	21	21
	Inpatient costs (£)	3040.13	3040.13
	Drug cost (£)	4.61	4.61
	Diagnostic cost (£)	2.23	2.23
	Total (£)	3046.96	3046.96

hospitalisation were derived from a recent UK cost-of-illness study.[16] The total cost estimates applied in the base-case model are reported in *Table 17*.

A series of sensitivity analyses were also undertaken to examine the robustness of the base-case analysis to alternative assumptions regarding the estimation of total costs. The first scenario (scenario A) assumed that patients responding at 3 weeks would be immediately discharged (at day 21), and that non-responders would continue to be hospitalised until the episode resolved naturally. The average length of hospitalisation reported in the Hospital Episode Statistics[61] (62 days) for manic or mixed bipolar patients was used to estimate the length of hospitalisation for non-responders. This analysis represents the most optimistic scenario in relation to the impact that response might have on the costs associated with the initial hospitalisation.

Two additional scenarios were included in the sensitivity analysis to explore the impact of including the additional costs of second- and third-line drug costs in patients who did not respond to first-line treatment. Patients who were non-responsive to first-line drug treatment were thus assumed to incur additional drug costs in comparison with patients who responded at 3 weeks. Second- and third-line costs were then assumed to be used for two subsequent intervals each lasting an additional 3 weeks (second line for days 22–42 and third line for days 43–63). Scenario B assumed that patients would be switched to the most costly of the first-line treatments as part of second- and third-line treatments. Scenario C assumed that patients would be switched to the cheapest of the first-line treatments as part of second- and third-line treatments. It is important to note that both scenarios B and C assume that patients not responding to the first-line therapy would remain non-responders despite receiving these alternative drug treatments. In other words, owing to absence of data, the scenarios relate only to the cost of second- and third-line therapies, not any effect on outcomes, The total costs assumed for responders and non-responders in each of these three scenarios are reported in Appendix 11.

The majority of studies reported results for response based on a modified intention to treat (MITT) approach using LOCF for patients who dropped out before the final assessment. Patients with no post-baseline assessment were thus

excluded from the MITT population. An additional sensitivity analysis (scenario D) was undertaken to examine the robustness of the base-case results to different assumptions concerning the effectiveness data used in the model. Scenario D was based on a 'worst case' scenario for patients excluded from the MITT analysis. Patients excluded from the original MITT were incorporated in this sensitivity analysis by including these patients as non-responders. The WinBUGS model used to estimate the response rates for each drug was re-run using this alternative assumption concerning the outcome for patients excluded from the MITT analysis.

Two sensitivity analyses were undertaken to examine the impact of using different assumptions concerning the costs of laboratory and diagnostic tests. In scenario E the costs of laboratory and diagnostics were reduced by 50% compared with the base-case analysis. In scenario F these costs were excluded entirely from the input costs applied in the model.

Analysis

The results of the model are presented in two ways. First, mean costs and response rates of the five strategies are presented and their cost-effectivenesses compared, estimating incremental cost-effectiveness ratios as appropriate, using standard decision rules.[68] The advantage of analysing the input effectiveness parameters using a stochastic approach is that this uncertainty can be propagated through the model and reflected in model outputs. To present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used.[69,70] These show the probability that each strategy is more cost-effective than the other four using alternative values for the maximum value that the health service is willing to pay for an additional responder in bipolar patients with acute mania.

Results

Base-case results

Table 18 details the results for mean costs and response rates for each of the five drugs considered in the model. Haloperidol has the lowest mean total costs (£3047) in comparison with lithium (£3162), valproate semisodium (£3139), quetiapine (£3165) and olanzapine (£3161). Mean response rates for olanzapine (0.54) and haloperidol (0.52) were higher than lithium (0.50), valproate semisodium (0.45) and quetiapine (0.47). *Table 18* also presents the analysis of the ICER for the base-case analysis. The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. When more than two programmes are being compared the ICERs are calculated using the following process:[68]

1. The strategies are ranked in terms of cost (from the least to the most expensive).
2. If a strategy is more expensive and less effective than the previous strategy, then this strategy is said to be dominated and is excluded from the calculation of the ICERs.
3. The ICERs are calculated for each successive alternative, from the cheapest to the most costly. If the ICER for a given strategy is higher than that of the next more effective strategy, then this strategy is ruled out on the basis of extended dominance.
4. Finally, the ICERs are recalculated excluding any strategies that are ruled out by principles of dominance or extended dominance.

Applying this process to the base-case results, lithium, valproate semisodium and quetiapine are dominated by haloperidol. The options under consideration in the base-case analysis of the ICER are, therefore, haloperidol and olanzapine. The ICER of olanzapine compared with haloperidol is £7179 per additional responder. Hence, 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 less than £7179 per additional responder, then haloperidol is the optimal decision. If the decision-maker is prepared to pay at least £7179 per additional responder, then olanzapine becomes the optimal decision.

Although the results of the ICER can be used to determine the optimal decision based on a comparison of mean costs and response rates, they do not incorporate the uncertainty surrounding this decision. *Figure 97* presents the base-case results in the form of cost-effectiveness acceptability curves (CEACs) for each strategy. These curves detail the probability that each strategy is cost-effective (1 – error probability) over a range of potential maximum values that the health service is prepared to pay for an additional responder (selected values are presented in the final four columns of *Table 18*). The results of the CEACs incorporate the uncertainty within the

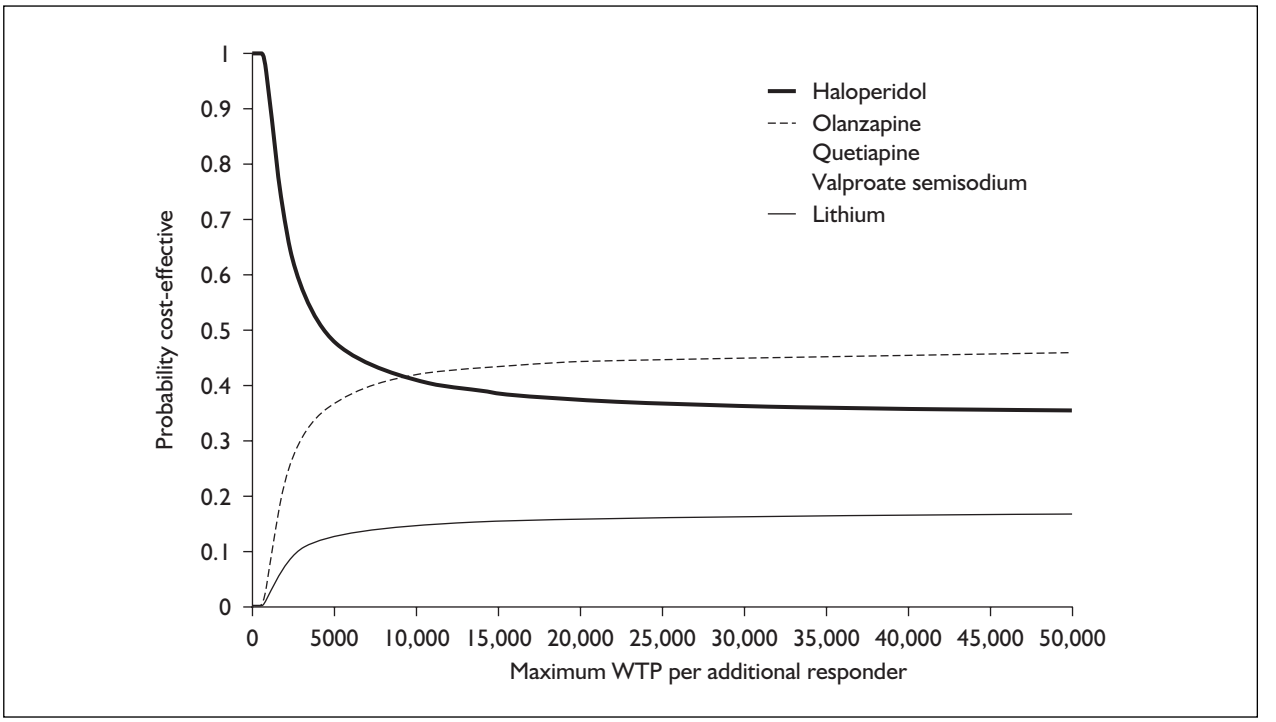

FIGURE 97 *Cost-effectiveness acceptability curve for base-case analysis*

TABLE 18 *Base-case estimates of mean costs and response rates for the five strategies, together with incremental analysis*

Drug	Cost (£)	Response	ICER	Probability cost-effective for maximum WTP[a]			
				£0	£10,000	£20,000	£30,000
Lithium	3162	0.4993	Dominated	0	0.1439	0.1549	0.1585
Valproate semisodium	3139	0.4519	Dominated	0	0.0105	0.0107	0.0107
Quetiapine	3165	0.4650	Dominated	0	0.0223	0.0242	0.0247
Olanzapine	3161	0.5371	£7179[b]	0	0.4163	0.4399	0.4484
Haloperidol	3047	0.5212		1	0.407	0.3703	0.3577

[a] The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay (WTP) for an additional responder.
[b] The ICER for olanzapine versus haloperidol.

model in relation to both the estimates of mean costs and response rates, and in the maximum willingness to pay for an additional responder. The CEACs demonstrate that the probability that olanzapine is cost-effective increases as the maximum willingness to pay increases: if the health service is prepared to pay £10,000 per additional responder, the probability that olanzapine is cost-effective is around 0.42, increasing to 0.45 if the maximum willingness to pay is £40,000.

Results of the sensitivity analyses

Tables 19–24 (scenarios A–F) detail the results of each individual sensitivity analysis undertaken to assess the robustness of the base-case model results to variation in the assumptions applied in the base-case model. None of the sensitivity analyses (except scenario F) on the cost parameters used to model the five strategies results in a change of the relative ordering of the strategies in terms of mean costs and response rates. In addition, in all analyses except scenario F, lithium, valproate semisodium and quetiapine are always dominated by olanzapine and haloperidol. Consequently, the calculation of the ICER in *Tables 19–23* is always based on a comparison of olanzapine with haloperidol. In scenario F, lithium was the cheapest strategy. The calculation of the ICERs in *Table 24* is based on a comparison of haloperidol with lithium and olanzapine with haloperidol.

TABLE 19 *Sensitivity analysis: scenario A estimates of mean costs and response rates for the five strategies (responders discharged early)*

Drug	Cost (£)	Response	ICER	Probability cost-effective for maximum WTP[a]			
				£0	£10,000	£20,000	£30,000
Lithium	6146	0.4993	Dominated	0.1314	0.1524	0.1575	0.1594
Valproate semisodium	6406	0.4519	Dominated	0.0109	0.0107	0.0106	0.0109
Quetiapine	6353	0.4650	Dominated	0.0185	0.0237	0.0246	0.0248
Olanzapine	5920	0.5371	£1236[b]	0.3822	0.4341	0.4462	0.4514
Haloperidol	5900	0.5212		0.4577	0.3791	0.3611	0.3534

[a, b] See Table 18.

TABLE 20 *Sensitivity analysis: scenario B estimates of mean costs and response rates for the five strategies (including costs of second- and third-line drug costs in non-responders – high cost estimate)*

Drug	Cost (£)	Response	ICER	Probability cost-effective for maximum WTP[a]			
				£0	£10,000	£20,000	£30,000
Lithium	9246	0.4993	Dominated	0	0.1444	0.1552	0.1585
Valproate semisodium	9235	0.4519	Dominated	0	0.0105	0.0107	0.0107
Quetiapine	9258	0.4650	Dominated	0	0.0223	0.0242	0.0247
Olanzapine	9236	0.5371	£6930[b]	0	0.4176	0.4402	0.4488
Haloperidol	9126	0.5212		1	0.4052	0.3697	0.3573

[a, b] See Table 18.

TABLE 21 *Sensitivity analysis: scenario C estimates of mean costs and response rates for the five strategies (including costs of second- and third-line drug costs in non-responders – low cost estimate)*

Drug	Cost (£)	Response	ICER	Probability cost-effective for maximum WTP[a]			
				£0	£10,000	£20,000	£30,000
Lithium	9128	0.4993	Dominated	0	0.1439	0.1549	0.1585
Valproate semisodium	9106	0.4519	Dominated	0	0.0105	0.0107	0.0107
Quetiapine	9131	0.4650	Dominated	0	0.0223	0.0242	0.0247
Olanzapine	9127	0.5371	£7165[b]	0	0.4165	0.4399	0.4484
Haloperidol	9013	0.5212		1	0.4068	0.3703	0.3577

[a, b] See Table 18.

TABLE 22 *Sensitivity analysis: scenario D estimates of mean costs and response rates for the five strategies (worst-case scenario for patients excluded from the MITT analysis)*

Drug	Cost (£)	Response	ICER	Probability cost effective for maximum WTP[a]			
				£0	£10,000	£20,000	£30,000
Lithium	3162	0.4941	Dominated	0	0.145	0.1534	0.1555
Valproate semisodium	3139	0.4424	Dominated	0	0.0067	0.0071	0.0074
Quetiapine	3165	0.4602	Dominated	0	0.0179	0.0199	0.0211
Olanzapine	3161	0.5365	£5051[b]	0	0.4554	0.4787	0.4861
Haloperidol	3047	0.5139		1	0.375	0.3409	0.3299

[a, b] See Table 18.

TABLE 23 *Sensitivity analysis: scenario E estimates of mean costs and response rates for the five strategies (laboratory and diagnostic costs reduced by 50%)*

Drug	Cost (£)	Response	ICER	Probability cost-effective for maximum WTP[a]			
				£0	£10,000	£20,000	£30,000
Lithium	3102	0.4993	Dominated	0	0.1734	0.1693	0.1671
Valproate semisodium	3115	0.4519	Dominated	0	0.0122	0.0111	0.0112
Quetiapine	3164	0.4650	Dominated	0	0.0203	0.0231	0.024
Olanzapine	3160	0.5371	£7109[b]	0	0.4	0.4319	0.44437
Haloperidol	3047	0.5212		1	0.3941	0.3646	0.354

[a, b] See Table 18.

TABLE 24 *Sensitivity analysis: scenario F estimates of mean costs and response rates for the five strategies (laboratory and diagnostic costs excluded entirely)*

Drug	Cost (£)	Response	ICER	Probability cost-effective for maximum WTP[a]			
				£0	£10,000	£20,000	£30,000
Lithium	3042	0.4993		0	0.1734	0.1693	0.1671
Valproate semisodium	3091	0.4519	Dominated	0	0.0122	0.0111	0.0112
Quetiapine	3163	0.4650	Dominated	0	0.0203	0.0231	0.024
Olanzapine	3159	0.5371	£7109[b]	0	0.4	0.4319	0.44437
Haloperidol	3045	0.5212	£103[c]	1	0.3941	0.3646	0.354

[a, b] See Table 18.
[c] The ICER for haloperidol versus lithium.

Assuming that patients who respond are discharged at 3 weeks and that patients who do not respond continue to be hospitalised until their symptoms resolve naturally results in a reduction in the ICER for olanzapine to £1236 and increases the probability that this strategy is cost-effective from 0.42 to 0.43 at a maximum WTP of £10,000 per additional responder. This analysis represents the most favourable scenario in relation to the impact of response on hospitalisation and, as such, represents the most optimistic ICER for olanzapine.

The impact of including the costs of additional drugs for second- and third-line treatment appears to have limited impact on the ICER of olanzapine in comparison with haloperidol. Using the highest cost estimate for second- and third-line drug costs results in a reduction in the ICER of olanzapine to £6930. Using the lowest cost estimates for second- and third-line drug costs reduces the ICER to £7165.

The base-case results are also robust to the assumptions concerning the outcomes of patients excluded from the MITT analysis. Taking a 'worst-case' scenario by assuming that the excluded patients were non-responders results in a reduction in the ICER of olanzapine to £5051 compared with the base-case ICER of £7179. The revised response rates using this approach are reported in *Table 25*.

TABLE 25 *Mean response rates for each strategy from multiparameter synthesis model using alternative assumptions for patients excluded from the MITT analysis*

Strategy	Pooled response rates	
	Mean	95% CI
Lithium	0.4941	0.3916 to 0.5924
Valproate	0.4424	0.361 to 0.5275
Quetiapine	0.4602	0.3686 to 0.5434
Olanzapine	0.5365	0.4609 to 0.6161
Haloperidol	0.5139	0.4034 to 0.6195

Reducing the diagnostic and laboratory costs by 50% in comparison with the base-case results has a minimal impact on the results, reducing the ICER of olanzapine to £7109. Excluding these costs altogether has a more significant impact. Under this scenario lithium is the cheapest strategy. Compared with lithium, the ICER of haloperidol is £103 per additional responder (the ICER for olanzapine compared with haloperidol is £7179). Although this analysis indicates that the base-case results are potentially sensitive to the assumptions of laboratory and diagnostic costs, it must be

TABLE 26 *Sensitivity analysis: scenario G estimates of mean costs and response rates for the five strategies (including costs of treating EPS for haloperidol)*

Drug	Cost (£)	Response	ICER	Probability cost effective for maximum WTP[a]	
				£10,000	£20,000
Lithium	3162	0.4993	Dominated	0.1444	0.1552
Valproate semisodium	3139	0.4519	Dominated	0.0105	0.0107
Quetiapine	3165	0.4650	Dominated	0.0223	0.0242
Olanzapine	3161	0.5371	£7050[b]	0.4165	0.4402
Haloperidol	3049	0.5212		0.4068	0.3697

[a, b] See Table 18.

recognised that these results were robust to reductions of 50% and that the exclusion of these costs entirely represents an extreme assumption.

Overall, the results from base-case analysis are fairly robust to the scenarios considered in this model. The results are most sensitive to the assumptions used concerning the potential reduction in length of stay for patients who respond to treatment. Presenting the most favourable scenario, that response at 3 weeks leads to immediate discharge, does not affect the relative rankings of the strategies. However, the ICER of olanzapine is reduced from £7179 in the base-case analysis to £1236. The inclusion of the additional costs of second- and third-line drug treatments for non-responders has a minimal impact on the results. Similarly, the results were not particularly sensitive to the alternative approach used to handle patients excluded from the MITT analysis.

Although it was not possible to consider formally the costs of adverse events in the base-case model, for reasons outlined earlier in the chapter, it is important to consider the potential implications that this might have on the base-case results. This seems particularly important given the inclusion of haloperidol, which is associated with higher EPS. The exclusion of any additional resource implications associated with treating EPS may overestimate the cost-effectiveness of haloperidol. A sensitivity analysis (scenario G) was therefore undertaken to explore a 'worst-case' scenario for haloperidol (i.e. using the least-favourable assumptions for haloperidol). The scenario assumed that EPS only occurred in patients treated with haloperidol (i.e. zero rate in all other drugs), and that all patients with EPS would incur the additional adjunctive antimuscarinic drug treatment costs. The model used the reported rate of EPS (35.4%) reported for haloperidol in the AstraZeneca stakeholder submission for Study 104 and assumed that patients would receive adjunctive treatment for the entire base-case period. The maximum daily cost reported in the BNF across the range of antimuscarinic drugs was then applied (£0.28 per day). The results of this sensitivity analysis are reported in *Table 26*.

The results of the base-case model did not appear to be sensitive to the inclusion of the additional costs for treating EPS adverse events in patients treated with haloperidol. Taking a 'worst-case' scenario for haloperidol reduced the ICER of olanzapine versus haloperidol to £7050 (compared with £7179 in the base-case model). The probability that olanzapine is cost-effective at £10,000 per additional responder was only marginally altered (0.4165 compared with 0.4163 in the base-case model).

Summary of results

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 less than £7179 per additional responder then haloperidol is the optimal decision. If the decision-maker is prepared to pay over £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. As a result lithium (with the exception of scenario F), valproate semisodium and quetiapine are subject to dominance in the base-case and sensitivity analyses. 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 ICER of olanzapine is reduced to £1236.

Chapter 6
Discussion

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. Bipolar disorder has complex genetic, biochemical and environmental pathways. Treatment is dependent on the phase of the disorder being experienced. With regard to mania, pharmacological intervention is almost always necessary. This review evaluated the clinical and cost-effectiveness of quetiapine, olanzapine and valproate semisodium for treatment of acute mania.

Main results

Quetiapine

Versus placebo (two RCTs)

[Some CIC data from Studies 104 and 105 have been removed.]

Quetiapine was more effective than placebo in improving GAS, PANSS and YMRS scores in two trials, but 'response' (using CGI-BP or YMRS criteria) and scores on the CGI-BP scale were equivocal. There was no significant difference between groups in risk of emergent depressive symptoms. People in the placebo group were more likely to leave the study early for any reason, owing to disease progression or to lack of efficacy. People in the quetiapine group were more likely to experience dry mouth, somnolence, weight gain or dizziness than people in the placebo group.

Overall, quetiapine appears superior to placebo in reducing manic symptoms, but is associated with side-effects such as somnolence, dry mouth and dizziness. However, both trials were small to medium sized with high rates of withdrawal.

Plus valproate semisodium versus placebo plus valproate semisodium (one RCT)

This trial reported data for adolescents only. There was a significantly greater reduction in YMRS scores for the quetiapine plus valproate semisodium compared with the placebo plus valproate semisodium group. There was no significant difference in response rates between the groups, although there was a trend favouring the quetiapine group. More participants withdrew from the quetiapine group (7/15) than the placebo group (1/15), but this difference was not significant. Participants in the quetiapine group were significantly more likely to report sedative effects. There were no other significant differences between groups in terms of treatment emergent events.

The evidence regarding the effectiveness of quetiapine plus valproate semisodium versus placebo plus valproate semisodium came from a very small trial (total $n = 30$), in which 27% (8/30) of participants withdrew early. Although adequate randomisation procedures were employed, it was unclear whether treatment allocation was concealed. In addition, although it was reported that outcome assessors, administrators and participants were blinded, the success of blinding was not assessed.

Versus placebo as adjunct to mood stabilisers (one RCT)

[CIC data from Study 100 have been removed.]

In Study 99, quetiapine was no more effective than placebo as an adjunct to mood stabilisers in improving CGI-BP, PANSS total or YMRS scores, but CGI-BP and YMRS response rates were higher in the quetiapine adjunct group. Results for PANSS agitation and aggression scores were equivocal. There was no significant difference between groups in risk of emergent depressive symptoms or in likelihood of leaving the study early. People in the quetiapine adjunct arm were more likely to experience dry mouth, somnolence, postural hypotension and asthenia.

Quetiapine 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, postural hypotension and asthenia. However, the trial was small to medium sized with high rates of withdrawal, and used ITT analysis for safety data only. For other outcomes, the LOCF method was employed, and therefore there were many proxy rather than actual data presented.

In summary, no reliable conclusions can be drawn about the effectiveness of quetiapine as an adjunct

to mood stabilisers in the treatment of mania associated with bipolar disorder because of methodological limitations, primarily that the trials were not sufficiently large and that many proxy data were presented.

Versus other comparators

[Some CIC data from Studies 100, 104 and 105 have been removed.]

Versus lithium (one RCT)

Insufficient data were reported to calculate whether lithium or quetiapine were more effective in improving health according to global checklists or improving PANSS scores. CGI-BP and YMRS response rates were not different between groups. There was no significant difference between groups in risk of emergent depressive symptoms or in likelihood of leaving the study early. People in the quetiapine group were more likely to experience dry mouth, somnolence or weight gain than people in the lithium group. People in the lithium group were more likely to experience tremor than people in the quetiapine group.

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. However, this trial was small to medium in size with high rates of withdrawal.

Versus haloperidol (one RCT)

Insufficient data were reported to calculate whether haloperidol or quetiapine was more effective in improving health according to global checklists. CGI-BP and YMRS response rates do not favour quetiapine or haloperidol. There was no significant difference between groups in risk of emergent depressive symptoms or in likelihood of leaving the study early. People in the haloperidol group were more likely than people in the quetiapine group to experience tremor, akathisia and EPS.

Quetiapine may have similar effectiveness to haloperidol in reducing mania, but haloperidol is associated with more EPS, such as akathisia and tremor. However, this trial was small to medium in size with high rates of withdrawal.

Olanzapine

Versus placebo

Two RCTs compared olanzapine with placebo. CGI Scale scores showed greater improvement in the olanzapine group over both trials for the mania subscale, but only one trial showed significant results favouring the olanzapine group on the total severity of illness score. YMRS scores showed significant improvement in the olanzapine group across both trials. Similarly, in both trials the olanzapine groups compared with the placebo groups recorded significantly more improvement in PANSS total scores, and also PANSS positive scores. The olanzapine groups did not differ significantly from the placebo groups in either trial on measures of PANSS negative and HAM-D. Significantly fewer participants in the olanzapine groups left the study before completion. Participants receiving olanzapine were more likely to report experiencing somnolence, dry mouth, dizziness and weight gain.

Overall, olanzapine appears superior to placebo in reducing manic symptoms, but is also associated with side-effects such as somnolence, dry mouth and dizziness. However, both trials were small (<100 participants receiving olanzapine) with high rates of withdrawal. In one trial it was unclear whether the method of randomisation was adequate, ITT analysis was employed for safety data only and for other outcomes the LOCF method was employed, and therefore there were many proxy rather than actual data presented.

Versus lithium

One small, 4-week RCT compared olanzapine with lithium carbonate. CGI Scale scores showed significantly greater improvement in the olanzapine group compared with the lithium group. However, there was no significant difference between the olanzapine and lithium groups on the measures of GAF or the BPRS. Similarly, although both groups showed significant improvements on the MAS from baseline at 4 weeks, there were no significant differences between the groups. There were no significant differences between groups in terms of treatment-emergent EPS.

There appears to be little difference between olanzapine and lithium in terms of clinical effectiveness and adverse events. However, this was a very small trial (N = 15 in each group), which was methodologically limited by lack of adequate randomisation procedures and failure to employ ITT analysis.

Versus haloperidol

One 6-week RCT evaluated the efficacy of olanzapine versus haloperidol. There was no significant difference between the groups in terms of response or remission as measured by the YMRS. Subgroup analysis between those with and

without psychotic features revealed remission differences between non-psychotic participants that favoured olanzapine. There were no differences between the groups in the likelihood of leaving the study early. Most measures of HRQoL favoured olanzapine over haloperidol, whereas none favoured haloperidol over olanzapine.

Overall, there appears to be little difference between olanzapine and haloperidol in terms of clinical effectiveness. However, compared with haloperidol, olanzapine appears to have a more favourable profile in terms of HRQoL. This evidence comes from one large RCT (total $N = 453$). The trial is limited in that it was unclear whether appropriate randomisation procedures were used, whether treatment allocation was concealed and, although participants were stated to be blinded, the success of blinding was not checked. More than 30% of participants left this trial early so many of the data presented are proxy data based on the LOCF method.

Plus valproate semisodium or lithium versus placebo plus valproate semisodium or lithium

One 4-week RCT evaluated the efficacy of olanzapine versus placebo when added to valproate or lithium. Thus the trial evaluated the additional benefits of olanzapine when added to monotherapy. The olanzapine group showed significantly more improvement than the placebo group on the CGI Scale. YMRS scores showed significantly more improvement in the olanzapine group, and the time to both response and remission was significantly shorter than in the placebo group. Significantly more participants in the placebo group discontinued treatment owing to lack of efficacy, whereas significantly more participants in the olanzapine group withdrew owing to adverse events. Participants in the olanzapine group were significantly more likely to report somnolence, dry mouth, weight gain, increased appetite, tremor and speech disorder.

Olanzapine as adjunct therapy to valproate or lithium 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. It was unclear to what extent this trial employed adequate randomisation procedures, concealed treatment allocation or completed adequate follow-up.

Versus lorazepam versus placebo

One 24-hour RCT compared intramuscular olanzapine versus lorazepam versus placebo. There were no significant differences between the groups on the CGI Scale. There were no significant differences between olanzapine and lorazepam on measures of mania using the PANNS-EC, ABS, ACES or the YMRS. However, comparisons between the olanzapine and placebo groups showed significant differences in favour of olanzapine for scores on PANNS-EC, ABS and ACES, but not for scores on the YMRS. The lorazepam group had a significantly larger proportion of treatment-emergent adverse events than the placebo group, whereas the olanzapine group did not differ significantly from either group.

Intramuscular olanzapine and lorazepam were equally effective and safe. However, this is a small trial (<100 in each group) over a short duration (24 hours), and had an unknown and hence potentially inadequate method of randomisation. In addition, although the authors state that they used ITT analysis, this was not apparent from the data that were presented.

In summary, no reliable conclusions can be drawn about the effectiveness of olanzapine in the treatment of mania associated with bipolar disorder because of methodological limitations. Specifically, the trials were small, employed potentially inadequate randomisation procedures and failed to use appropriate ITT analysis.

Valproate semisodium

Versus placebo

Two RCTs compared valproate semisodium with placebo. GAS scores were significantly higher for valproate semisodium in one small trial but not significantly different in the larger trial. YMRS scores and YMRS 'response' were significantly higher in the valproate semisodium group in one small trial and SADS-C MRS total scores and SADS-C response rate were also significantly higher in the valproate semisodium group in the larger RCT. Total BPRS-A scores were significantly higher in the valproate semisodium group in one small RCT and ADRS mania, elated and psychosis subscales scores significantly higher in the valproate semisodium group in the larger trial. People in the placebo group were more likely to leave the study early owing to lack of efficacy, and received more lorazepam. People receiving valproate semisodium were more likely to experience gastrointestinal symptoms than those receiving placebo.

Valproate semisodium appears superior to placebo in reducing manic symptoms, but may cause

gastrointestinal side-effects. The evidence comes from two small trials (N = 20 and 69 receiving valproate semisodium), both of which failed to employ ITT analysis, despite withdrawals.

Versus lithium

Three RCTs (two in adults and one in children) compared valproate semisodium with lithium.

For adults, one trial reported no significant difference in GAS scores between groups. One trial which reported SADS-C mania rating change scores reported no significant difference between groups for total score or 'response', but the subscales of increased activity and less need for sleep favoured valproate semisodium over lithium. One trial reported no significant difference between groups for mania, psychosis and elated subscales of the ADRS. No significant differences in attrition or receipt of lorazepam were seen between valproate semisodium and lithium groups. No adverse effects were significantly more or less likely in the valproate semisodium than the lithium group in one study.

For children, one trial reported no significant difference in CGI-I 'response' or YMRS 'response' between groups. No significant differences in attrition were seen between valproate semisodium and lithium groups. No significant difference was seen between groups for the most commonly reported adverse event of nausea.

Valproate semisodium may be slightly more effective than lithium. The evidence comes from three trials that suffered from limitations such as lack of ITT analysis and potentially inadequate randomisation procedures.

Versus carbamazepine

One RCT in children compared valproate semisodium with carbamazepine. No significant difference was seen between groups in terms of CGI-I response, YMRS response, attrition or adverse events. This trial was small (total N = 42), with unclear randomisation procedures and with potential differences between groups at baseline.

Versus haloperidol

One small, 6-day RCT compared valproate semisodium with haloperidol in patients with psychotic features. No significant differences were seen between groups in YMRS end-point scores, YMRS 'response', length of hospital stay or SAPS scores. EPS were significantly more likely to occur in the haloperidol than the valproate semisodium group.

Valproate semisodium was as effective as haloperidol in a small, short-term trial of patients with psychotic features, but haloperidol caused more EPS. The evidence comes from one small trial (total N = 36) of short duration (6 days), and in which it was unclear whether adequate randomisation procedures were employed.

In summary, no reliable conclusions can be drawn about the effectiveness of valproate semisodium in the treatment of mania associated with bipolar disorder because of methodological limitations. Specifically, the trials were small, employed potentially inadequate randomisation procedures and failed to use appropriate ITT analysis.

Valproate semisodium versus olanzapine

Two RCTs compared olanzapine and valproate semisodium. No significant difference was reported between groups for the CGI-I Scale scores or MRS scores in one study. In the other study YMRS change scores, YMRS 'response' and YMRS 'remission' favoured olanzapine. Both trials found no significant difference between groups on the HAM-D Scale scores. One trial found no difference between groups on the BPRS score. Both trials reported attrition rate, which was not significantly different between groups. People receiving olanzapine had a greater risk of dry mouth, increased appetite, oedema, somnolence, speech disorder and weight gain. People receiving valproate semisodium had an increased risk of nausea. In one trial, people receiving olanzapine had a worse result on the SAS (a measure of Parkinson-like symptoms) than people receiving valproate semisodium. One study found no significant differences between groups in QoL.

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. The evidence comes from two trials (total N = 120 and 251) in which it was unclear whether adequate randomisation procedures were used or whether treatment allocation was concealed. In summary, therefore, methodological limitations prevent the drawing of reliable conclusions.

Assumptions, limitations and uncertainties

A total of 18 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. The quality of the included trials was limited. Only eight trials reported adequate randomisation procedures, only three trials reported clearly that allocation was concealed and only five trials reported sufficiently that outcome assessors were blinded. Although most reported that participants were blinded, none assessed the extent to which blinding was successful, and only seven trials reported full ITT analysis, with another four trials conducting ITT analysis for safety data only. In addition, the sample size in many of the trials was small (<100 patients). Overall, key methodological criteria were not met in most trials.

DSM-IV criteria for mania associated with bipolar disorder are clear, and this is the preferred diagnostic tool.[1] All but five trials used DSM-IV criteria, three used DSM-IIIR criteria and in two trials it was unclear what diagnostic tool was employed. In general, therefore, the potential for diagnostic error, beyond that more usually anticipated, appears to be minimal.

There were high attrition rates across both treatment and placebo groups, sometimes approaching 50%. This has serious implications for the reliability of the data, since many of the end-point data are based not on actual figures but proxy data (LOCF). Moreover, this is surprising given that the treatment duration was short, typically 3 weeks, and that most patients were hospitalised for the duration of the treatment. A full explanation concerning the reasons for withdrawal was often lacking and would have been beneficial.

Nevertheless, analysis should take into account the dropouts by, for example, the use of ITT analysis. This was done in most cases by use of the LOCF method, which makes the assumption that people leaving the study early did not get any worse or better from the moment they left the study until the end of the study. This assumption may or may not be appropriate. Where possible, our analyses were based on ITT analysis treating dropouts as non-responders. This is a worst-case scenario, but given the high rates of attrition and the lack of explanation, it seems the wisest approach. However, we were only able to do this for a handful of participants that had been excluded from all reported analyses. We were unable to carry out this worst-case analysis for most of the people who had left the trials early as they had already been added back in by the trial authors using the LOCF assumption, and end-point data were reported for the group as a whole. We were therefore unable to separate the real end-point data for trial completers from the proxy end-point data for people who dropped out.

Three weeks has been suggested as a sufficient length of time to demonstrate a significant drug–placebo difference in acute mania.[1] However, to regard a patient as a responder at 3 weeks may be premature, as it would inevitably miss some cases. To allow for full detection of response and remission rates, a longer period of treatment and/or follow-up would be desirable. There are few data to inform on how long this period ought to be. Although a period of between 8 and 16 weeks has been suggested,[1] most trials were of shorter duration.

As the scope of this review was limited to treatment of acute mania, we are necessarily unable to comment upon the long-term effects of these interventions, both positive and negative. This is important because in practice these interventions, if effective in the short term, may continue to be used as a form of maintenance therapy. Given the scope of this review, we have not investigated the long-term effects of these drugs, and it is our view that an appropriately informed decision concerning the use of these drugs should necessarily reflect their long-term effects.

Implications for research

Despite practical difficulties, it is possible to evaluate efficacy in short-term acute treatment of mania in placebo-controlled studies, yet there remains a need for well-conducted, randomised, double-blind placebo-controlled studies 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. Regarding demographic characteristics, age may be an important factor. There is evidence to suggest that the earlier the onset, the more severe is the course of the disorder and, hence, early effective intervention may be especially important.[1] There was only one randomised trial that evaluated the effectiveness of treatments for the young.[54] However, because this trial failed to include a placebo control, it fails to provide

sufficiently rigorous evidence for efficacy as the underlying placebo response rate is unknown. At present, therefore, it is impossible to comment on the relative efficacy of treatments in children.

Similarly, there is a lack of evidence regarding the effectiveness of treatments for the elderly. Strategies for treatment often become more complex and a variety of combinations of mood stabilisers are often used, principally because resistance to monotherapy may increase with time.[71] Indeed, it has been suggested that the elderly reflect a largely resistant subgroup.[1] The use of adjunctive therapy raises the issue of safety and pharmacokinetic interactions, and long-term safety issues will need to be investigated in the elderly.

Regarding diagnostic characteristics, many of the included trials were broad in their inclusion criteria, with manic and mixed included in the same trial. Clearer presentation of subgroup analysis would have been beneficial. There is some evidence that, for example, those suffering from mania with depressive symptoms (mixed diagnosis) respond differently to treatment.[49] Similarly, in rapid cycling bipolar disorder, the subtype, bipolar I or II, may help in investigating the variance in treatment response. It would be helpful to identify population subgroups in advance for subanalysis in order to identify pharmacological differences.

An important issue for future research concerns treatment duration and follow-up time. As noted previously, this review has focused on acute treatment of mania and has not investigated the long-term effects of these drugs. 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.

Cost-effectiveness

The limitations of existing studies of the cost-effectiveness of alternative drugs for the acute manic episode for bipolar disorder were clearly highlighted in the review of economic evidence in Chapter 4. An alternative decision-analytic model was thus developed to address this issue more formally and to provide significant additional information in relation to the likely cost-effectiveness of alternative drug treatments for the first-line treatment of bipolar patients during the acute manic episode. An important component of the model was the use of the mixed comparison model to synthesise the effectiveness data. This approach offers several advantages over conventional approaches in situations where there exists both direct head-to-head evidence and indirect evidence in relation to a common comparator (e.g. placebo). Conventional approaches to incorporating this evidence are limited in that they are forced either to make selective use of the data or require the cost-effectiveness of alternative treatments to be presented using a series of pairwise comparisons rather than in comparison with the full range of potential treatments. The use of the mixed comparison model allows the characterisation of the joint distribution of the efficacy of the treatments, based on the complete evidence base, and facilitates a direct comparison of the cost-effectiveness of a wider range of potential treatments. These methods are a valuable means of synthesising indirect evidence and are based on few additional assumptions over standard meta-analysis. However, when indirect evidence is used to estimate a series of treatment effects, it is not possible to rule out the introduction of bias, and the results of the model should be interpreted accordingly. Furthermore, systematic searches for all possible comparators were not undertaken. Hence there may be additional indirect evidence on the effectiveness of these comparators which could be included alongside the evidence presented in this report.

In addition, the model presented here has several potential limitations which need to be considered in conjunction with the results reported here. First, the analytic timeframe is constrained to the short-term treatment of the acute manic episode only. The cost-effectiveness of these drugs as part of maintenance treatment is outside the scope of this review and consequently is not considered in the model. As a result, no conclusions can be made concerning the potential cost-effectiveness of these drugs beyond the acute period. If the treatments are continued beyond the acute period, the additional costs and benefits need to be considered and should be incorporated alongside the short-term decision model presented here. From a longer term perspective, the exclusion of the costs and quality of life impact of adverse events (in particular EPS) from the model represents a significant limitation. Although the model considers the inclusion of the additional short-term treatment costs associated with the use of antimuscarinic agents for EPS, the longer term impact on a patient's QoL and the risk of a

patient developing long-term tardive dyskinesia may have a significant impact on the relative cost-effectiveness of the alternative drugs beyond the initial acute episode.

Second, although the use of the mixed comparisons model allowed direct comparison of a broader range of strategies than those considered in any of the existing studies, the limitations of the available data precluded the inclusion of combination therapies using either quetiapine or olanzapine in conjunction with conventional drug treatments. Hence it is not possible to draw any conclusions concerning the relative cost-effectiveness of these drugs as part of combination therapy. Similarly, the lack of available data on the effectiveness of the alternative drugs as part of second- and third-line treatments (for patients who fail to respond to previous drug treatments), meant that it was only possible to assess the cost-effectiveness of the alternative drug treatments as part of first-line therapy.

In addition, the use of response rates as the primary effectiveness measure used in the model has potential limitations in assisting decisions about resource allocation. Comparisons are restricted to other interventions which report using a similar outcome. Ideally, a generic measure of outcome (e.g. QALYs) would be used to enable a broad range of comparisons to be made across different disease areas. No suitable data were reported in the literature review and hence it was not possible to include QoL estimates in the model. In the absence of QoL data, response rates were used as the primary health outcome on the basis of clinical relevance and to maximise the number of studies that could be considered in the model. This approach has a number of potential drawbacks: (1) studies which did not report the use of response rates were excluded from consideration in the cost-effectiveness analysis and (2) the use of response rates does not encompass all relevant aspects of health improvement.

Finally, it is important to note that the synthesis of response rates indicates that there appear to be only small differences in effectiveness between the drugs and the clinical relevance of these differences may be limited. Indeed, using standard error probabilities, the effects are not statistically different from each other. The results from the cost-effectiveness analysis in the base-case analysis are thus driven largely by the lower acquisition and monitoring costs associated with haloperidol in the short-term acute period.

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.

Chapter 7
Conclusions

Clinical effectiveness

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

In comparison with haloperidol, there appears to be little difference for quetiapine or olanzapine in terms of clinical effectiveness. All drugs were associated with adverse events. However, compared with quetiapine, haloperidol was associated with a greater likelihood of tremor, akathisia and EPS. Similarly, when compared with olanzapine, haloperidol was associated with more negative outcomes for HRQoL.

Cost-effectiveness

The systematic literature search identified only two studies which met the criteria for inclusion in the cost-effectiveness review. In addition to these two studies, supplementary economic evidence was also 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, reported in detail in Chapter 4, 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. In particular, no single study directly compared the full range of possible strategies that would appear to be relevant to the NHS. In addition, the existing studies used a variety of alternative analytic structures and assumptions concerning the estimates of effectiveness, costs and appropriate time horizon. These alternative approaches precluded direct comparison of the different results obtained in each of the studies. In addition, in several of the studies, the estimates of cost-effectiveness were based on the use of drugs for both the acute treatment for the manic episode and for longer term maintenance therapy. As such, it is not clear whether the conclusions for these studies would alter significantly based on an evaluation of treatment for the acute episode only. Finally, the two studies identified in the systematic literature search used resource use and cost data from the USA and consequently the relevance of these findings to the NHS is unclear.

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. The cost-effectiveness of these drugs as part of maintenance treatment was outside the scope of this review and is not considered in the model. The model estimates costs from the perspective of the NHS and health outcomes in terms of response rate. 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. A series of sensitivity analyses is used to determine the robustness of the base-case results to alternative assumptions.

In the base-case analysis, lithium, valproate semisodium and quetiapine are dominated by haloperidol as they are both more expensive and less effective. The ICER of olanzapine compared with haloperidol is £7179 per additional responder. The relative ordering of strategies based on their mean costs and outcomes appears robust to the uncertainty in the cost assumptions used in the base-case model. As a result, lithium, valproate semisodium and quetiapine are subject to dominance in the base-case and sensitivity analyses. Under the most favourable scenario considered in the sensitivity analyses, the ICER of olanzapine is reduced to £1236.

Several limitations of the cost-effectiveness analysis exist which inevitably means that the results should be treated with some caution. These

include: (1) the possible bias introduced by using indirect evidence; (2) the limited timeframe of the analysis and the exclusion of the costs and QoL impact of adverse events; (3) the exclusion of olanzapine and quetiapine combination therapies from the base-case models; (4) the lack of data concerning the effectiveness of the drugs when used in second- and third-line treatments; and (4) the lack of suitable data on QoL.

The available evidence derives from trials that are too small and methodologically flawed and which rely on proxy data, that is, 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.

Acknowledgements

We wish to thank the expert reviewers for their useful advice and constructive comments on the draft protocol and report: Clive Adams (University of Leeds), Sarah Byford (King's College London) and Sarah Garner (NICE).

We also wish to thank Dr Tony Ades and Dr Goubing Lu of the MRC Health Services Research Collaboration at the University of Bristol for their help and advice on the use of the mixed comparison model applied in the economic model.

This report was commissioned by the NHS R&D HTA programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA programme. All responsibility for the content of the report remains with the authors.

References

1. Angst J, Bowden CL, Calabrese JR, Chengappa R, Goodwin G, Lecrubier Y, *et al*. ECNP consensus meeting March 2000: NICE guidelines for investigating efficacy in bipolar disorder. *Eur Neuropsychopharmacol* 2001;**11**:79–88.
2. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; **349**:1436–42.
3. Dinan TG. Lithium in bipolar mood disorder. *BMJ* 2002;**324**:989–90.
4. Muller Oerlinghausen B, Berghofer A, Bauer M. Bipolar disorder. *Lancet* 2002;**359**:241–7.
5. Daly I. Mania. *Lancet* 1997;**349**:1157–60.
6. Miller-Oerlinghausen B, Muser-Causemann B, Volk J. Suicides and parasuicides in a high risk patient group on and off lithium long-term medication. *J Affect Disord* 1992;**25**:261–9.
7. Carlson GA, Strober M. Manic depressive-illness in early adolescence: a study of clinical and diagnostic characteristics in six cases. *J Am Acad Child Adolesc Psychiatry* 1978;**17**:138–53.
8. Woznniak J, Biederman J, Mundy E, Mennin D, Faraone SV. A pilot family study of childhood-onset mania. *J Am Acad Child Adolesc Psychiatry* 1995;**34**:1577–83.
9. DeLong GR, Aldershof AL. Long-term experience with lithium treatment in childhood: correlation with clinical diagnosis. *J Am Acad Child Adolesc Psychiatry* 1987;**26**:389–94.
10. Koegal P, Burman MA, Farr RK. The prevalence of specific psychiatric disorders among homeless individuals in the inner city of Los Angeles. *Arch Gen Psychiatry* 1988;**45**:1085–92.
11. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 1998;**50**:143–51.
12. McGuffin P, Katz R. Nature, nurture and affective disorder. In Deakin JWF, editor. *The biology of depression*. London: Gaskell; 1986. pp. 26–51.
13. Nurnberger JI, Gershon E. Genetics. In Paykel ES, editor. *Handbook of affective disorders*. 2nd ed. New York: Churchill Livingstone; 1992. pp. 131–48.
14. Goodwin FK, Jamison KR. *Manic-depressive illness*. New York: Oxford University Press; 1990.
15. Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. *Am J Psychiatry* 1993;**150**:720–7.
16. Das Gupta R, Guest JF. Annual cost of bipolar disorder to UK society. *Br J Psychiatry* 2002; **180**:227–33.
17. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary*. London: BMA and Royal Pharmaceutical Society of Great Britain; 2002. p. 43.
18. Moore NA, Tye NC, Axton MS, Risius FC. The behavioral pharmacology of olanzapine, a novel 'atypical' antipsychotic agent. *J Pharmacol Exp Ther* 1992;**262**:545–51.
19. Keck PE, Jr, McElroy SL. Pharmacological treatments for bipolar disorder. In Nathan PE, Gorman JM, editors. *A guide to treatments that work*. 2nd ed. Oxford: Oxford University Press; 2002. pp. 277–99.
20. Saller CF, Salama AI. Sequel: biochemical profile of a potential atypical antipsychotic. *Psychopharmacology* 1993;**112**:285–92.
21. Fariello R, Smith MC. Valproate: mechanisms of action. In Schatzberg AF, editor. *Antiepileptic drugs*. New York: Raven Press; 1989. pp. 567–75.
22. Chen G, Huang LD, Zeng WZ, Manji HK. Mood stabilizers regulate cytoprotective and mRNA-binding proteins in the brain: long-term effects on cell survival and transcript stability. *Int J Neuropsychopharmacol* 2001;**4**:47–64.
23. NHSCRD. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews: CRD report 4*. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.
24. Drummond MF, O' Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford Medical Publications; 1997.
25. National Institute for Clinical Excellence. *Technical guidance for manufacturers and sponsors on making a submission to a technology appraisal*. London: National Institute for Clinical Excellence; 2001.
26. AstraZeneca UK Ltd. *The clinical and cost effectiveness of newer drugs for the treatment of mania associated with bipolar affective disorder: submission of evidence from AstraZeneca UK Ltd regarding the atypical antipsychotic quetiapine*. Alderley Park, Macclesfield: AstraZeneca UK Ltd; October 2002.

27. AstraZeneca UK Ltd. *The clinical and cost effectiveness of newer drugs for the treatment of mania associated with bipolar affective disorder: submission of evidence from AstraZeneca UK Ltd regarding the atypical antipsychotic quetiapine*. Alderley Park, Macclesfield: AstraZeneca UK Ltd; November 2002.

28. Sachs G, Mullen JA, Devine NA, Sweitzer DE. Quetiapine vs placebo as adjunct to mood stabilizer in the treatment of acute mania [meeting abstract]. *Eur Neuropsychopharmacol* 2002; **12** (Suppl 3):S235.

29. Mullen J, Paulsson B. Quetiapine in combination with lithium or divalproex for the treatment of mania associated with bipolar disorder. In *Fifth International Conference on Bipolar Disorder*; 12–14 June 2003, Piitsburgh, PA.

30. Brecher M, Huizar K. Quetiapine monotherapy for acute mania associated with bipolar disorder. In *Fifth International Conference on Bipolar Disorder*, 12–14 June 2003, Pittsburgh, PA.

31. Jones M, Huizar K. Quetiapine monotherapy for mania associated with bipolar disorder. In *Fifth International Conference on Bipolar Disorder*, 12–14 June 2003, Pittsburgh, PA.

32. Jones M, Huizar K. Quetiapine monotherapy for mania associated with bipolar disorder. In *166th Annual Meeting of the American Psychiatric Association*, 17–22 May 2003, San Francisco, CA.

33. DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 2002;**41**:1216–23.

34. Paulsson B, Huizar K. Quetiapine monotherapy for the treatment of bipolar mania. In *Fifth Annual International Conference on Bipolar Disorder*, 12–14 June 2003, Pittsburgh, PA.

35. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, *et al*. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. *Am J Psychiatry* 1999;**156**:702–9.

36. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, *et al*. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. *Arch Gen Psychiatry* 2000; **57**:841–9.

37. Tohen M, Zhang F, Feldman PD, Evans AR, Breier AF. Olanzapine versus haloperidol in the treatment of acute mania [meeting abstract]. *2001 Annual Meeting of the American Psychiatric Association*, 5–10 May 2001, New Orleans, LA.

38. Shi L, Namjoshi MA, Zhang F, Ghandi G, Edgell ET, Tohen M, *et al*. Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *Int Clin Psychopharmacol* 2002;**17**:227–37.

39. Shi L, Namjoshi M, Tohen MF, Zhang F, Breier AF, Edgell ET. Olanzapine versus haloperidol: a prospective comparison of clinical and humanistic outcomes in bipolar disorder [meeting abstract]. In *2001 Annual Meeting of the American Psychiatric Association*, 5–10 May 2001, New Orleans, LA.

40. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int Clin Psychopharmacol* 1999; **14**:339–43.

41. Tohen M, Chengappa KNR, Suppes T, Zarate CA, Jr, Calabrese JR, Bowden CL, *et al*. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry* 2002; **59**:62–9.

42. Meehan K, Zhang F, David S, Tohen M, Janicak P, Small J, *et al*. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol* 2001;**21**:389–97.

43. Meehan K, Breier A, David SR, Koch KE, Rizk R, Tohen M, *et al*. Efficacy and safety of intramuscular (im) olanzapine versus im lorazepam and im placebo in acutely agitated patients diagnosed with mania associated with bipolar disorder. *Schizophr Res* 2001;**49**:239.

44. Namjoshi M, Shi L, Zhang F, Edgell ET, Tohen MF, Breier AF. Olanzapine versus haloperidol: improvements in quality of life and compliance with treatment in patients with bipolar disorder. In *2001 Annual Meeting of the American Psychiatric Association*, 5–10 May 2001, New Orleans, LA.

45. Tohen KF, Tohen M, Timpe TM, Risser R, Chengappa KR, Suppes TR, *et al*. Efficacy of olanzapine combined with mood stabilizers in the treatment of bipolar disorder. *Schizophr Res* 2001; **49**:248.

46. Tohen M, Jacobs TG, Meyers TM, Risser RC, Keeter EL, Feldman PD, *et al*. Efficacy of olanzapine combined with mood stabilizers in the treatment of bipolar disorder. *Int J Neuropsychopharmacol* 2000;**3** (Suppl 1):S335.

47. Tohen M, Jacobs TG, Timpe TM, Risser RC, Keeter EL, Chengappa KNR, *et al*. Efficacy of olanzapine combined with valproate or lithium in the treatment of bipolar disorder. *Biol Psychiatry* 2001;**49**:385.

48. Pope HG, Jr., McElroy SL, Keck PE, Jr, Hudson JI. Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry* 1991; **48**:62–8.

49. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, *et al*. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *JAMA* 1994; **271**:918–24.

50. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, *et al*. Depression during mania: treatment response to lithium or divalproex. *Arch Gen Psychiatry* 1997;**54**:37–42.

51. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. *Am J Psychiatry* 1999;**156**:1264–6.

52. Bowden CL, Davis J, Morris D, Swann A, Calabrese J, Lambert M, *et al*. Effect size of efficacy measures comparing divalproex, lithium and placebo in acute mania. *Depress Anxiety* 1997;**6**:26–30.

53. Hirschfeld RM, Allen MH, McEvoy JP, Keck PE, Jr, Russell JM. Safety and tolerability of oral loading divalproex sodium in acutely manic bipolar patients. *J Clin Psychiatry* 1999;**60**:815–18.

54. Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, *et al*. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:713–20.

55. McElroy SL, Keck PE, Stanton SP, Tugrul KC, Bennett JA, Strakowski SM. A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. *J Clin Psychiatry* 1996;**57**:142–6.

56. Tohen M, Baker RW, Altshuler LL, Zarate CA, Suppes T, Ketter TA, *et al*. Olanzapine versus divalproex in the treatment of acute mania. *Am J Psychiatry* 2002;**159**:1011–17.

57. Zajecka J, Weisler R, Sommerville KW, Tracy K, Swann AC, Sachs G, *et al*. Divalproex sodium vs olanzapine for the treatment of mania in bipolar disorder. In *39th Annual Meeting of the American College of Neuropsychopharmacology*, 10–14 December 2000, San Juan, Puerto Rico. Nashville, TN: Vanderbilt University Medical Center, American College of Neuropsychopharmacology; 2000. p. 257.

58. Keck PE, Jr, Nabulsi AA, Taylor JL, Henke CJ, Chmiel JJ, Stanton SP, *et al*. A pharmacoeconomic model of divalproex semisodium vs. lithium in the acute and prophylactic treatment of bipolar I disorder. *J Clin Psychiatry* 1996;**57**:213–22.

59. Keck PE, Jr., McElroy SL, Strakowski SM, West SA, Hawkins JM, Huber TJ, *et al*. Outcome and comorbidity in first- compared with multiple-episode mania. *J Nerv Ment Dis* 1995;**183**:320–4.

60. McElroy SL, Strakowski SM, Keck PE, Jr, Tugrul KL, West SA, Lonczak HS. Differences and similarities in mixed and pure mania. *Compr Psychiatry* 1995; **36**:187–94.

61. Department of Health. *Hospital episode statistics (HES) 2000/01 [monograph online]*. 2002. Available at http://www.doh.gov.uk/hes/ [accessed 2002].

62. Briggs A, Goeree R, Blackhouse G, O'Brien B. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making* 2002;**22**:290–308.

63. McAlistair F, Laupacis A, Wells G, Sackett D. Users' guide to the medical literature. XIX Applying clinical trial results. B. Guidelines for determining whether a drug is exerting (more than) a class effect. *JAMA* 1999;**282**:1371–77.

64. Hasselblad V. Meta-analysis of multi-treatment studies. *Med Decis Making* 1998;**18**:37–43.

65. Higgins J, Whitehead J. Borrowing strength from external clinical trials in a meta-analysis. *Stat Med* 1996;**15**:2733–49.

66. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002;**21**:2313–24.

67. Ades A. *A chain of evidence with mixed comparisons: models for multi-parameter evidence synthesis and consistency of evidence*. Paper presented to DEEM workshop, 11–12 April, Oxford. Available at http://www.ihs.ox.ac.uk/herc/DEEM/Ades.pdf [accessed 2002].

68. Johannesson M, Weinstein M. On the decision rules of cost-effectiveness analysis. *J Health Econ* 1993;**12**:459–67.

69. Van Hout B, Gordon G, Rutten F. Costs, effects and C/E ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19.

70. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–89.

71. Maj M, Priozzi R, Kemali D. Long term outcome of lithium prolaxis in patients initially classified as complete responders. *Neuropharmacology* 1988; **98**:535–8.

72. Allen D. Olanzapine in the treatment of acute mania in the community. *Psychiatr Bull R Coll Psychiatr* 1998;**22**:189–190. Available at http://pb.rcpsych.org/.

73. Anon. Zyprexa: short-term treatment of acute manic episodes of bipolar disorder. *Formulary* 2000;**35**:388–90.

74. Anon. Multicenter study confirms value of divalproex for mania. *Am J Hosp Pharm* 1994; **51**:388–90.

75. Anon. Disodium valproate: new preparation: an alternative for acute mania after lithium failure or intolerance. *Prescrire Int* 2001;**10**:113–15.

76. Anon. Combination therapy is most appropriate for acute mania. *Drugs Ther Perspect* 1995;**6**:12–14.

77. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. *Can J Psychiatry* 1998;**43**:73–7.

78. Baker RW, Kinon BJ, Liu H, Richey A, Hill AL, Bergstrom RF, *et al*. Effectiveness of rapid initial dose escalation of oral olanzapine for acute agitation [meeting abstract]. In *Meeting of American Psychiatric Association*, 18–23 May 2002, Philadelphia, PA, USA.

79. Baker RW, Tohen M, Risser RC, Stauffer VL, Breier A, Tollefson GD. Depression during mania: treatment response to olanzapine or placebo [meeting abstract]. *Eur Neuropsychopharmacol* 2000;**10**:S246.

80. Baker RW, Milton DR, Tohen M, Stauffer VL, Breier A. Olanzapine is not associated with exacerbation of bipolar mania [meeting abstract]. *Biol Psychiatry* 2001;**49** (Suppl 8):43S.

81. Baker RW, Milton DR, Tohen MF, Stauffer VL, Breier AF. Olanzapine is not associated with exacerbation of bipolar mania [meeting abstract]. In *52nd Meeting of Institute on Psychiatric Services*, 25–29 October 2000, Philadelphia, PA.

82. Baker CB, Woods SW, Sernyak MJ. Cost-effectiveness of divalproex versus lithium. *J Clin Psychiatry* 1997;**58**:363–4.

83. Bares M, Hrdlicka M, Propper L. Atypical neuroleptic drug, olanzapine, in the treatment of impaired mood. *Prakt Lek* 2000;**80**:329–32.

84. Berney A, Bryois C. Treatment of acute mania using valproate: open study. *Schweiz Arch Neurol Psychiatr* 1999;**150**:233–7.

85. Beyzarov EP. Antipsychotic drug receives indication for bipolar disorder. *Drug Topics* 2000; **144**:29.

86. Bhana N, Perry CM. Olanzapine: a review of its use in the treatment of bipolar I disorder. *CNS Drugs* 2001;**15**:871–904.

87. Bowden CL, Swann AC, Calabrese JR, McElroy SL, Morris D, Petty F, *et al*. Maintenance clinical trials in bipolar disorder: design implications of the divalproex–lithium–placebo study. *Psychopharmacol Bull* 1997;**33**:693–9.

88. Bowden CL. Dosing strategies and time course of response to antimanic drugs. *J Clin Psychiatry* 1996;**57** (Suppl 13):4–9; discussion, 10–12.

89. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, *et al*. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry* 2000;**57**:481–9.

90. Bowden CL. Efficacy of divalproex vs lithium and placebo in mania: in reply. *JAMA* 1994;**272**:1006. Available at http://jama ama-assn org/

91. Brasfield KH. Pilot study of divalproex sodium versus valproic acid: drug acquisition costs versus all related costs. *Curr Ther Res Clin Exp* 1999; **60**:138–44.

92. Brown WA. A correction: efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. *Arch Gen Psychiatry* 2002;**59**:91.

93. Brown S, Nejtek VA, Perantie DC, Bobadilla L. Quetiapine in patients with bipolar disorder and cocaine dependence. *Biol Psychiatry* 2001;**49**:178.

94. Calabrese JR, Shelton MD, Rapport DJ, Kujawa M, Kimmel SE, Caban S. Current research on rapid cycling bipolar disorder and its treatment. *J Affect Disord* 2001;**67**:241–55.

95. Calabrese JR, Markovitz PJ, Kimmel SE, Wagner SC. Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. *J Clin Psychopharmacol* 1992;**12**(Suppl.):53–6.

96. Carroll BT, Thalassinos A, Fawver JD. Loading strategies in acute mania. *CNS Spectr* 2001; **6**:919–22, 930.

97. Cavazzoni P, Berg PH, Baker RW, Evans AR, Tohen M. Extrapyramidal symptoms of olanzapine versus placebo or haloperidol in the treatment of acute mania and contrasts to schizophrenia. *Schizophr Res* 2002;**53**:169–70.

98. Chou JY. Drug treatment of acute mania. *Drugs Today* 1992;**28**:119–30.

99. Conney J, Kaston B. Pharmacoeconomic and health outcome comparison of lithium and divalproex in a VA geriatric nursing home population: influence of drug-related morbidity on total cost of treatment. *Am J Manag Care* 1999; **5**:197–204.

100. Cookson J. Use of antipsychotic drugs and lithium in mania. *Br J Psychiatry* 2001;**178** (Suppl 41):s148–56.

101. Dalkilic A, Diaz E, Baker CB, Pearsall HR, Woods SW. Effects of divalproex versus lithium on length of hospital stay among patients with bipolar disorder. *Psychiatr Serv* 2000;**51**:1184–6.

102. Dardennes RM, Even C. Is divalproex a cost-effective alternative in the acute and prophylactic treatment of bipolar I disorder? *J Clin Psychiatry* 1997;**58**:495–6.

103. David SR, Battaglia J, Alaka K, Meehan K, Wright P. Calming versus sedative effects of IM olanzapine in agitated patients [meeting abstract]. *Biol Pyschiatry* 2002;**51**:197S.

104. Davis JM, Wang Z, Janicak PG. A quantitative analysis of clinical drug trials for the treatment of

affective disorders. *Psychopharmacol Bull* 1993; **29**:175–81.

105. Dose M, Emrich HM. Acute mania: practical therapeutic guidelines. *CNS Drugs* 1995;**3**:427–35.

106. Dunayevich E. Quetiapine in the treatment of mania. *Schizophr Res* 2001;**49**:226.

107. Dunayevich E, Strakowski SM. Quetiapine for treatment-resistant mania. *Am J Psychiatry* 2000; **157**:1341.

108. Dunayevich E, McElroy SL. Atypical antipsychotics in the treatment of bipolar disorder: pharmacological and clinical effects. *CNS Drugs* 2000;**13**:433–41.

109. Ellenor G, Lohr JB, Ito M, Dishman B, Gammariello A. The comparative efficacy of divalproex low and high serum level in bipolar disorder and schizophrenia. *New Clinical Drug Evaluation Unit Meeting* 1995;563.

110. Emrich HM, Gunther R, Dose M. Current perspectives in the pharmacopsychiatry of depression and mania. *Neuropharmacology* 1983; **22**:385–8.

111. Falsetti AE. Olanzapine: psychopharmacology, clinical efficacy, and adverse effects. *Hosp Pharm* 1999;**34**:423–35.

112. Feldstein JH, Curtis JL. Update on the costs of Depakote and Depakene. *Ment Retard* 1995;**33**:62.

113. Fellows L, Jones M, Mehnert A. Inpatient treatment of bipolar disorder: a comparison of outcomes with risperidone and olanzapine [meeting abstract]. *Eur Neuropsychopharmacol* 2001; **11** (Suppl 3):S249.

114. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J Clin Psychiatry* 2002;**63**:442–6.

115. Frazier JA, Biederman J, Jacobs TG, Tohen MF, Toma V, Feldman PD, *et al*. Olanzapine in the treatment of bipolar-disorder in juveniles. *Schizophr Res* 2000;**41**:B49.

116. Frazier JA, Tohen M, Biederman J, Jacobs T, Toma V, Feldman P. Olanzapine in the treatment of juvenile bipolar disorder. *Int J Neuropsychopharmacol* 2000;**3** (Suppl 1):S330.

117. Frye MA, Altshuler LL, Szuba MP, Finch NN, Mintz J. The relationship between antimanic agent for treatment of classic or dysphoric mania and length of hospital stay. *J Clin Psychiatry* 1996; **57**:17–21.

118. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry* 1992;**149**:108–11.

119. Garza-Trevino ES. Alternatives to lithium therapy in the treatment of acute mania. *Drugs Today* 1998; **34**:295–305.

120. Geddes J, Goodwin G. Bipolar disorder: clinical uncertainty, evidence-based medicine and large-scale randomised trials. *Br J Psychiatry* 2001; **178** (Suppl 41):s191–4.

121. Gerner RH, Stanton A. Algorithm for patient management of acute manic states: lithium, valproate, or carbamazepine? *J Clin Psychopharmacol* 1992;**12**:57s–63s.

122. Ghaemi SN. New treatments for bipolar disorder: the role of atypical neuroleptic agents. *J Clin Psychiatry* 2000;**61** (Suppl 14):33–42.

123. Ghaemi SN, Sachs GS, Goodwin FK. Divalproex vs. lithium in the treatment of bipolar disorder. *Biol Psychiatry* 1999;**45**:204.

124. Ghaemi N. Erratum: the use of quetiapine for treatment-resistant bipolar disorder (*Annals of Clinical Psychiatry* (1999) **11** (137–140)). *Ann Clin Psychiatry* 2000;**12**:63.

125. Ghaemi SN, Katzow JJ. The use of quetiapine for treatment-resistant bipolar disorder: a case series. *Ann Clin Psychiatry* 1999;**11**:137–40.

126. Goldberg JF, Altshuler LL, Frye M, Keck PE, Jr. Pharmacoeconomics of lithium and divalproex sodium in the treatment of bipolar disorder. In Powell SM, editor. *The Hatherleigh guide to psychopharmacology*. New York: Hatherleigh Press; 1999. pp. 141–67.

127. Goodwin G. Drug treatment in mania. *Prescr J* 1994;**34**:19–26.

128. Haddad P, Chaudhry I, Soni S. Adjunctive use of olanzapine in the treatment of mania. *Int J Psychiatry Clin Pract* 1999;**3**:213–15. Available at www.tandf.co.uk/journals/md/13651501.html

129. Hamilton D. Medical minute. Zyprexa offers hope in the treatment of manic depression. *Los Angeles Times* 4 December 2000;Sect. S3.

130. Hellewell JSE. A continuing role for antipsychotics in the treatment of bipolar disorders: the story so far. *Continuing Professional Development Bull Psychiatry* 2000;**2**:107–14.

131. Hilger E, Barnas C. Atypical antipsychotics in the treatment of bipolar affective disorders. *Fortschr Neurol Psychiatr* 2002;**70**:234–42.

132. Hilty DM, Brady KT, Hales RE. A review of bipolar disorder among adults. *Psychiatr Serv* 1999; **50**:201–13.

133. Hirschfeld RM, Weisler RH, Keck PE, Ahern E, Revicki D. Cost-effectiveness evaluation of divalproex sodium versus lithium in the treatment of bipolar disorder [meeting abstract]. In *152nd Annual Meeting of the American Psychiatric Association*, 15–20 May 1999, Washington, DC; 1999. pp. 262–3.

134. Icovino J, Haddad H, Detoledo J. Carbamazepine and sodium divalproex in the treatment of bipolar and schizoaffective disorders in the mentally retarded: a prospective study. *Neurology* 1994; **44** (Suppl 2):A401.

135. Jacobsen FM, Comas-Diaz L. Dose-severity responses to divalproex in bipolar illness [meeting abstract]. *Clin Pharmacol Ther* 1995;**57**:207.

136. Jagadheesan K. Olanzapine in acute bipolar mania. *Arch Gen Psychiatry* 2002;**59**:188.

137. James ACD, Javaloyes AM. Practitioner review: the treatment of bipolar disorder in children and adolescents. *J Child Psychol Psychiatry* 2001; **42**:439–49.

138. Janicak PG, Newman RH, Davis JM. Advances in the treatment of mania and related disorders: a reappraisal. *Psychiatr Ann* 1992;**22**:92–103.

139. Jann MW, Garrelts JC, Ereshefsky L, Saklad SR. Alternative drug therapies for mania: a literature review. *Drug Intell Clin Pharm* 1984;**18**:577–89.

140. Janowsky DS. New treatments of bipolar disorder. *Curr Psychiatry Rep* 1999;**1**:111–13.

141. Jonnalagada JR, Norton JW. Acute dystonia with quetiapine. *Clin Neuropharmacol* 2000;**23**:229–30.

142. Kafantaris V. Treatment of bipolar disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1995;**34**:732–41.

143. Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM. Adjunctive antipsychotic treatment of adolescents with bipolar psychosis. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:1448–56.

144. Kaiser CJ, Beyer JL, Siegel A, Kennedy JS, Tohen K, Berg P, *et al*. Olanzapine, divalproex, and placebo treatment comparison of older adult acute mania. *Am J Geriatr Psychiatry* 2002;**10**:99.

145. Keck PE Jr, McElroy SL. Clinical pharmacodynamics and pharmacokinetics of antimanic and mood-stabilizing medications. *J Clin Psychiatry* 2002;**63**:3–11.

146. Keck PE, Jr, McElroy SL, Stanton SP, Bennett JA. Pharmacoeconomic aspects of the treatment of bipolar disorder. *Psychiatr Ann* 1996; **26** (7 Suppl):S449–53.

147. Keck PE, Jr, McElroy SL, Bennett JA. Health-economic implications of the onset of action of antimanic agents. *J Clin Psychiatry* 1996; **57** (Suppl 13):13–18; discussion, 19–22.

148. Keck PE, Martin J, Thomas JH, Allen MH, Hirschfeld RM, Sommerville K. Safety and efficacy of oral loading divalproex sodium in acutely manic bipolar patients [meeting abstract]. In *152nd Annual Meeting of the American Psychiatric Association*, 15–20 May 1999, Washington, DC p. 192.

149. Keck PE, Jr, Welge JA, McElroy SL, Arnold LM, Strakowski SM. Placebo effect in randomized, controlled studies of acute bipolar mania and depression. *Biol Psychiatry* 2000;**47**:748–55.

150. Keck PE, Jr, McElroy SL, Strakowski SM, Soutullo CA. Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. *J Clin Psychiatry* 2000;**61** (Suppl 4):33–8.

151. Keck PE, Jr, Mendlwicz J, Calabrese JR, Fawcett J, Suppes T, Vestergaard PA, *et al*. A review of randomized, controlled clinical trials in acute mania. *J Affect Disord* 2000;**59** (Suppl 1):S31–7.

152. Kennedy JS, Bymaster FP, Schuh L, Calligaro DO, Nomikos G, Felder CC, *et al*. A current review of olanzapine's safety in the geriatric patient: from pre-clinical pharmacology to clinical data. *Int J Geriatr Psychiatry* 2001;**16** (Suppl 1):S33–61.

153. Kerwin R. Olanzapine was more effective than lorazepam at 2 hours but not at 24 hours in bipolar mania with acute agitation. *Evid Based Ment Health* 2002;**5**:18.

154. Ketter TA, Wang PW, Winsberg ME, Sachs N, Tate DL, Strong CM, *et al*. Baseline hypofrontality and divalproex response in bipolar disorders. *Biol Psychiatry* 2000;**47**:412.

155. Kravitz HM, Fawcett J. Efficacy of divalproex vs lithium and placebo in mania. *JAMA* 1994; **272**:1005–6.

156. Kupka RW, Nolen WA, Altshuler LL, Denicoff KD, Frye MA, Leverich GS, *et al*. The Stanley Foundation Bipolar Network. 2. Preliminary summary of demographics, course of illness and response to novel treatments. *Br J Psychiatry* 2001; **178** (Suppl 41):s177–83.

157. Lacerda ALT, Soares JC, Tohen M. The role of atypical antipsychotic agents in the treatment of bipolar disorder: a literature review. *Rev Bras Psiquiatr* 2002;**24**:34–43.

158. Lemoine P, Fondarai J, Faivre T. Valpromide increases amplitude of heart rate circadian rhythm in remitted bipolar and unipolar disorders: a placebo-controlled study. *Eur Psychiatry* 2000; **15**:424–32.

159. Levine J, Chengappa KNR, Parepally H. Side effect profile of enteric-coated divalproex sodium versus valproic acid. *J Clin Psychiatry* 2000; **61**:680–1.

160. Licht RW. Drug treatment of mania: a critical review. *Acta Psychiatr Scand* 1998;**97**:387–97.

161. Licht RW. Typical and atypical antipsychotics in bipolar disorder. *Acta Neuropsychiatr* 2000; **12**:115–19.

162. Licht RW. Limitations in randomised controlled trials evaluating drug effects in mania. *Eur Arch Psychiatry Clin Neurosci* 2001;**251**:66–71.

163. Madhusoodanan S, Sinha S, Brenner R, Gupta S, Bogunovic O. Use of olanzapine for elderly patients with psychotic disorders: a review. *Ann Clin Psychiatry* 2001;**13**:201–13.

164. Masand PS, Wang X, Manjooran J, Schwartz T, Saba M, Hardoby W, *et al*. Comparison of risperidone and olanzapine in bipolar and schizoaffective disorders [meeting abstract]. *Biol Psychiatry* 2000;**47** (Suppl 8):90S.

165. Maggi JD, Halman MH. The effect of divalproex sodium on viral load: a retrospective review of HIV-positive patients with manic syndromes. *Can J Psychiatry* 2001;**46**:359–62.

166. Martinez JM, Russell JM, Hirschfeld RM. Tolerability of oral loading of divalproex sodium in the treatment of acute mania. *Depress Anxiety* 1998;**7**:83–6.

167. McClellan J, Werry J. Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder. American Academy of Child and Adolescent Psychiatry. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:157s–76s.

168. McElroy SL, Keck PE, Jr. Pharmacologic agents for the treatment of acute bipolar mania. *Biol Psychiatry* 2000;**48**:539–57.

169. Mehnert A, Jones M. Risperidone and olanzapine in inpatient treatment of bipolar disorder [meeting abstract]. *Eur Psychiatry* 2001; **17** (Suppl 1):105s.

170. Miller DS, Yatham LN, Lam RW. Comparative efficacy of typical and atypical antipsychotics as add-on therapy to mood stabilizers in the treatment of acute mania. *J Clin Psychiatry* 2001; **62**:975–80.

171. Milton DR, Baker RW, Stauffer VL, Tohen M, Breier A. Olanzapine is not associated with exacerbation of bipolar mania [meeting abstract]. In *Annual Meeting of the American Psychiatric Association*, 5–10 May 2001, New Orleans, LA.

172. Müller-Oerlinghausen B, Retzow A. Treatment of acute manic episodes with valproate as an adjunct to neuroleptic medication [meeting abstract]. In *9th Congress of the Association of European Psychiatrists*, 20–24 September 1998, Copenhagen. p. 204s.

173. Müller Oerlinghausen B, Retzow A, Henn FA, Giedke H, Walden J. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. European Valproate Mania Study Group. *J Clin Psychopharmacol* 2000;**20**:195–203.

174. Namjoshi MA, Rajamannar G, Jacobs T, Sanger TM, Risser R, Tohen MF, *et al*. Economic, clinical, and quality-of-life outcomes associated with olanzapine treatment in mania: results from a randomized controlled trial. *J Affect Disord* 2002; **69**:109–18.

175. Namjoshi M, Rajamannar G, Risser R, Tohen M, Breier A. Impact of olanzapine added to lithium or valproate on the quality of life of patients with bipolar disorder. *Int J Neuropsychopharmacol* 2000; **3** (Suppl 1):S235.

176. Namjoshi M, Rajamannar G, Jacobs T, Feldman P, Sanger T, Tohen M, *et al*. Clinical, humanistic, and economic outcomes associated with long-term treatment of mania with olanzapine [meeting abstract]. *Int J Neuropsychopharmacol* 2000; **3** (Suppl 1):S332.

177. Namjoshi M, Rajamannar G, Jacobs TG, Feldman PD, Sanger TM, Tohen MF, *et al*. Clinical, humanistic and economic outcomes associated with long-term olanzapine treatment of mania [meeting abstract]. In *153rd Annual Meeting of the American Psychiatric Association*, 13–18 May 2000, Chicago, IL.

178. Namjoshi M, Jacobs T, Sanger TM, Gannon KS, Tohen M, Breier A. Changes in health-related quality of life of patients with bipolar disorder treated with olanzapine. *Eur Neuropsychopharmacol* 1999;**9** (Suppl 5):S245–6.

179. Namjoshi M, Risser RC, Shi L, Edgell ET, Tohen MF, Breier AF. Impact of olanzapine added to lithium or valproate on the quality of life of patients with bipolar disorder. In *2001 Annual Meeting of the American Psychiatric Association*, 5–10 May 2001, New Orleans, LA.

180. Noaghiul S, Narayan M, Nelson JC. Divalproex treatment of mania in elderly patients. *Am J Geriatr Psychiatry* 1998;**6**:257–62.

181. Ozcan Y, Ozcan ME, Boztepe AV, Karlidag R. Akut manide lityum, karbamazepin ve sodyum valproatyn klinik etkinliginin karsylastyrylmasy: bir oen calysma [Comparison of the clinical efficacy of lithium, carbamazepine and sodium valproate in acute mania: preliminary results]. *Klin Psikofarmakol Buelt* 1999;**9**:203–7.

182. Ozcan ME, Boztepe AV. Lithium, carbamazepine and valproate in acute mania. *Klin Psikofarmakol Buelt* 2001;**11**:90–5.

183. Papatheodorou G, Kutcher SP. Divalproex sodium treatment in late adolescent and young adult acute mania. *Psychopharmacol Bull* 1993;**29**:213–19.

184. Papatheodorou G, Kutcher SP, Katic M, Szalai JP. The efficacy and safety of divalproex sodium in the treatment of acute mania in adolescents and young adults: an open clinical trial. *J Clin Psychopharmacol* 1995;**15**:110–16.

185. Piepho RW. Cardiovascular effects of antipsychotics used in bipolar illness. *J Clin Psychiatry* 2002;**63** (Suppl 4):20–3.

186. Poolsup N, Li Wan Po A, de Oliveira IR. Systematic overview of lithium treatment in acute mania. *J Clin Pharmacol Ther* 2000;**25**: 139–56.

187. Post RM, Denicoff KD, Frye MA, Leverich GS. Algorithms for bipolar mania. *Mod Probl Pharmacopsychiatry* 1997;**25**:114–45.

188. Price PL. Olanzapine to treat the acute mania of bipolar disorder. *S D J Med* 2000;**53**:523.

189. Procyshyn RM, Zerjav S. Drug utilization patterns and outcomes associated with in-hospital treatment with risperidone or olanzapine. *Clin Ther* 1998;**20**:1203–17.

190. Reddy YCJ, Srinath S. Juvenile bipolar disorder. *Acta Psychiatr Scand* 2000;**102**:162–70.

191. Rossler W. Cui bono or who needs health economics? *Psychiatr Prax* 2001:S29–31.

192. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. *Medication treatment of bipolar disorder 2000*. Minneapolis: Healthcare Information Programs, McGraw-Hill Healthcare Information Group; 2000.

193. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry* 2002;**159**:1146–54.

194. Sajatovic M, Gerhart C, Semple W. Association between mood-stabilizing medication and mental health resource use in the management of acute mania. *Psychiatr Serv* 1997;**48**:1037–41.

195. Sanger TM, Tohen M, Tollefson GD, McElroy SL, Greaney MG, Toma V. Olanzapine vs placebo in the treatment of acute Mania [meeting abstract]. *Schizophr Res* 1998;**29**:152.

196. Sanger T, Tohen MF, Jacobs T, Gannon KS, Greaney M, Tollefson GD. Long-term olanzapine treatment of mania [meeting abstract]. In *152nd Annual Meeting of the American Psychiatric Association*, 15–20 May 1999, Washington, DC. p. 190.

197. Sanger TM, Grundy SL, Gibson PJ, Namjoshi MA, Greaney MG, Tohen MF. Long-term olanzapine therapy in the treatment of bipolar I disorder: an open-label continuation phase study. *J Clin Psychiatry* 2001;**62**:273–81.

198. Sanger T, Tohen M, Tollefson G, David S, Greaney M. Olanzapine versus placebo in rapid-cycling bipolar disorder [meeting abstract]. *Eur Neuropsychopharmacol* 1998;**8** (Suppl 2):S227.

199. Schneider RK. Divalproex did not differ from placebo or lithium in preventing recurrence of new mood episodes in bipolar I disorder, remission phase. *Evid Based Ment Health* 2001;**4**:9.

200. Schwartz TL, Boylan D, Kuhles ID, Gupta S, Chengappa KNR, Parepally H, *et al*. Clinical effectiveness of divalproex sodium in lithium carbonate refractory Bipolar spectrum patients. *Pharmacy and Therapeutics* 2000;**25**:410–17.

201. Segal J, Walton S, Clark H, Berk M. Pharmacotherapy of mania: a review. *Int J Psychiatry Clin Pract* 2000;**4**:171–93.

202. Shi L, Zhu B, Namjoshi M, Tunis S, Baker R, Tohen M, *et al*. Improvement in health-related quality of life was associated with antidepressant property: evidence from an acute mania clinical trial of olanzapine versus divalproex [meeting abstract]. In *Annual Meeting of American Psychiatric Association*; 18–23 May 2002, Philadelphia, PA.

203. Solomon DA, Keitner GI, Miller IW, Shea MT, Keller MB. Course of illness and maintenance treatments for patients with bipolar disorder. *J Clin Psychiatry* 1995;**56**:5–13.

204. Solomon DA, Ryan CE, Keitner GI, Miller IW, Shea MT, Kazim A, *et al*. A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. *J Clin Psychiatry* 1997;**58**:95–9.

205. Steffens DC, Krishnan KR. Decision model for the acute treatment of mania. *Depress Anxiety* 1996; **4**:289–93.

206. Strakowski SM, DelBello MP, Adler CM. Comparative efficacy and tolerability of drug treatments for bipolar disorder. *CNS Drugs* 2001;**15**:701–18.

207. Swann AC. Prediction of treatment response in acute mania: controlled clinical trials with divalproex. *Encephale* 2001;**27**:277–9.

208. Tohen M, Chengappa KNR, Suppes T, Baker RW, Risser RC, Evans AR, *et al*. Olanzapine combined with mood stabilizers in prevention of recurrence in bipolar disorder: an 18 month study [meeting abstract]. In *23rd CINP Congress*; 23–27 June 2002, Montreal Collegium Internationale Neuro-Psychopharmacologium.

209. Tohen M, Zhang F, Taylor CC, Burns P, Zarate C, Sanger T, *et al*. A meta-analysis of the use of typical antipsychotic agents in bipolar disorder. *J Affect Disord* 2001;**65**:85–93.

210. Tohen M, Zhang F, Keck PE, Feldman PD, Risser RC, Tran PV, *et al*. Olanzapine versus haloperidol in schizoaffective disorder, bipolar type. *J Affect Disord* 2001;**67**:133–40.

211. Tohen M, Chengappa KNR, Suppes T, Baker RW, Risser RC, Evans AR, *et al*. Olanzapine versus haloperidol in the treatment of acute mania. *Biol Psychiatry* 2002;**51**:541.

212. Tohen M, Zarate CA, Jr. Antipsychotic agents and bipolar disorder. *J Clin Psychiatry* 1998; **59** (Suppl 1):38–48; discussion, 49.

213. Tohen M, Jacobs TG, Feldman PD. Onset of action of antipsychotics in the treatment of mania. *Bipolar Disord* 2000;**2**:261–8.

214. Tohen M, Grundy S. Management of acute mania. *J Clin Psychiatry* 1999;**60** (Suppl 5):31–4; discussion, 35–6.

215. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, *et al*. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Rev Psiquiatr Clin* 2001; **28**:218.

216. Tohen M, Risser R, Grundy SL. Olanzapine in acute bipolar mania: in reply. *Arch Gen Psychiatry* 2002;**59**:188.

217. Toren P, Laor N, Weizman A. Use of atypical neuroleptics in child and adolescent psychiatry. *J Clin Psychiatry* 1998;**59**:644–56.

218. Townes P, Swartz CM. Comparison of valproic acid and lithium in mania. *J Clin Psychiatry* 1997; **58**:273–4.

219. Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology* 2000;**150**:15–23.

220. Woods SW. The economic burden of bipolar disorder. *J Clin Psychiatry* 2000; **61** (Suppl 13):38–41.

221. Woods SW. Classic mania: treatment response to divalproex or lithium. *Arch Gen Psychiatry* 1998; **55**:1050.

222. Yatham LN, Kusumakar V, Parikh SV, Haslam DRS, Matte R, Sharma V, *et al*. Bipolar depression: treatment options. *Can J Psychiatry* 1997; **42** (Suppl 2):87s–91s.

223. Young LT, Joffe RT, Robb JC, MacQueen GM, Marriott M, Patelis Siotis I. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. *Am J Psychiatry* 2000;**157**:124–6.

224. Zarate CA, Jr, Tohen M, Narendran R, Tomassini EC, McDonald J, Sederer M, *et al*. The adverse effect profile and efficacy of divalproex sodium compared with valproic acid: a pharmacoepidemiology study. *J Clin Psychiatry* 1999;**60**:232–6.

225. Zhu B, Lage MJ, Shi L, Tunis S, Tohen M. Long-term quality-of-life and economic outcomes associated with the use of olanzapine versus divalproex for acute mania [meeting abstract]. *Eur Neuropsychopharmacol* 2001;**11** (Suppl 3):S260.

226. Tohen M, Sanger T, Tollefson GD, McElroy SL, Greaney MG, Toma V. Experience using olanzapine in the treatment of acute bipolar mania [meeting abstract]. In *151st Annual Meeting of the American Psychiatric Association*, 30 May–4 June 1998, Toronto. p. 306.

227. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Grundy SL, Greaney M, *et al*. Olanzapine versus placebo in the treatment of acute mania [meeting abstract]. *Eur Neuropsychopharmacol* 1998; **8** (Suppl 2):S178.

228. Sanger TM, Tohen M, Tollefson GD, Jacobs T, David S. Olanzapine vs. placebo in rapid-cycling bipolar disorder [meeting abstract]. *Schizophr Res* 1998;**29**:152.

229. Toben M, Zarate C, Jr, Sanger IM. A placebo-controlled trial of olanzapine in psychotic or non-psychotic acute mania [meeting abstract]. *Schizophr Res* 1998;**29**:204.

230. Tohen M, Jacobs T, Sanger TM, Grundy S, Greaney M, Toma V, *et al*. Safety of the novel antipsychotic olanzapine in the acute treatment of bipolar I disorder. *Schizophr Res* 1999;**1**:358.

231. Tohen M, Jacobs T, Gannon KS, Sanger TM, Greaney M, Toma V, *et al*. Long-term olanzapine treatment: cognitive and mood improvement in psychotic and nonpsychotic manic patients. *Schizophr Res* 1999;**36**:299.

232. Tohen M, Baker RW, Altshuler L, Zarate CA, Suppes T, Ketter TA, *et al*. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Biol Psychiatry* 2002;**51**:208.

233. Merideth C, Sommerville KW, Zajecka J, Tracy K, Swann AC, Sachs G, *et al*. Divalproex sodium vs. Olanzapine for the treatment of mania in bipolar disorder: effects on body weight change and related outcomes. In *39th Annual Meeting of the American College of Neuropsychopharmacology*, 10–14 December 2000, San Juan, Puerto Rico. Vanderbilt university Medical Center, American College of Neuropsychopharmacology; 2000. p. 258.

Appendix 1

Search strategy

MEDLINE: Silverplatter. CD-ROM. 1966–June 2002. 8 July 2002

The MEDLINE search covered the date range 1966 to June 2002. The search was carried out on 8 July 2002 and identified 660 records.

#1	explode "Bipolar-Disorder"/ all subheadings
#2	(bipolar* near2 disorder*) in ti,ab
#3	(bipolar* near2 depress*) in ti,ab
#4	(bipolar* near2 illness*) in ti,ab
#5	(bipolar* near2 disease*) in ti,ab
#6	(bipolar* near2 episod*) in ti,ab
#7	mania in ti,ab
#8	manic in ti,ab
#9	(hypomanic or hypomania) in ti,ab
#10	cyclothym* in ti,ab
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12	olanzapine in ti,ab,pn
#13	(zyprex* or lanzac or midax or olansek) in ti,ab,pn
#14	(LY170053 or LY 170053) in ti,ab
#15	132539-06-1 in cas
#16	quetiapine in ti,ab,pn
#17	seroquel in ti,ab,pn
#18	(ICI 204 636 or ICI 204636 or ICI204636) in ti,ab
#19	(111974-69-7 or 111974-72-2) in cas
#20	"Valproic-Acid"/ all subheadings
#21	valproate in ti,ab,pn
#22	valproi* in ti,ab,pn
#23	(divalproex or divalproate) in ti,ab,pn
#24	(depakote or depacon or depakene or depakin) in ti,ab,pn
#25	(epival or ergenyl) in ti,ab,pn
#26	(76584-70-8 or 99-66-1) in cas
#27	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28	#11 and #27
#29	tg=animal
#30	tg=human
#31	#29 not (#29 and #30)
#32	#28 not #31

EMBASE: Silverplatter. CD-ROM. 1980–June 2002. 8 July 2002

The EMBASE search covered the date range 1980 to June 2002. The search was carried out on 8 July 2002 and identified 1456 records.

#1	explode "manic-depressive-psychosis"/ all subheadings
#2	explode "mania"/ all subheadings
#3	(bipolar* near2 disorder*) in ti,ab
#4	(bipolar* near2 depress*) in ti,ab
#5	(bipolar* near2 illness*) in ti,ab
#6	(bipolar* near2 disease*) in ti,ab
#7	(bipolar* near2 episod*) in ti,ab
#8	mania in ti,ab
#9	manic in ti,ab
#10	(hypomanic or hypomania) in ti,ab
#11	cyclothym* in ti,ab
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	"olanzapine"/ all subheadings
#14	olanzapine in ti,ab,rn,mn
#15	(zyprex* or lanzac or olansek or midax) in ti,ab,tn,mn
#16	(LY170053 or LY 170053) in ti,ab,tn
#17	132539-06-1 in rn
#18	"quetiapine"/ all subheadings
#19	quetiapine in ti,ab,rn,mn
#20	seroquel in ti,ab,tn,mn
#21	(ICI 204 636 or ICI 204636) in ti,ab,tn
#22	(111974-69-7 or 111974-72-2) in rn
#23	"valproate-semisodium"/ all subheadings
#24	"valproic-acid"/ all subheadings
#25	valproate in ti,ab,rn,mn
#26	valproi* in ti,ab,rn,mn
#27	(divalproex or divalproate) in ti,ab,tn,mn
#28	(depakote or depacon or depakene or depakin) in ti,ab,tn,mn
#29	(epival or ergenyl) in ti,ab,tn,mn
#30	(76584-70-8 or 99-66-1) in rn
#31	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	#12 and #31

#33 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep) in ti,ab,su
#34 (explode "animal"/ all subheadings) or (explode "animal experiment"/ all subheadings)
#35 "nonhuman"/ all subheadings
#36 (explode "human"/ all subheadings) or (explode "human experiment"/ all subheadings)
#37 #33 or #34 or #35
#38 #37 not (#37 and #36)
#39 #32 not #38

PsycINFO: Silverplatter. CD-ROM. 1887–May 2002. 9 July 2002

The PsycINFO search covered the date range 1887 to May 2002. The search was carried out on 9 July 2002 and identified 552 records.

#1 explode "Bipolar-Disorder"
#2 explode "Mania"
#3 (bipolar* near2 disorder*) in ti,ab
#4 (bipolar* near2 depress*) in ti,ab
#5 (bipolar* near2 illness*) in ti,ab
#6 (bipolar* near2 disease*) in ti,ab
#7 (bipolar* near2 episod*) in ti,ab
#8 mania in ti,ab
#9 manic in ti,ab
#10 (hypomanic or hypomania) in ti,ab
#11 cyclothym* in ti,ab
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 olanzapine in ti,ab
#14 (zyprex* or lanzac or midax or olansek) in ti,ab
#15 quetiapine in ti,ab
#16 seroquel in ti,ab
#17 "Valproic-Acid" in DE
#18 valproate in ti,ab
#19 valproi* in ti,ab
#20 (divalproex or divalproate) in ti,ab
#21 (depakote or depacon or depakene or depakin) in ti,ab
#22 (epival or ergenyl) in ti,ab
#23 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24 #12 and #23

Cumulative Index to Nursing and Allied Health Literature (CINAHL): Silverplatter. CD-ROM. 1982–May 2002. 9 July 2002

The CINAHL search covered the date range 1982 to May 2002. The search was carried out on 9 July 2002 and identified 32 records.

#1 explode "Bipolar-Disorder"/ all subheadings
#2 (bipolar* near2 disorder*) in ti,ab
#3 (bipolar* near2 depress*) in ti,ab
#4 (bipolar* near2 illness*) in ti,ab
#5 (bipolar* near2 disease*) in ti,ab
#6 (bipolar* near2 episod*) in ti,ab
#7 mania in ti,ab
#8 manic in ti,ab
#9 (hypomanic or hypomania) in ti,ab
#10 cyclothym* in ti,ab
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 olanzapine in ti,ab
#13 (zyprex* or lanzac or midax or olansek) in ti,ab
#14 quetiapine in ti,ab
#15 seroquel in ti,ab
#16 "Valproic-Acid"/ all subheadings
#17 valproate in ti,ab
#18 valproi* in ti,ab
#19 (divalproex or divalproate) in ti,ab
#20 (depakote or depacon or depakene or depakin) in ti,ab
#21 (epival or ergenyl) in ti,ab
#22 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 #11 and #22

BIOSIS-Web: EDINA. Internet. 1985–June 2002. 9 July 2002

The BIOSIS search covered the date range 1985 to June 2002. The search was carried out on 9 July 2002 and identified 552 records.

((bipolar* n2 disorder*) or (bipolar* n2 depress*) or (bipolar* n2 illness*) or (bipolar* n2 disease*) or (bipolar* n2 episod*) or mania or manic)) and (olanzapine or zyprex* or quetiapine or seroquel or valproate or valproi* or divalproex or depakote)

NHS Economic Evaluation Database (NHS EED): NHS Centre for Reviews and Dissemination internal database, CAIRS. 1994–June 2002. 9 July 2002

The NHS EED search covered the date range 1994 to June 2002. The search was carried out on 9 July 2002 and identified 11 records.

s1 s bipolar$(2w)disorder$
s2 s bipolar$(2w)depress$
s3 s bipolar$(2w)illness$
s4 s bipolar$(2w)disease$
s5 s bipolar$(2w)episod$
s6 s mania or manic
s7 s s1 or s2 or s3 or s4 or s5 or s6
s8 s olanzapine or zyprex$ or lanzac or midax or olansek
s9 s quetiapine or seroquel
s10 s valproate or valproi$ or divalproex or depakote
s11 s s8 or s9 or s10
s12 s s7 and s11

Health Economic Evaluations Databases (HEED): OHE-IFPMA Database Ltd. CD-ROM. 1995–June 2002. 9 July 2002

The HEED search covered the date range 1995 to June 2002. The search was carried out on 9 July 2002 and identified eight records.

(bipolar$ disorder$ or bipolar$ depress$ or bipolar$ illness$ or bipolar$ disease$ or bipolar$ episod$ or mania or manic) and (olanzapine or zyprex$ or quetiapine or seroquel or valproate or valproi$ or divalproex or depakote)

Cochrane Controlled Trials Register (CCTR): Cochrane Library, 2002:2. CD-ROM. 9 July 2002

The CCTR search was carried out on 9 July 2002 and identified 140 records.

#1 BIPOLAR-DISORDER*:ME
#2 (BIPOLAR* near DISORDER*)
#3 (BIPOLAR* near DISEASE*)
#4 (BIPOLAR* near ILLNESS*)
#5 (BIPOLAR* near DEPRESS*)
#6 (BIPOLAR* near EPISOD*)
#7 MANIA
#8 MANIC
#9 (HYPOMANIC or HYPOMANIA)
#10 CYCLOTHYM*
#11 (((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10)
#12 (OLANZAPINE or ZYPREX*)
#13 (QUETIAPINE or SEROQUEL)
#14 VALPROIC-ACID*:ME
#15 (VALPROATE or VALPROI*)
#16 (DIVALPROEX or DEPAKOTE)
#17 ((((#12 or #13) or #14) or #15) or #16)
#18 (#11 and #17)

Latin American and Caribbean Health Sciences (LILACS): Virtual Health Library (VHL). Internet. 1980–June 2002. 9 July 2002

The LILACS search covered the date range 1980 to June 2002. The search was carried out on 9 July 2002 and identified 14 records.

(bipolar$ disorder$ or bipolar$ depress$ or bipolar$ illness$ or bipolar$ disease$ or bipolar$ episod$ or mania or manic) and (olanzapine or zyprex$ or quetiapine or seroquel or valproate or valproi$ or divalproex or depakote)

Science Citation Index (SciSearch): ISI Web of Science. Internet. 1981–June 2002. 10 July 2002

The SciSearch search covered the date range 1981 to June 2002. The search was carried out on 10 July 2002 and identified 673 records.

(bipolar* disorder* or bipolar* depress* or bipolar* illness* or bipolar* disease* or bipolar* episod* or mania or manic) and (olanzapine or zyprex* or quetiapine or seroquel or valproate or valproi* or divalproex or depakote)

Internet resources

A number of Internet sites were searched for further information about bipolar disorder.

'Bipolar Disorder', 'Manic Depression', 'olanzapine', 'quetiapine' and 'divalproex' were used as search terms.

The results were not particularly useful. The sites found on Alta Vista and Google had already been found on Copernic. Nearly all sites provided information about what Bipolar Disorder is and how to treat it, how to live with it and where to find help. There was very little about relevant research.

A number of background information pages, leaflets and some American-based guidelines were printed off or saved as HTML files.

Copernic
http://www.copernic.com
This site was searched on 11 July 2002 and was limited to the first 100 hits.

Google
http://www.google.com/
This site was searched on 12 July 2002 and all relevant hits had already been retrieved on Copernic.

Alta Vista
http://www.altavista.com/
This site was searched on 12 July 2002 and all relevant hits had already been retrieved.

OMNI
http://omni.ac.uk/
This site was searched on 12 July 2002 and had seven relevant hits, most having already been retrieved.

The Royal College of Psychiatrists
http://www.rcpsych.ac.uk/index.htm
This site was searched on 16 July 2002 and found useful background information.

American Psychiatric Association
http://www.psych.org/index.cfm
This site was searched on 16 July 2002 and found some useful guidelines.

National Institute of Mental Health
http://www.nimh.nih.gov/home.cfm/
This site was searched on 16 July 2002 and provided background information, research information and further links.

National Depressive and Manic Depressive Association (NDMDA)
http://www.ndmda.org/
This site was searched on 16 July 2002 and provided background information and research news.

The search results from BIOSIS, CCTR, CINAHL, EMBASE, HEED, LILACS, MEDLINE, NHS EED, PsycINFO and SciSearch were downloaded and imported into Endnote (ISI ReSearchSoft, USA) reference management software and duplicate records were deleted.

The search results from the Internet were printed or saved as HTML files.

Appendix 2
Excluded studies

Study	Bipolar acute manic episode?	Olanzapine, quetiapine or valproate semisodium?	Systematic review?	RCT?	Economic evaluation?	Reason for exclusion
Allen, 1998[72]	Yes	Yes	No	No	No	Case report
Angst, 2001[1]	No	No	No	No	No	Guidelines for efficacy trials in bipolar disorder
Anon., 2000[73]	No	No	No	No	No	Brief company report
Anon., 1994[74]	Yes	Yes	No	No	No	Report of results of Bowden 1994
Anon., 2001[75]	Yes	Yes	No	No	No	Non-systematic review of disodium valproate (Depakote)
Anon., 1995[76]	Yes	Yes	No	No	No	Non-systematic review of drugs for acute mania
Baetz, 1998[77]	No	Yes	No	Yes	No	People with panic disorder and mood instability. $N = 10$
Baker, 2002[78]	No	Yes	No	Yes	No	Non bipolar mania participants
Baker, 2000[79]	Yes	Yes	No	No	No	Non-systematic review
Baker, 2001[80]	Yes	Yes	No	No	No	Non-systematic review
Baker, 2000[81]	Yes	Yes	No	No	No	Non-systematic review
Baker, 1997[82]	Yes	Yes	No	No	No	Critique of an economic model of valproate semisodium (Keck 1996)
Bares, 2000[83]	Yes	Yes	No	No	No	Non-systematic review of olanzapine use in mood disorders. In Czech
Berney, 1999[84]	Yes	No	No	No	No	No control group. Does not state whether sodium or semisodium valproate
Beyzarov, 2000[85]	Yes	Yes	No	No	No	Report on olanzapine receiving a licence for bipolar mania
Bhana, 2001[86]	Yes	Yes	Yes	No	No	Review
Bowden, 1997[87]	No	Yes	No	No	No	Discusses methodology of long-term maintenance studies in bipolar disorder
Bowden, 1996[88]	Yes	No	No	No	No	Non-systematic review of dosing strategies
Bowden, 2000[89]	No	Yes	No	Yes	No	Maintenance treatment not mania
Bowden, 1994[90]	Yes	Yes	No	No	No	Letter, reply to critique of Bowden 1994
Brasfield, 1999[91]	No	Yes	No	No	No	Economic study but not acute mania, timescale unclear
Brown, 2002[92]	No	Yes	No	No	No	Letter to editor
Brown, 2001[93]	No	Yes	No	No	No	Not specifically acute mania, no control group

continued

Study	Bipolar acute manic episode?	Olanzapine, quetiapine or valproate semisodium?	Systematic review?	RCT?	Economic evaluation?	Reason for exclusion
Calabrese, 2001[94]	No	Yes	No	No	No	Non-systematic review of rapid cycling bipolar disorder
Calabrese, 1995[95]	Yes	No	No	No	No	Retrospective chart review of adverse effects. Does not say whether valproate sodium or semisodium
Carroll, 2001[96]	Yes	Yes	No	No	No	Non-systematic review of loading strategies in acute mania
Cavazzoni, 2002[97]	Yes	Yes	No	No	No	Non-systematic review
Chou, 1992[98]	Yes	No	No	No	No	Non-systematic review of drug treatments for acute mania, out of date
Conney, 1999[99]	Yes	Yes	No	No	No	Retrospective review of geriatric patients treated with lithium or valproate semisodium.
Cookson, 2001[100]	Yes	Yes	No	No	No	Non-systematic review
Dalkilic 2000[101]	Yes	Yes	No	No	No	Serbian, probably not RCT
Daly, 1997[5]	Yes	No	No	No	No	Non-systematic review
Dardennes, 1997[102]	Yes	Yes	No	No	No	Critique of a pharmacoeconomic study[58]
Das Gupta, 2002[16]	No	No	No	No	No	Non-systematic review of economic costs of bipolar disorder (not mania)
David, 2002[103]	No	Yes	No	Yes	No	Non-manic participants
Davis, 1993[104]	Yes	Yes	Yes	No	No	A systematic review that includes only one trial of interest, i.e. Pope 1991[48]
Dinan, 2002[3]	Yes	Yes	No	No	No	Letter
Dose, 1995[105]	Yes	No	No	No	No	Non-systematic review of drug treatments for acute mania
Dunayevich, 2001[106]	Yes	Yes	No	No	No	No control group
Dunayevich, 2000[107]	Yes	Yes	No	No	No	Case report
Dunayevich, 2000[108]	Yes	Yes	No	No	No	Non-systematic review of atypical antipsychotics in bipolar disorder
Ellenor, 1995[109]	No	Yes	No	No	No	Non-randomised trial including non-manic patients
Emrich, 1983[110]	No	No	No	No	No	Non-systematic review of opioids in the treatment of depression and mania
Falsetti, 1999[111]	No	Yes	No	No	No	Non-systematic review of efficacy of olanzapine in schizophrenia
Feldstein, 1995[112]	No	Yes	No	No	No	Short report on price change of Depakote
Fellows, 2001[113]	No	Yes	No	No	Yes	Non-manic participants
Frankenburg, 2002[114]	No	Yes	No	Yes	No	Not acute mania, people with borderline personality disorder and comorbid bipolar II received the drug for 6 months
Frazier, 2000[115]	Yes	Yes	No	No	No	Non-randomised trial

continued

Study	Bipolar acute manic episode?	Olanzapine, quetiapine or valproate semisodium?	Systematic review?	RCT?	Economic evaluation?	Reason for exclusion
Frazier, 2000[116]	Yes	Yes	No	No	No	Non-RCT
Frye, 1996[117]	Yes	Yes	No	No	No	Non-RCT
Freeman, 1992[118]	Yes	No	No	Yes	No	Think it is about sodium valproate, not valproate semisodium
Garza-Trevino, 1998[119]	Yes	No	No	No	No	Non-systematic review of drugs for acute mania. Out of date
Geddes, 2001[120]	Yes	No	No	No	No	Methodology
Gerner, 1992[121]	Yes	No	No	No	No	Does not look at any drugs of interest
Ghaemi, 2000[122]	Yes	Yes	No	No	No	Non-systematic review of atypical antipsychotics in bipolar disorder
Ghaemi, 1999[123]	No	Yes	No	No	No	Non-randomised trial with non-manic patients
Ghaemi, 1999[124]	No	Yes	No	No	No	Erratum message relating to Ghaemi and Katzow[125]
Goldberg, 1999[126]	No	No	No	No	No	Economics paper – sodium not semisodium
Goodwin, 1994[127]	Yes	No	No	No	No	Non-systematic review of drug treatments in mania
Haddad, 1999[128]	Yes	Yes	No	No	No	Two case reports
Hamilton, 2000[129]	No	Yes	No	No	No	Newspaper question and answer article
Hellewell, 2000[130]	Yes	Yes	No	No	No	Non-systematic review of antipsychotics in all stages of bipolar disorder
Hilger, 2002[131]	No	Yes	No	No	No	Non-systematic review
Hilty, 1999[132]	No	No	No	No	No	Not a systematic review (despite MEDLINE search), of bipolar disorder among adults, all aspects
Hirschfeld 1999[133]	Yes	Yes	No	No	Yes	Arrived too late
Icovino, 1994[134]	No	Yes	No	No	No	Not acute mania (assessed over 18-month period), not randomised
Jacobsen, 1995[135]	No	Yes	No	No	No	Non-randomised trial with non-manic patients
Jagadheesan, 2002[136]	No	No	No	No	No	Commentary
James, 2001[137]	No	No	No	No	No	Non-systematic review of treatments for bipolar disorder
Janicak, 1992[138]	Yes	No	No	No	No	Non-systematic review of treatments for mania and related disorders (not of olanzapine, quetiapine or valproate semisodium)
Jann, 1984[139]	Yes	No	No	No	No	Non-systematic review on drug treatments for mania. Out of date
Janowsky, 1999[140]	Yes	Yes	No	No	No	Report of a conference abstract, olanzapine vs placebo, Tohen 1999[35]
Jonnalagada, 2000[141]	Yes	Yes	No	No	No	Two case reports of acute dystonia with quetiapine

continued

Study	Bipolar acute manic episode?	Olanzapine, quetiapine or valproate semisodium?	Systematic review?	RCT?	Economic evaluation?	Reason for exclusion
Kafantaris, 1995[142]	No	No	No	No	No	Non-systematic review of treatment of bipolar disorder in children and adolescents. No controlled studies of acute mania
Kafantaris, 2001[143]	Yes	No	No	No	No	Non-randomised and non-target intervention
Kaiser, 2002[144]	Yes	Yes	No	No	No	Pooled indirect comparisons presenting within-group treatment response to placebo, valproate semisodium and olanzapine
Keck, 2002[145]	Yes	Yes	No	No	No	Non-systematic review
Keck, 1996[146]	Yes	Yes	No	No	No	Non-systematic review of drug treatments for bipolar disorder
Keck, 1996[147]	Yes	No	No	No	No	Discussion paper of the issues related to health economic issues associated with antimanic agents
Keck, 1999[148]	Yes	Yes	No	Yes	No	Arrived too late
Keck, 2000[149]	Yes	No	Yes	No	No	Examines the placebo effect within RCTs of acute bipolar mania
Keck, 2000[150]	Yes	Yes	No	No	No	Non-systematic review of antipsychotics in mood disorders and risk of tardive dyskinesia
Keck, 2000[151]	Yes	Yes	No	No	No	Non-systematic review
Kennedy, 2001[152]	No	Yes	No	No	No	Technical non-systematic review of olanzapine in the elderly. Unclear what diagnosis they were looking at
Kerwin, 2002[153]	Yes	Yes	No	No	No	Commentary on Ref. 42
Ketter, 2000[154]	No	No	No	No	No	Non-randomised study investigating markers/predictors of divaproex response
Kravitz, 1994[155]	Yes	Yes	No	No	No	Letter, critique of Ref. 49
Kupka, 2001[156]	Yes	Yes	No	No	No	Non-systematic review
Lacerda, 2002[157]	Yes	Yes	No	No	No	Non-systematic review
Lemoine, 2000[158]	No	No	No	No	No	People with remitted recurrent bipolar or unipolar disorder. Valpromide
Levine, 2000[159]	Yes	Yes	No	No	No	Case report
Licht, 1998[160]	Yes	Yes	No	No	No	Non-systematic review of mania treatment
Licht, 2000[161]	Yes	Yes	No	No	No	Non-systematic review of drug treatment with antipsychotics for mania
Licht, 2001[162]	Yes	No	No	No	No	Discusses the methodological problems associated with randomised trials evaluating drug effects in mania
Madhusoodanan, 2001[163]	Yes	Yes	No	No	No	Non-systematic review of olanzapine in psychotic elderly

continued

Study	Bipolar acute manic episode?	Olanzapine, quetiapine or valproate semisodium?	Systematic review?	RCT?	Economic evaluation?	Reason for exclusion
Masand, 2000[164]	Yes	Yes	No	No	No	Non-RCT
Maggi, 2001[165]	No	Yes	No	No	No	Retrospective study of 15 patients with HIV-associated mania and the effects of valproate semisodium on viral load
Martinez, 1998[166]	Yes	Yes	No	No	No	Retrospective chart review
McClellan, 1997[167]	No	No	No	No	No	Non-systematic review of assessment and treatment of children and adults with bipolar disorder
McElroy, 2000[168]	Yes	Yes	No	No	No	Non-systematic review
McElroy, 1995[60]	Yes	No	No	No	No	Non-systematic review
Mehnert, 2001[169]	No	Yes	No	No	No	Non-manic participants
Miller, 2001[170]	Yes	Yes	No	No	No	Chart review
Milton 2001[171]	Yes	Yes	No	No	No	Pooled analysis from RCTs, not referenced
Müller-Oerlinghausen, 1998[172]	Yes	No	No	Yes	No	Examines the effectiveness of sodium valproate
Müller-Oerlinghausen, 2000[173]	Yes	No	No	Yes	No	Sodium valproate, not semisodium
Namjoshi, 2002[174]	Yes	Yes	No	Yes	Yes	Follow-up data
Namjoshi, 2000[175]	No	Yes	No	Yes	No	Non-manic patients
Namjoshi, 2000[176]	Yes	Yes	No	Yes	No	Not acute phase
Namjoshi, 2000[177]	Yes	Yes	No	Yes	No	Not acute phase
Namjoshi, 1999[178]	No	Yes	No	Yes	No	Bipolar disorder generally, rather than mania associated with bipolar disorder
Namjoshi 2001[179]	Yes	Yes	No	Yes	No	Non-manic patients
Noaghiul, 1998[180]	Yes	Yes	No	No	No	No control group
Ozcan, 1999[181]	Yes	Yes	No	No	No	Turkish, non-RCT
Ozcan, 2001[182]	Yes	No	No	Yes	No	Examines the effectiveness of sodium valproate and not valproate semisodium
Papatheodorou, 1993[183]	Yes	Yes	No	No	No	Preliminary report of a non-randomised trial
Paptheodorou, 1995[184]	Yes	Yes	No	No	No	No control group
Piepho, 2002[185]	No	Yes	No	No	No	Non-systematic review on cardiac side-effects of antipsychotics – may be useful for adverse effects?
Poolsup, 2000[186]	Yes	No	Yes	No	No	Evaluates the effectiveness of lithium
Post, 1997[187]	Yes	Yes	No	No	No	Guidelines on algorithms for treatment of mania
Price, 2000[188]	Yes	Yes	No	No	No	Short non-systematic review of olanzapine in acute mania

continued

Study	Bipolar acute manic episode?	Olanzapine, quetiapine or valproate semisodium?	Systematic review?	RCT?	Economic evaluation?	Reason for exclusion
Procyshyn, 1998[189]	No	Yes	No	No	No	Non-randomised trial including non-manic patients
Reddy, 2000[190]	No	No	No	No	No	Non-systematic review of bipolar disorder in young people
Rossler, 2001[191]	No	No	No	No	No	Not relevant intervention
Sachs, 2000[192]	Yes	No	No	No	No	Treatment guidelines
Sachs, 2002[193]	Yes	No	No	Yes	No	Non-relevant intervention
Sajatovic 1997[194]	Yes	Yes	No	No	No	Serbian, probably not RCT
Sanger, 1998[195]	Yes	Yes	No	No	No	Non-RCT
Sanger, 1999[196]	Yes	Yes	No	Yes	No	Continuation phase after acute phase RCT, no relevant outcomes
Sanger, 2001[197]	No	Yes	No	No	No	Continuation phase of an included RCT;[35] all patients were given olanzapine
Sanger, 1998[198]	No	Yes	No	Yes	No	Patients were rapid-cycling rather than manic
Schneider, 2001[199]	Yes	Yes	No	No	No	Commentary on Ref. 89
Schwartz, 2000[200]	Yes	Yes	No	No	No	Retrospective chart review
Segal, 2000[201]	Yes	Yes	No	No	No	Non-systematic review of drugs for mania
Shi, 2002[202]	Yes	Yes	No	Yes	No	Long-term data only, not acute phase
Solomon, 1995[203]	No	No	No	No	No	Non-systematic review of long-term treatments for bipolar disorder
Solomon, 1997[204]	No	Yes	No	Yes	No	Continuation and maintenance treatment, not acute mania
Steffens, 1996[205]	Yes	No	No	No	No	Decision model for acute treatment of mania – does not list olanzapine, quetiapine or valproate semisodium
Strakowski, 2001[206]	Yes	Yes	No	No	No	Non-systematic review of drugs for bipolar disorder
Swann, 2001[207]	Yes	Yes	No	No	No	Acute phase not randomised. RCT of continuation phase (not acute)
Tohen, 2002[208]	No	Yes	No	Yes	No	Non-manic participants
Tohen, 2001[209]	No	No	No	No	No	Non-systematic review of antipsychotic agents in the treatment of patients with bipolar disorder, and not mania only
Tohen, 2001[210]	No	Yes	No	Yes	Yes	Participants with schizoaffective disorder
Tohen, 2002[211]	No	Yes	No	Yes	No	Patients were not currently experiencing a manic episode
Tohen, 1998[212]	Yes	Yes	No	No	No	Non-systematic review of antipsychotics in bipolar affective disorder

continued

Study	Bipolar acute manic episode?	Olanzapine, quetiapine or valproate semisodium?	Systematic review?	RCT?	Economic evaluation?	Reason for exclusion
Tohen, 2000[213]	Yes	Yes	No	No	No	A non-systematic review of onset of action of antipsychotics in the treatment of mania
Tohen, 1999[214]	Yes	Yes	No	No	No	Non-systematic review of treatments for acute mania
Tohen, 2001[215]	Yes	Yes	No	No	No	Commentary (in Spanish?) on Ref. 36
Tohen, 2002[216]	Yes	Yes	No	No	No	Letter
Toren, 1998[217]	No	Yes	No	No	No	Non-systematic review of atypical antipsychotics in child and adolescent psychiatry
Townes, 1997[218]	Yes	No	No	No	No	Letter, critique of a study comparing lithium and valproic acid
Vasudev, 2000[219]	Yes	No	No	Yes	No	Carbamazepine vs sodium valproate
Woods, 2000[220]	No	No	No	No	Yes	Non-systematic review of the economic burden of bipolar disorder (not mania)
Woods, 1998[221]	Yes	No	No	No	No	Letter to editor
Yatham, 1997[222]	No	No	No	No	No	Non-systematic review of treatments for bipolar depression
Young, 2000[223]	No	Yes	No	Yes	No	Treatment of bipolar depression (not mania) with valproate semisodium
Zarate, 1999[224]	Yes	Yes	No	No	No	Retrospective study of patient records, valproate semisodium vs valproic acid. Majority had bipolar affective disorder but there were other diagnoses. Could be useful for adverse events
Zhu, 2001[225]	No	Yes	No	Yes	Yes	Data for maintenance rather than acute treatment

Appendix 3

Details about data extraction

Clinical effectiveness data

Clinical effectiveness data were extracted and entered into a Microsoft Access form under the headings given below. In the following lists, [ ] indicates a list of options included in a pull-down box, ( ) indicates a click on/off button, where on represents 'yes' and off 'no', and { } indicates free text entered in a box.

Study details

- name of trial {trial name, I.D. or 'not stated'}
- endnote reference {endnote reference number}
- primary source [database, handsearching, company submission]
- author {i.e. Jones *et al.*}
- date {i.e. year of publication or date of interim data collection}
- type of report [abstract, full manuscript, interim report]
- comparison group included [placebo, alternative drug, unclear, not stated]
- intervention {i.e. drug(s) name(s)}
- dose of intervention {dose}
- length of intervention {length}
- comments about interventions {summary of comments or 'none'}.

Participants

- disease status [ICD, DSM, not stated]
- previous treatment {summary of drugs or other treatments, or 'not applicable'}
- age or age range of participants {age(s)}
- other participant characteristics {summary of characteristics}
- comments about participants {summary of comments or 'none'}.

Numbers in conditions

- number recruited or accrued {summary or 'not stated'}
- length of follow-up after treatment finishes {summary or 'not stated'}
- number and times of follow-up measurements {summary or 'not stated'}
- attrition intervention {summary of number involved and reasons for loss}
- per protocol analysis performed [yes, no, not stated, unclear]
- comments {summary of comments or state 'none'}.

Results (data for all outcomes specified in the protocol will be entered in the following format)

- outcome 1 {description of outcome measure}
- intervention 1 baseline data {data for outcome 1}
- intervention 2 baseline data {data for outcome 1}
- intervention 1 follow-up data {data for outcome 1}
- intervention 2 follow-up data {data for outcome 1}
- comments on outcome 1 {summary of comments}
- overall comments {summary of comments}

Economic evaluation data

Economic evaluation data were extracted and entered into an Access form under the headings given below.

- endnote reference {in the form of xyz, no '#'}
- primary source [database, handsearching, company submission]
- author {i.e. Jones *et al.*}
- date {i.e. year of publication or date of interim data collection}
- type of economic evaluation [cost-effectiveness analysis, cost–utility analysis, cost–benefit analysis]
- currency used [$US, $AS, £Sterling … , not stated]
- year to which costs apply {enter year or not stated}
- perspective used {e.g. health service, societal, hospital, third-party payer, patient, unclear}
- study population {describe the population characteristics}
- intervention 1 {description of intervention 1}
- intervention 2 {description of intervention 2}
- source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]

- source of resource use data [single study, review/synthesis of previous studies, expert opinion, not stated]
- source of unit cost data [literature, data from actual source, combination of literature and data from actual source, not stated]
- link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected, …]
- clinical outcomes measured and methods of valuation used {summary of outcomes and valuation methods used}
- cost data handled appropriately {summary of methods used, e.g. to discount, inflate}
- modelling {summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs}
- outcome measures used in economic evaluations {summary of outcome measures used in economic evaluations, e.g. incremental cost-effectiveness ratio, net benefit, cost-effectiveness acceptability curve}
- direction of result with appropriate quadrant location
- statistical analysis for patient-level stochastic data {summary of analyses used}
- appropriateness of statistical analysis {comment on appropriateness}
- uncertainty around cost-effectiveness expressed
- appropriateness of method of dealing with uncertainty around cost-effectiveness
- sensitivity analysis {list summary of analysis}
- appropriateness of sensitivity analysis {comment on appropriateness}
- modelling inputs and techniques appropriate
- author's conclusions {list as in publication}
- implications for practice {summary of implications}
- comments {summary of comments}

Appendix 4

Quality assessment criteria for randomised controlled trials of clinical effectiveness

1. Was the method used to assign participants to the treatment groups really random? (*Computer-generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week.*)
2. Was the allocation of treatment concealed? (*Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque.*)
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
5. Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who were administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
13. Were the reasons for any withdrawals stated?
14. Was an intention to treat analysis included?

Items will be graded in terms of ✔ yes (item adequately addressed), ✘ no (item not adequately addressed), ✔/✘ partially (item partially addressed), **?** unclear or not enough information, **NA** not applicable or **NS** not stated.

Appendix 5

Quality assessment criteria for studies of cost-effectiveness

Study question

1. Costs and effects examined.
2. Alternatives compared.
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society).

Selection of alternatives

4. All relevant alternatives are compared (including do nothing if applicable).
5. The alternatives being compared are clearly described (who did what, to whom, where and how often).
6. The rationale for choosing the alternative programmes or interventions compared is stated.

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

Effectiveness data

9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion).
10. Effectiveness data from RCT or review of RCTs.
11. Potential biases identified (especially if data not from RCTs).
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).

Costs

13. All the important and relevant resource use included.
14. All the important and relevant resource use measured accurately (with methodology).
15. Appropriate unit costs estimated (with methodology).
16. Unit costs reported separately from resource-use data.
17. Productivity costs treated separately from other costs.
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and valuation

19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life years, QALYs, etc.).
20. Methods to value health states and other benefits are stated (e.g. time trade-off).
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.).

Decision modelling

22. Details of any decision model used are given (e.g. decision tree, Markov model).
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified.
24. All model outputs described adequately.

Discounting

25. Discount rate used for both costs and benefits.
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and confidence intervals are given for stochastic data.
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Deterministic analysis

34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis).
35. The choice of variables for sensitivity analysis is justified.
36. The ranges over which the variables are varied are stated.

Presentation of results

37. Incremental analysis is reported using appropriate decision rules.
38. Major outcomes are presented in both a disaggregated and an aggregated form
39. Applicable to the NHS setting.

All items will be graded as either ✔ yes (item adequately addressed), ✘ no (item not adequately addressed), **?** unclear or not enough information, **NA** not applicable or **NS** not stated.

Appendix 6

Data extraction tables – clinical effectiveness

Quetiapine

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): AstraZeneca Study 99 (2002)[26–28]	**Intervention**: Quetiapine plus mood stabiliser (lithium or valproate semisodium) ***N***: 91 **Dose**: Quetiapine: target dose 100–400 mg days 1–4 then 200–600 mg day 5 and 200–800 mg thereafter. Lithium at serum concentration 0.7–1.0 mEq/l. Valproate semisodium at serum concentration 50–100 μg/ml **Control**: Placebo plus mood stabiliser (lithium or valproate semisodium) ***N***: 100 **Dose**: Lithium at serum concentration 0.7–1.0 mEq/l. Valproate semisodium at serum concentration 50–100 μg/ml **Duration**: 3 weeks **Washout**: Not stated **Concomitant medications**: Lorazepam and hypnotic medications were down-titrated over days 1–10	**Age**: mean 40.5 years **Sex**: 96 M, 74 F **Illness**: Bipolar I disorder (acute mania) **Diagnosis**: DSM-IV ***N***: 191 **Duration of illness**: Not stated **Length of follow-up**: 3 weeks **Special characteristics**: Hospitalised for at least 7 days after randomisation. 34.7% manic moderate, 22.9% manic severe (no psychotic features), 42.4% manic severe with psychotic episodes. 69 assigned unblinded to lithium and 101 to valproate semisodium (numbers similar in quetiapine and placebo groups) **Inclusion/exclusion criteria**: Age ≥ 18 years. Hospitalised for recurrent episode of mania, manic or mixed phase, with or without psychotic features. Excluded if treated with clozapine within 4 weeks. YMRS score ≥ 20 and score of at least 4 on two of the following items: irritability, speech, content and disruptive/aggressive behaviour. CGI-BP severity of illness score ≥ 4 **Comments**: Age and sex details and some other participant details given for only 170 participants	**Intervention group *n***: 35 withdrew (2 lost to follow-up, 5 adverse events, 4 non-compliance, 15 withdrew consent, 7 lack of efficacy), 9 excluded from efficacy analyses **Control group *n***: 51 withdrew (4 progression of disease, 2 lost to follow-up, 6 adverse events, 5 non-compliance, 17 consent withdrawal, 14 lack of efficacy), 11 excluded from efficacy analyses	Somnolence: I 36/90, C 10/100 Headache: I 24/90, C 21/100 Dry mouth: I 17/90, C 4/100 Asthenia: I 10/90, C 3/100 Postural hypotension: I 10/90, C 3/100 Dizziness: I 9/90, C 6/100 Weight change: I males +1.3 kg, females +0.8 kg, C males –0.2 kg, females +0.8 kg Gained ≥ 7% in weight: I 4/90, C 1/100 ($p = 0.335$)	**Authors' conclusions**: – **Comments**: –

RESULTS				
General comments	**Outcome 1**	**Outcome 2[a]**	**Outcome 3**	**Outcome 4**
–	**Outcome**: YMRS change scores **Intervention**: –13.76 (SE 1.556) **Control**: –9.93 (SE 1.509, $p = 0.021$)	**Outcome**: Response (≥ 50% decrease in YMRS) **Intervention**: 44/90 **Control**: 29/100	**Outcome**: Remission (see comments) **[CIC data removed]** Using a YRMS threshold score (=12), quetiapine was better than placebo. This is a *post hoc* analysis	**Outcome**: Change scores (CGI-BP; GAS; PANSS) **Intervention**: CGI-BP: –1.38 (SE 0.169) PANSS activation and aggression: –4.64 PANSS total: –12.47 GAS: no significant difference between groups **Control**: CGI-BP: –0.78 (SE 0.163, $p = 0.001$) PANSS activation and aggression: –2.84 ($p = 0.020$) PANSS total: –10.14 ($p = 0.323$) GAS: no significant difference between groups
	Outcome 5	**Outcome 6[a]**	**Outcome 7[a]**	
	Outcome: Change scores (SAS) **Intervention**: SAS –1.0 **Control**: SAS –0.3	**Outcome**: CGI-BP 'improved' **Intervention**: 41/90 **Control**: 28/100	**Outcome**: Emergent depressive symptoms (MADRS ≥ 18; increase from baseline of ≥ 4 at 2 consecutive visits) **Intervention**: 14/90 **Control**: 12/100 ($p = 0.469$)	

I, intervention; C, control; SE, standard error.
[a] Efficacy results are given out of 170 rather than 190. Have added the missing people back in as non-responders where possible.

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): AstraZeneca study 104 (2002)[30]	**Intervention**: Quetiapine ***N***: 102 **Dose**: target dose 100–400 mg/days 1–4 then 200–600 mg day 5 and 200–800 mg thereafter **Control**: Haloperidol ***N***: 99 **Dose**: 2× per day: target dose 2 mg days 1–2, 3 mg day 3, 4 mg day 4, 2–6 mg day 5, 2–8 mg thereafter **Control 2**: Placebo ***N***: 101 **Dose**: Matching haloperidol **Duration**: 12 weeks, assessed initially at 3 weeks **Washout**: Not stated **Concomitant medications**: Lorazepam and hypnotic medications were down-titrated over days 1–10	**Age**: mean 40.6–45.1 years **Sex**: 110 M, 189 F **Illness**: Bipolar I disorder (acute mania) **Diagnosis**: DSM-IV ***N***: 302 **Duration of illness**: Not stated **Length of follow-up**: Not stated **Special characteristics**: Quetiapine group higher proportion with severe bipolar disease. Episode type (overall) manic moderate 29%, manic severe without psychotic features 29%, manic severe with psychotic features 42% **Inclusion/exclusion criteria**: Age ≥ 18 years. Hospitalised for recurrent episode of mania, manic or mixed phase, with or without psychotic features. Excluded if intolerant/resistant to clozapine. YMRS score ≥ 20 and score of at least 4 on two of following items: irritability, speech, content and disruptive/aggressive behaviour. CGI-BP severity of illness score ≥ 4 **Comments**: Demographic details given for 299 patients only	**Intervention group *n***: 47 withdrew (9 disease progression, 2 lost to follow-up, 5 adverse events, 4 non-compliance, 9 consent withdrawal, 18 lack of efficacy) **Control group 1 *n***: 45 withdrew (15 disease progression, 1 lost to follow-up, 10 adverse events, 1 non-compliance, 8 consent withdrawal, 10 lack of efficacy) **Control group 2 *n***: 59 withdrew (14 disease progression, 2 lost to follow-up, 6 adverse events, 3 non-compliance, 5 consent withdrawal, 29 lack of efficacy)	Insomnia: I 20/102, C1 14/99, C2 20/101 Somnolence: I 13/102, C1 9/99, C2 5/101 Tremor: I 8/102, C1 30/99, C2 6/101 Akathisia: I 6/102, C1 33/99, C2 6/101 EPS: I 6/102, C1 35/99, C2 6/101 Mean weight change: I + 0.3 kg, C1 –0.1 kg, C2 –0.1 kg	**Authors' conclusions**: – **Comments**: –

RESULTS				
General comments	**Outcome 1**	**Outcome 2[a]**	**Outcome 3[a]**	**Outcome 4**
Remission defined as a YMRS score of 12 points	**Outcome**: YMRS change scores **Intervention**: –12.3 **Control 1**: –15.7 **Control 2**: –8.3 ($p = 0.010$ compared to quetiapine, $p < 0.001$ compared to haloperidol) SDs not given	**Outcome**: Response (≥ 50% decrease in YMRS) Numbers not reported, only bar chart given	**Outcome**: (YMRS <12) Numbers not reported, only bar chart given	**Outcome**: Change scores (MADRS; CGI-BP severity of illness score; GAS; PANSS) Numbers not given
	Outcome 5	**Outcome 6[a]**	**Outcome 7[a]**	
	[CIC data removed]	**Outcome**: CGI-BP response rate Numbers not given	**Outcome**: emergent depressive symptoms (MADRS ≥ 18; increase from baseline of ≥ 4 at 2 consecutive visits) **Intervention**: 0/102 **Control 1**: 1/99 **Control 2**: 7/101	
[CIC data from Studies 100, 104 and 105 removed.] [a] Efficacy results are given out of 299 rather than 302. Have added the missing people back in as non-responders where possible.				

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): DelBello (2002)[33]	**Intervention**: Quetiapine plus divalproex ***N***: 15 **Dose**: Quetiapine initial dose 25 mg b.d., titrated to max. 150 mg t.d.s. by day 7 Divalproex initial dose 20 mg/kg/day, titrated to serum level 800–130 mg/dl **Route**: Oral **Control**: Placebo plus divalproex ***N***: 15 **Dose**: Divalproex initial dose 20 mg/kg/day, titrated to serum level 80–130 mg/dl **Route**: Oral **Duration**: 6 weeks **Concomitant medications**: Lorazepam max. 2 mg/day was permitted during 1st 14 days of the study	**Age**: 14.1–14.5 years **Sex**: 14 F, 16 M **Illness**: Bipolar I disorder, currently mixed or manic **Diagnosis**: DSM-IV ***N***: 30 **Duration of illness**: 3.5–6.1 years **Length of follow-up**: 6 weeks **Special characteristics**: 14 also had psychosis; 18 had ADHD; 23 had mixed episode **Inclusion/exclusion criteria**: 12–18 years old, YMRS score ≥ 20. Excluded if pregnant, manic symptoms secondary to substance intoxication or withdrawal, substance use disorder within previous 3 months, mental retardation, unstable medical or neurological disorder, cataracts, baseline lab. abnormalities, history of hypersensitivity, non-response or intolerance to quetiapine or valproate. Also excluded if treated with depot neuroleptic within 3 months and antidepressant or antipsychotic within 1 week or an antiepileptic agent, benzodiazepine or psychostimulant within 72 hours	**Intervention group *n***: 7 withdrew before 6 weeks (1 due to lack of efficacy, 1 refused blood draws, 2 parental non-compliance, 1 patient non-compliance, 1 transfer to distant residential facility and 1 developed a major depressive episode after resolution of mania **Control group *n***: 1 withdrew before 6 weeks owing to lack of efficacy	Sedation: I 12/15, C 5/15 Nausea/vomiting: I 4/15, C 6/15 Dizziness: I 5/15, C 3/15 Headache: I 7/15, C 7/15 GI irritation: I 7/15, C 5/15 Joint pain: I 2/15, C 2/15 Dry mouth: I 5/15, C 2/15	**Authors' conclusions**: The findings of this study indicate that quetiapine in combination with divalproex is more effective for the treatment of adolescent bipolar mania than divalproex alone. In addition, the results suggest that quetiapine is well tolerated when used in combination with divalproex for the treatment of mania **Comments**: –

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
–	**Outcome**: YMRS response (≥ 50%) **Intervention**: 13/15 **Control**: 9/15	**Outcome**: YMRS score Numbers not extractable, represented on small graphs only. Intervention group had a significantly greater reduction in YMRS score than control group ($p = 0.03$)	**Outcome**: CDRS; PANSS-P; CGAS Numbers not presented. No significant differences between groups in change from baseline to endpoint in CDRS ($p = 1.0$), PANSS-P ($p = 0.8$) and CGAS ($p = 0.2$) scores	**Outcome**: Receipt of lorazepam **Intervention**: 2/15 **Control**: 3/15
	Outcome 5			
	Outcome: AIMS; BAS; SAS change scores (SD) **Intervention**: 0 (0); –0.1 (0.3); 0 (0.8) **Control**: 0 (0); 0.1 (0.3); –0.1 (1.1)			

Olanzapine

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Berk (1999)[40]	**Intervention**: Olanzapine ***N***: 15 **Dose**: 10 mg daily (+ morning placebo to achieve b.d. dose) **Control**: Lithium carbonate ***N***: 15 **Dose**: 10 mg daily (+ morning placebo to achieve b.d. dose) **Duration**: 4 weeks **Washout**: 1 day **Concomitant medications**: Lorazepam, 4–12 mg daily, was given when necessary for control of aggression. No other psychotropic medication permitted. Anticholinergic medication allowed for acute dystonia and severe parkinsonian symptoms (used as secondary outcome measure) **Comments**: There was a third limb of the study using lamotrigine, data not presented here	**Age**: range 20–59 years. Mean not reported **Sex**: Not clear (mistake in table) **Illness**: Patients suffering from bipolar disorder, mania, acute manic episode **Diagnosis**: DSM-IV ***N***: 30 **Duration of illness**: Not stated. **Length of follow-up**: 4 weeks (28 days). **Special characteristics**: Study sample was severely ill (baseline BPRS: 53.3; MAS: 35.1) **Inclusion/exclusion criteria**: Age: 18–65 years, admitted with an acute manic episode. Patients were required to meet DSM-IV criteria for bipolar disorder, manic phase. Women: a negative serum chorionic gonadotrophin, and using safe contraceptive method. Exclusion: abnormal liver functions, thyroid function or haematological findings, as well as those with an acute medical disorder, or medical disorder requiring frequent changes in medication. Also patients with pre-existing cardiac disease and patients who had a neuroleptic depot preparation in the last month, or fluoxetine within 5 weeks, and a history of recent drug or alcohol abuse, and those severely disturbed (unable to comply with requirements of informed consent or treatment protocol)	**Intervention group *n***: 1 premature discontinuation at week 4 for agitation **Control group *n***: 3 premature discontinuations at week 2 and 3 (withdrew consent), and week 3 (epilepsy seizure)	Olanzapine did not differ from lithium in terms of treatment-emergent EPS effects as measured by the SAS	**Authors' conclusions**: Olanzapine appears to be at least as effective as lithium in the treatment of mania **Comments**: Conclusions and study objective relate to equivalence, study underpowered to assess equivalence

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
Conclusions and study objective relate to equivalence, study underpowered to assess equivalence	**Outcome**: BPRS **Intervention**: Baseline: 53.0 End-point: 28.0 **Control**: Baseline: 46.8 Difference at baseline: $p = 0.077$ End-point: 28.2 Difference at day 28: $p = 0.439$	**Outcome**: CGI-I and CGI-S Scales **Intervention**: Baseline severity: 4.67 Baseline improvement: 4.27 **End-point severity**: 2.29 End-point improvement: 2.36 **Control**: Baseline severity: 4.67 Difference at baseline: $p = 1.000$ Baseline improvement: 4.27 Difference at baseline: $p = 0.808$ **End-point severity**: 2.83 Difference at day 28: $p = 0.025$ End-point improvement: 2.75 Difference at day 28: $p = 0.163$	**Outcome**: MAS **Intervention**: Baseline 31.7 End-point 10.2 **Control**: Baseline 31.6 Difference at baseline: $p = 0.900$ End-point 13.2 Difference at day 28: $p = 0.315$	**Outcome**: GAF Scale **Intervention**: End-point 57.9 **Control**: End-point 56.2 Difference at day 28: $p = 0.583$

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Meehan (2001)[42,43]	**Intervention**: Based on clinical judgement, patients received one to three i.m. injections of olanzapine within 24 hours ***N***: 99 **Dose**: First and second injections were 10 mg and the third was 5 mg **Route**: i.m. **Intervention 2**: Based on clinical judgement, patients received 1–3 i.m. injections of lorazepam within 24 hours ***N***: 51 **Dose**: First and second injections were 2 mg and the third was 1 mg **Route**: i.m. **Control**: Patients received two placebo injections and, if necessary, a third injection of olazapine (10 mg) ***N***: 99 **Dose**: First and second injections were 10 mg and the third was 5 mg **Route**: i.m. **Duration**: 24 hours **Concomitant medications**: Lithium and valproate were permitted if started before study entry. Benztropine, biperiden or procyclidine permitted for control of EPS	**Age**: Mean 40.0 years (SD 11.3) **Sex**: 53% male **Illness**: Bipolar disorder, manic or mixed **Diagnosis**: DSM-IV ***N***: 201 **Duration of illness**: Approximately 16 years since age of onset **Length of follow-up**: 24 hours **Special characteristics**: 52.3% current manic, mixed, with psychotic features, 87.5% mood congruent, and 52.2% rapid cycling. **Inclusion/exclusion criteria**: At least 18 years of age, deemed by site physician to be severely agitated, have a minimum score of 14 on the PANSS-EC and have at least one individual item score of at least 4, with the 1–7 scoring system, immediately before randomisation	**Intervention group *n***: Not reported, though data for between 1 and 4 patients are missing on the various measures **Intervention 2**: Not reported, though data for between 1 and 2 patients are missing on the various measures **Control group *n***: Not reported, though data for between 1 and 25 patients are missing on the various measures	Lorazepam group had a significantly larger proportion of treatment emergent adverse events ($N = 26$, 51%, $p = 0.014$) than placebo ($N = 13$, 34.3%), whilst olanzapine did not differ significantly from either group. Somnolence was the most frequently reported adverse event – 13.1% olanzapine, 9.8% lorazepam and 5.9% placebo. Dizziness was the next most frequent adverse event – 13.7% lorazepam, 9.1% olanzapine and 2% placebo. No other adverse event had an incidence of more than 10% in any group	**Authors' conclusions**: Intramuscular olanzapine is a safe and effective treatment for reducing acute agitation in patients with bipolar mania **Comments**: Ref. 43 is an abstract of the full paper and adds no additional information

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
Ref. 43 is an abstract of this paper and adds no additional information	**Outcome**: PANSS-EC **Intervention 1**: Baseline: 12.96 (3.18) 2-hour change = –9.60 (4.75) 24-hour change = –5.78 (4.72) **Intervention 2**: Baseline: 12.39 (2.97) 2-hour change = –6.75 (5.20) 24-hour change = –5.65 (5.20) **Control**: Baseline: 12.72 (3.10) 2-hour change = –4.84 (4.66) 24-hour change = –3.94 (4.32) Significance levels of comparisons between groups: At 2 hours: olanzapine vs lorazepam $p < 0.001$, olanzapine vs placebo $p < 0.001$, lorazepam vs placebo $p = 0.053$. At 24 hours: olanzapine vs lorazepam $p = 0.808$, olanzapine vs placebo $p = 0.025$, lorazepam vs placebo $p = 0.080$	**Outcome**: ABS **Intervention 1**: Baseline: 28.79 (5.84) 2-hour change = –11.30 (6.09) 24-hour change = –7.04 (6.07) **Intervention 2**: Baseline: 28.14 (5.43) 2-hour change = –6.75 (5.20) 24-hour change = –5.65 (5.20) **Control**: Baseline: 27.66 (4.74) 2-hour change = –4.78 (5.49) 24-hour change = –3.88 (5.15) Significance levels of comparisons between groups: At 2 hours: olanzapine vs lorazepam $p < 0.006$, olanzapine vs placebo $p < 0.001$, lorazepam vs placebo $p = 0.003$. At 24 hours: olanzapine vs lorazepam $p = 0.866$, olanzapine vs placebo $p = 0.002$, lorazepam vs placebo $p = 0.010$	**Outcome**: ACES **Intervention 1**: Baseline: 2.24 (0.50) 2-hour change = 2.90 (1.80) 24-hour change = 1.04 (0.85) **Intervention 2**: Baseline: 2.33 (0.55) 2-hour change = 1.88 (1.77) 24-hour change = 1.06 (0.79) **Control**: Baseline: 2.26 (0.56) 2-hour change = 0.82 (1.40) 24-hour change = 0.56 (0.99) Significance levels of comparisons between groups: At 2 hours: olanzapine vs lorazepam $p = 0.001$, olanzapine vs placebo $p < 0.001$, lorazepam vs placebo $p = 0.002$. At 24 hours: olanzapine vs lorazepam $p = 0.952$, olanzapine vs placebo $p = 0.002$, lorazepam vs placebo $p = 0.005$	**Outcome**: PANNS derived BPRS total **Intervention 1**: Baseline: 30.48 (10.36) 2-hour change = –17.29 (10.78) 24-hour change = –13.13 (11.41) **Intervention 2**: Baseline: 29.24 (9.71) 2-hour change = –11.65 (9.72) 24-hour change = –11.71 (10.48) **Control**: Baseline: 29.02 (9.10) 2-hour change = –9.08 (8.85) 24-hour change = –8.20 (9.48) Significance levels of comparisons between groups: At 2 hours: olanzapine vs lorazepam $p = 0.001$, olanzapine vs placebo $p < 0.001$, lorazepam vs placebo $p = 0.232$. At 24 hours: olanzapine vs lorazepam $p = 0.368$, olanzapine vs placebo $p = 0.008$, lorazepam vs placebo $p = 0.117$
	Outcome 5		**Outcome 6**	
	Outcome: YMRS **Intervention 1**: Baseline: 26.17 (7.55) 24-hour change = –9.69 (8.97) **Intervention 2**: Baseline: 25.14 (8.96) 24-hour change = –9.16 (8.19) **Control**: Baseline: 26.59 (6.94) 24-hour change = –8.15 (8.87) Significance levels of comparisons between groups: At 24 hours: olanzapine vs lorazepam $p = 0.664$, olanzapine vs placebo $p = 0.340$, lorazepam vs placebo $p = 0.575$		**Outcome**: CGI-S **Intervention 1**: Baseline: 4.58 (0.80) 24-hour change = –0.77 (0.93) **Intervention 2**: Baseline: 4.37 (0.70) 24-hour change = –0.63 (0.81) **Control**: Baseline: 4.55 (0.69) 24-hour change = –0.70 (1.27) Significance levels of comparisons between groups: At 24 hours: olanzapine vs lorazepam $p = 0.424$, olanzapine vs placebo $p = 0.750$, lorazepam vs olanzapine $p = 0.768$	

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Tohen (1999)[35,197]	**Intervention**: Olanzapine ***N***: 70 **Dose**: Two 5-mg tablets adjusted upwards or downwards as clinically indicated by 5 mg within allowed dosage range of 5–20 mg/day **Route**: Oral **Control**: Placebo ***N***: 69 **Dose**: Two 5-mg tablets adjusted upwards or downwards as clinically indicated by 5 mg within allowed dosage range of 5–20 mg/day **Route**: Oral **Duration**: 3 weeks **Washout**: Not stated **Concomitant medications**: Lorazepam up to 4 mg/day if necessary. To alleviate severe agitation during 1st 7 days of therapy; then during next 3 days, 2 mg/day could be used. Benztropine up to max. dose of 2 mg/day could be used for treatment-emergent EPS only	**Age**: Mean 39.5 years (SD 11.0) **Sex**: 72 M, 67 F **Illness**: Bipolar disorder, manic or mixed episode **Diagnosis**: DSM-III-R ***N***: 139 **Duration of illness**: Not stated **Length of follow-up**: Not stated **Special characteristics**: The majority of the patients (82.7%) were experiencing a manic episode, and the rest (17.3%) were experiencing a mixed episode. Overall 53.2% displayed psychotic features. Of those with psychotic symptoms, 85.1% displayed mood-congruent psychotic features. A DSM-IV defined rapid-cycling course was present in 32.4% of the patients **Inclusion/exclusion criteria**: Met DSM-IV criteria for bipolar disorder either manic or mixed episode (with or without psychotic features) on basis of DSM-III R structural clinical interview. Manic or mixed episodes were of at least 2-weeks' duration. Minimum total score of 20 on YMRS required. Exclusions were: serious, unstable illness such that hospitalisation was anticipated within 3 months or death anticipated within 3 years; DSM-IV defined substance dependence (except nicotine or caffeine) within past 3 months and serious risk of suicide **Further details**: Minimum of 1 week of hospitalisation was required. After 1 week patients with a CGI, Bipolar version, severity of mania score of ≥ 3 and a reduction of ≥ 50% in YMRS total score could be discharged if clinically appropriate	**Intervention group *n***: 27 of 70 (38.6%) **Control group *n***: 45 of 69 (65.2%)	No olanzapine patients discontinued therapy because of adverse events whereas 2 placebo-treated patients discontinued (one because of convulsions and one because of dystonia) Somnolence: I 32.9%, C 17.4%, $p = 0.05$ Dry mouth: I 25.7%, C 8.7%, $p = 0.01$ Dizziness: I 22.9%, C 5.8%, $p = 0.007$ Agitation: I 18.6%, C 23.2% Asthenia: I 18.6%, C 7.2% Headache: I 17.1%, C 15.9% Anxiety: I 14.3%, C 10.1% Depression: I 12.9%, C 11.6% Constipation: I 11.4%, C 2.9% Pain: I 11.4%, 4.3% Weight gain: I 11.4% C 1.4%, $p = 0.03$ Hostility: I 8.6%, C 11.6% Nervousness: I 8.6%, C 13.0% Personality disorder: I 7.1%, C 11.6%	**Authors' conclusions**: Olanzapine is effective in the treatment of acute mania. Olanzapine was well tolerated with no dropouts due to adverse events **Comments**: On YMRS individual items olanzapine group showed a greater mean improvement on all items except insight. Significant for sleep and irritability (–1.9 vs –0.61, $p = 0.04$ and –1.20 vs –0.24, $p = 0.04$, respectively) QoL: no statistically significant difference on 9 of 10 components of SF-36 except for physical functioning subscore [mean 4.01 (13.27) vs 1.84 (14.50), $p = 0.02$] See Ref. 177 abstract for follow-up data Ref. 226 also describes trial but adds nothing Ref. 227 also describes this trial but adds nothing Ref. 228 also describes this trial but adds nothing Ref. 229 also describes this trial but adds nothing Ref. 230 also describes this trial from safety angle but adds nothing Ref. 231 describes a 53-week follow-up to this trial but it is an open-label trial

RESULTS		
General comments	**Outcome 1**	**Outcome 2**
On YMRS individual items olanzapine group showed a greater mean improvement on all items except insight. Significant for sleep and irritability (–1.9 vs –0.61, $p = 0.04$ and –1.20 vs –0.24, $p = 0.04$, respectively) QoL: no statistically significant difference on 9 of 10 components of SF-36 except for physical functioning subscore [mean 4.01 (13.27) vs 1.84 (14.50), $p = 0.02$]	**Outcome**: YMRS Total baseline to end-point change **Intervention**: Baseline mean 28.66 (6.71) Mean change –10.26 (13.43) ($p = 0.019$) **Control**: Baseline mean 27.65 (6.46) Mean change –4.88 (11.64)	**Outcome**: Response (≥ 50% decrease in total score on YMRS) **Intervention**: 34 (48.6%), $p = 0.004$ **Control**: 16 (24.2%)

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Tohen (2000)[36]	**Intervention**: Olanzapine ***N***: 55 **Dose**: 15 mg/day for first day of therapy, with daily dose adjusted as clinically indicated by 5-mg, increase or decrease within dose range of 5–20 mg/day **Route**: Oral **Control**: Placebo ***N***: 60 **Dose**: 15 mg/day for first day of therapy, with daily dose adjusted as clinically indicated by 5-mg increase or decrease within dose range of 5–20 mg/day **Route**: Oral **Duration**: 4 weeks **Concomitant medications**: Lorazepam allowed up to 2 mg/day for first 4 days of treatment and then up to 1 mg/day for 6 days – no lorazepam permitted beyond 10 days after randomisation. Benztropine permitted for EPS up to 2 mg/day for study duration. See comments **Comments**: Hospitalised for a minimum of 1 week. Psychotherapy permitted but not controlled for during the study. This trial is stated to address problems of an earlier trial by using a more aggressive olanzapine-dosing schedule and less concomitant lorazepam	**Age**: Mean (SD) I 38.3(10.7), C 39.0(10.1) **Sex**: 50% of entire sample were male **Illness**: Bipolar disorder., Manic or mixed, with or without psychotic features **Diagnosis**: DSM-IV ***N***: 115 **Duration of illness**: I 15 years, C 18 years (derived from mean age and mean age at onset) **Length of follow-up**: 4 weeks **Special characteristics**: Mean age 39 years, 80% white, 50% male. 43% mixed episode, 56% experiencing psychotic features. Mean YMRS 29.10 (range 14–49) **Inclusion/exclusion criteria**: Patients aged 18–70 years with DSM-IV diagnosis of bipolar disorder, manic or mixed, with or without psychotic features were eligible for inclusion. Minimum score of at least 20 on the YMRS required at screening and on day of randomisation. Excluded for serious unstable medical illness, substance dependence (except nicotine or caffeine) within past 3 months, serious suicidal risk **Further details**: YMRS score of at least 20 needed for inclusion, though one participant had a score of 14 at baseline	**Intervention group *n***: 21 (38%) failed to complete. Reasons were adverse event (2), lack of efficacy (15), unavailable for follow-up (1), and patient decision (3) **Control group *n***: 35 (58%) failed to complete. Reasons were adverse event (1), lack of efficacy (23), unavailable for follow-up (3), patient decision (5), and physician decision (3)	3 patients discontinued treatment owing to an adverse event (placebo, agitation; olanzapine, unintended pregnancy and rash). Somnolence in the olanzapine group was significantly more frequent, $p < 0.001$. Significantly more agitation in the placebo group ($p = 0.03$)	**Authors' conclusions**: Olanzapine demonstrated greater efficacy than placebo in the treatment of acute bipolar mania and was generally well tolerated

RESULTS			
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**
–	**Outcome**: YMRS change scores **Intervention**: Baseline 28.76 (6.72) Change from baseline = –14.78 (12.49) **Control**: Baseline 29.43 (6.77) Change from baseline = –8.13 (12.72)	**Outcome**: YMRS response (at least 50% improvement) **Intervention**: 35/55 **Control**: 24/60	**Outcome**: YMRS remission (score of ≤ 12) **Intervention**: 33/55 **Control**: 20/60

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Tohen 2001[37–39,44]	**Intervention**: Olanzapine ***N***: 234 **Dose**: 5–20 mg/day **Route**: Oral **Control**: Haloperidol ***N***: 219 **Dose**: 3–15 mg/day **Route**: Oral **Duration**: 6 weeks (plus 6-week continuation phase) **Concomitant medications**: Adjunctive benzodiazepine and anticholinergic therapy were permitted at a minimum level up to a max. of 4 mg lorazepam equivalents for 14 cumulative days. If EPS occurred benztropine mesylate or biperiden could be given up to a maximum of 6 mg/day **Washout**: 2–7 days	**Age**: Mean 38.0–40.3 years **Sex**: 60% F **Illness**: Bipolar I disorder **Diagnosis**: DSM-IV ***N***: 453 **Duration of illness**: Not stated **Length of follow-up**: 6 weeks continuation phase **Special characteristics**: Acute manic or mixed episode (with or without psychotic features) **Inclusion/exclusion criteria**: Baseline YMRS ≥ 20. Patients with serious unstable medical illness, DSM-IV substance dependence (except nicotine or caffeine) within past 30 days, intolerant or resistant to olanzapine or haloperidol or at serious risk of suicide were excluded	**Intervention group *n***: 68/234 withdrew before 6 weeks (14 due to adverse events, 33 due to lack of efficacy, 21 other) **Control group *n***: 78/219 withdrew before 6 weeks (20 due to adverse events, 24 due to lack of efficacy, 35 other)	Insomnia: I 25/234, C 30/219 Somnolence: I 24/234, C 15/219 Weight gain: I 23/234, C 6/219 Akathisia: I 13/234, C 57/219 Tremor: I 11/234, C 31/219 Infection: I 10/234, C 1/219 Hypertonia: I 9/234, C 38/219 Fever: I 8/234, C 0/219 EPS: I 5/234, C 49/219 Dystonia: I 3/234, C 14/219 Hypokinesia: I 1/234, C 8/219 Increased salivation: I 1/234, C 15/219 Dyskinesia: I 0/234, C 6/219	**Authors' conclusions**: Olanzapine and haloperidol were similarly effective in treating the acute symptoms of mania in the first 6 weeks of treatment. Olanzapine offered advantages over haloperidol with respect to a superior improvement in YMRS scores from weeks 6 to 12, superiority in the rate of remission at week 6 among non-psychotic patients, improvement of depressive symptoms, lower risk of switch into depression and lower risk of EPS, all of which may translate to a superior QoL outcome over the entire 12-week treatment period **Comments**: Used LOCF assumption for missing persons

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
Efficacy and safety results reported in Tohen 2001 poster.[37] HRQoL and work status presented in Shi 2002.[38] 6-week data presented here. A subgroup analysis of responders vs non-responders was carried out but results were not split by intervention	**Outcome**: Remission (YMRS ≤ 12 and HAM-D ≤ 8) **Intervention**: 122/234 **Control**: 101/219	**Outcome**: HRQoL (SF-36) change scores **Intervention**: $n = 161$, physical 0.27 (SD 9.35); mental 1.50 (SD 13.42); bodily pain 3.99 (SD 25.46); general health –1.09 (SD 20.76); mental health 2.45 (SD 21.54); physical functioning 1.79 (SD 24.27); role-emotional problem 6.04 (SD 51.51); role-physical problem 3.28 (SD 46.93); social functioning 10.95 (SD 36.73); vitality –6.66 (SD 22.08) **Control**: $n = 137$ physical –4.27 (SD 8.79, $p = 0.010$); mental 0.74 (SD 13.35, $p = 0.58$); bodily pain 3.93 (SD 23.92, $p = 0.74$); general health –7.36 (SD 20.67, $p = 0.01$); mental health –0.96 (SD 20.74, $p = 0.173$); physical functioning –10.96 (SD 27.25, $p < 0.001$); role-emotional problem 3.46 (SD 58.49, $p = 0.543$); role-physical problem –15.63 (SD 46.74, $p < 0.001$); social functioning 2.13 (SD 36.48, $p = 0.036$); vitality –14.11 (SD 22.85, $p = 0.002$) None favoured haloperidol	**Outcome**: Work status **Intervention**: In work 167/234 **Control**: In work 148/219 No significant differences in change on streamlined longitudinal interview clinical evaluation for the longitudinal interval follow-up evaluation (SLICE/LIFE) work activities impairment and household activities impairment scores	**Outcome**: YMRS response (≥ 50%) **Intervention**: 167/231 **Control**: 158/213
	Outcome 5	**Outcome 6**	**Outcome 7**	
	Outcome: MADRS, HAM-D mean change **Intervention**: –1.97; –3.01 **Control**: –0.50 ($p = 0.028$); –2.00	**Outcome**: Switching to depression (HAM-D total ≤ 8 baseline and ≥ 15 post-baseline) **Intervention**: 6/128 **Control**: 16/131	**Outcome**: Remission – subgroup analysis **Intervention**: Psychotic 63/130; non-psychotic 59/104 **Control**: Psychotic 64/130, non-psychotic 37/89	

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Tohen (2002)[41,45–47]	**Intervention**: Olanzapine in combination with valproate or lithium ***N***: 229 **Dose**: Two 5 -mg capsules titrated up in increments of 1 capsule or down by any number of decrements at investigator discretion according to patient tolerance **Route**: Oral **Control**: Placebo in combination with valproate or lithium ***N***: 115 **Dose**: Two 5-mg capsules titrated up in increments of 1 capsule or down by any number of decrements at investigator discretion acc to patient tolerance **Route**: Oral **Duration**: 6 weeks **Concomitant medications**: Patients permitted adjunctive use of benzodiazepine (≤ 2 mg/day) throughout the study for treatment of EPS but not for prophylaxis	**Age**: Mean 40.6 years (SD 11.1) **Sex**: 165 M, 179 F **Illness**: Bipolar disorder, manic or mixed episode with or without psychotic features **Diagnosis**: DSM-IV ***N***: 344 **Duration of illness**: Not stated **Length of follow-up**: Not stated **Special characteristics**: All patients diagnosed with BD, manic or mixed episode with or without psychotic features acc to DSM-IV SCID **Inclusion/exclusion criteria**: Patients had to have at least 2 previous depressed, manic or mixed episodes as well as YMRS total score of ≥ 16 at visit 1 and visit 2 (2–7 days later). Patients required to have had a documented trial of treatment with a therapeutic blood level of lithium (0.6–1.2 mmol/l) or valproate (50–125 μg/ml) for at least 2 weeks prior to visit 1. Patients included only if showed inadequate response to monotherapy (YMRS total score ≥ 16)	**Intervention group *n***: 69 (30.1%) did not complete study **Control group *n***: 33 (28.7%) did not complete study Significantly more patients in the control group discontinued treatment owing to lack of efficacy (12.2% vs 3.1%, $p = 0.002$), whereas significantly more patients in the intervention group withdrew owing to adverse events (10.9% vs 1.7%, $p = 0.002$)	Significantly more patients in intervention group withdrew owing to adverse events (10.9% vs 1.7%, $p = 0.002$) Somnolence: I 51.5%, C 27.0% ($p < 0.001$) Dry mouth: I 31.9%, C 7.8 % ($p < 0.001$) Weight gain: I 26.2%, C 7.0% ($p < 0.001$) Increased appetite: I 23.6%, C 7.8% ($p < 0.001$) Tremor: I 23.1%, C 13.0% ($p = 0.03$) Asthenia: I 18.3%, C 13.0% Depression: I 17.9%, C 17.4% Headache: I 15.7%, C 18.3% Dizziness: I 13.5%, 7.0% Diarrhoea: I 11.8%, C 14.8% Nervousness: I 10.5%, C 14.8% Thirst: I 10.0%, C 6.1% Speech disorder: I 6.6%, C 0.9% ($p = 0.02$)	**Authors' conclusions**: In patients with bipolar manic or mixed episodes who demonstrate inadequate responsiveness to at least 2 weeks of mood stabiliser monotherapy, the combination of lithium or valproate plus olanzapine may provide additional efficacy compared with either agent alone. Patients treated with combination therapy experienced more adverse events but none seemed to be life-threatening. The response in patients without psychotic features and the improvement of depressive symptoms suggests that the combination of olanzapine and lithium or valproate may have mood-stabilising properties in the acute treatment of bipolar manic or mixed episodes **Comments**: Abstract Ref. 45 describes the same study but adds nothing

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
Abstract Ref. 45 describes the same study but adds nothing	**Outcome**: YMRS total score **Intervention**: Mean total 22.31 (5.39) Decrease in mean total score of 13.1 (8.53) points. 58.8% improvement from baseline (significant, $p = 0.003$) **Control**: Mean total 22.67 (5.15) Decrease in mean total score 9.10 (9.36). 40.1 % improvement from baseline	**Outcome**: YMRS total score of ≤ 12 **Intervention**: 173 of 220 (78.6%) achieved YMRS total score of ≤ 12 (significant $p = 0.01$) **Control**: 75 of 114 (65.8%) achieved YMRS total score of ≤ 12 **Time to remission**: Intervention: 14 days Control: 22 days ($p = 0.002$)	**Outcome**: Improvement of ≥ 50% in YMRS total **Intervention**: 149 (67.7%) of 220 patients made a 50% improvement ($p < 0.001$) **Control**: 51 (44.7%) of 114 patients improved by 50% **Time to response**: Intervention: 18 days Control: 28 days ($p = 0.002$)	**Outcome**: CGI-BP overall **Intervention**: Baseline mean (SD): 4.10 (0.74) Mean change (SD): –1.20 (1.16) **Control**: Baseline mean (SD): 4.18 (0.72) Mean change (SD): –0.89 (1.31)
	Outcome 5			
	Outcome: PANNS total **Intervention**: Baseline mean (SD): 62.10 (17.28) Mean change (SD): –12.90 (15.72) **Control**: Baseline mean (SD): 61.75 (15.51) Mean change (SD): –6.96 (16.39)			

Valproate semisodium

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Bowden (1994)[49]	**Intervention**: Divalproex sodium ***N***: 69 **Dose**: Initial dose 750 mg/day (3 divided doses). On day 3 total dose was increased to 1000 mg. Serum concentrations were measured and dose adjustments made **Route**: Oral **Control 1**: Lithium carbonate ***N***: 36 **Dose**: Initial dose 750 mg/day (3 divided doses). On day 3 total dose was increased to 1000 mg. Serum concentrations were measured and dose adjustments made **Route**: Oral **Control 2**: Placebo ***N***: 74 **Dose**: 3 divided doses. **Route**: Oral **Duration**: 21 days **Washout**: 3–21 days (see comments) **Concomitant medications**: Chloral hydrate (max. 4 g/day to day 4 then 2 g to day 10) or lorazepam (max. 2 mg/day to day 4 then 1 mg to day 10) as needed for control of agitation, irritability, restlessness, insomnia and hostile behaviours. Not in 8 h before assessments. **Comments**: Washout period was the longer of 3 days or 5 half-lives of the psychoactive drug taken on admission with the longest half-life	**Age**: Mean 1 40.4 (12.8), C1 39.1 (11.2), C2 39.0 (10.0) years **Sex**: 1 52% M, C1 72% M, C2 57% M **Illness**: Manic disorder **Diagnosis**: Other ***N***: 212 **Duration of illness**: Mean 1 18.0 years (12.4), C1 16.1 years (11.0), C2 18.0 years (10.4) **Length of follow-up**: No extra follow-up **Special characteristics**: 4 or more major mood episodes per year in last 2 years: 1 11, C1 1, C2 6 4 or more episodes of mania per year in last 2 years: 1 8, C1 0, C2 0 **Inclusion/exclusion criteria**: Aged 18–65 years. Diagnosed with manic disorder as detailed. MRS scores ≥ 14 on last washout day with scores of ≥ 2 on at least 4 items. Undetectable serum lithium concentrations prior to randomisation. Usual exclusion criteria (pregnancy, CNS or neuromuscular disorders, uncontrolled diseases, drug or AIDS-induced mania, positive toxicology tests, concomitant medications, substance abuse) plus lithium intolerance, prior treatment with valproate semisodium or valproic acid, schneiderian 1st rank symptoms **Further details**: Diagnosis of manic disorder using Research Diagnostic Criteria, based on structured interview and rating scale of SADS	**Intervention group *n***: 33 failed to complete 21 days (21 lack of efficacy, 4 intolerance to treatment, 3 met recovery criteria, 1 non-compliance, 4 administrative reason) **Control group *n***: 22 failed to complete 21 days (12 lack of efficacy, 4 intolerance to treatment, 2 met recovery criteria, 1 non-compliance, 1 intercurrent illness, 2 administrative reason) **Control group 2**: 47 failed to complete 21 days (38 lack of efficacy, 2 intolerance to treatment, 2 met recovery criteria, 3 non-compliance, 2 administrative reason)	**Any adverse event**: 1 58, C1 33, C2 58 Asthenia: 1 9, C1 7, C2 7 Constipation: 1 7, C1 6, C2 5 Diarrhoea: 1 8, C1 5, C2 13 Dizziness: 1 11, C1 3, C2 4 Fever: 1 1, C1 5, C2 3 Headache: 1 15, C1 14, C2 24 Nausea: 1 16, C1 11, C2 11 Pain: 1 13, C1 1, C2 15 Somnolence: 1 13, C1 7, C2 11 Twitching: 1 2, C1 3, C2 0 Vomiting: 1 10, C1 9, C2 3 Significant differences were found only for vomiting (I and C1 > C2), fever (C1 > I), general pain (I and C2 > C1) and twitching (C1 > C2)	**Authors' conclusions**: Both valproate semisodium and lithium were significantly more effective than placebo in reducing the symptoms of acute mania. The efficacy of valproate semisodium appears to be independent of prior responsiveness to lithium. **Comments**: Subgroup analyses from this study are presented in Refs 50–52

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
Subgroup analyses from this study are presented in Refs 50–52	**Outcome**: SADS-C MRS score **Intervention**: Baseline: 38.2 in previous lithium responders, 38.6 in non-responders Change –7.4 in previous lithium responders, –10.8 in non-responders. Manic syndrome subscale at least 50% improvement: 48% ($p = 0.004$ compared with placebo) Valproate semisodium: significantly greater improvement (compared with placebo) in elevated mood, less need for sleep, excessive activity and motor hyperactivity **Control 1**: 37.6 in previous lithium responders, 36.2 in non-responders Significant improvement (compared with placebo) in excessive activity and motor hyperactivity. Change –15.3 in previous lithium responders, –1.0 in non-responders. Manic syndrome subscale score at least 50% improvement: 49% ($p = 0.025$ compared with placebo) **Control 2**: 39.6 in previous lithium responders, 39.1 in non-responders Change –4.0 in previous lithium responders, –3.2 in non-responders. Manic syndrome subscale at least 50% improvement: 25%	**Outcome**: GAS change scores **Intervention**: 7.6 Valproate semisodium: significantly greater improvement (compared with placebo) in elevated mood, less need for sleep, excessive activity and motor hyperactivity **Control 2**: 3.8 ($p = 0.06$)	**Outcome**: ADRS change scores **Intervention**: Significant (compared with placebo): mania –4.9, elation/grandiosity –2.6, psychosis –2.7 **Control 1**: Significant (compared with placebo): mania –5.9 **Control 2**: Mania –0.2, elation/grandiosity –0.7, psychosis +0.6	**Outcome**: Response (Mania Syndrome Subscale; MRS) **Intervention**: 32/69; 29/69 **Control 1**: 17/36; 16/36 **Control 2**: 18/74; 15/74

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Swann (1997)[50] **Trial ID** Bowden 1994[49] subgroup analysis	See Bowden 1994[49] for description of interventions, participants, etc.	***N***: 179 **Inclusion/exclusion criteria**: Compared 3 definitions of depressive mania that varied in stringency: SADS-C: presence of ≥ 2 items of SADS-C depression subscale. Each of the 9 items was scored from 0 (absent) to 5, a score of ≥ 2 indicates that the symptom was present SADS-C/DM: score of ≥ 1 on SADS-C depressive mood item and on at least 1 other item from the depression subscale. These were the subset of those meeting the SADS-C criteria in which one of the positive items was depressed mood SADS-C/ADRS: score >2 on ADRS (scored 0 if absent) plus score ≥ 2 on SADS-C depression subscale **Special characteristics**: 58% met criteria 1 for depressive mania, 38% met criteria 2 and 53% met criteria 3 **Further details**: Subgroup analysis of Bowden 1994[49] – the primary outcome measure, change in mania factor scores, derived from SADS-C, was compared in patients with and without depressive symptoms at baseline according to nurse- or physician-rated scales	**Intervention group *n***: SADS-C, classic mania 48% (lack of effect 40%, other 8%), depressive mania 40% (lack of effect 26%, intolerance 9%, other 5%). SADS-C/DM, classic mania 49% (lack of effect 40%, intolerance 2%, other 7%), depressive mania 31% (lack of effect 15%, intolerance 12%, other 4%) **Control group 1 *n***: SADS-C, classic mania 48% (lack of effect 24%, intolerance 18%, other 6%), depressive mania 64% (lack of effect 42%, intolerance 11%, other 11%). SADS-C/DM, classic mania 48% (lack of effect 29%, intolerance 14%, other 5%), depressive mania 66% (lack of effect 40%, intolerance 13%, other 13%) **Control group 2 *n***: SADS-C, classic mania 65% (lack of effect 56%, intolerance 3%, other 6%), depressive mania 55% (lack of effect 46%, intolerance 2%, other 7%). SADS-C/DM, classic mania 59% (lack of effect 50%, intolerance 2%, other 7%), depressive mania 63% (lack of effect 52%, intolerance 4%, other 7%)	Not reported	**Authors' conclusions**: These data suggest that even a modest level of pretreatment depression-related symptoms is a robust predictor of lithium non-response, and is associated with better response to valproate semisodium. Although their overall efficacies in acute mania are similar, lithium and valproate semisodium may be most effective in clinically and biologically distinct groups of patients **Comments**: Authors state that depressive presentation was associated with a poorer response to lithium, with less improvement (or even slight deterioration) in all 3 scales compared with classic mania. Depressive symptoms had no significant effect on response to valproate semisodium, although with the more stringent criteria, a trend was observed toward more improvement in behaviour–ideation and mania rating scores in depressive than in classic mania. People experiencing depressive mania had better response to valproate semisodium than to lithium but the reverse was true for classic mania Denominators (numbers in each group meeting classic and depressive criteria) do not seem to be reported. Actual scale scores are not given

RESULTS			
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**
Authors state that depressive presentation was associated with a poorer response to lithium, with less improvement (or even slight deterioration) in all 3 scales compared with classic mania. Depressive symptoms had no significant effect on response to valproate semisodium, although with the more stringent criteria, a trend was observed toward more improvement in behaviour–ideation and mania rating scores in depressive than in classic mania. People experiencing depressive mania had better response to valproate semisodium than to lithium but the reverse was true for classic mania Denominators (numbers in each group meeting classic and depressive criteria) do not seem to be reported. Actual scale scores are not given	**Outcome**: SADS-C mania syndrome scale **Intervention**: Patients meeting SADS-C criteria had similar response to valproate semisodium, regardless of depressive symptoms. SADS-C/DM criteria: response seemed better in depressive-manic episodes **Control**: SADS-C criteria: similar to placebo in patients with depressive mania but robust in classic mania. SADS-C/DM criteria: results were similar	**Outcome**: Behaviour–ideation scale **Intervention**: Results were similar to outcome 1 **Control**: Results were similar to outcome 1	**Outcome**: MRS **Intervention**: Not reported **Control**: SADS-C criteria: highly significant difference in response in depressive and classic episodes. SADS-C/DM criteria: significant interaction between drug response and depressive presentation

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Swann (1999)[51] **Trial ID** Bowden 1994[49] subgroup analysis	See Bowden 1994[49] for a description of the interventions and participants	***N***: 179 **Inclusion/exclusion criteria**: 154 of the 179 randomised had treatment and history data adequate for the analyses in this report. This is an investigation of the relationship between number of lifetime episodes of affective disorder and the antimanic response to lithium, valproate semisodium or placebo	Not reported	Not reported	**Authors' conclusions**: A history of many previous episodes was associated with poor response to lithium or placebo but not to valproate semisodium **Comments**: Response to treatment diverged sharply as the number of episodes increased. Values for improvement with a low number of episodes were 5.6 (SD 1.2) for lithium, 5.9 (SD 1.1) for valproate semisodium and 2.4 (0.7) for placebo. Placebo differed significantly from lithium ($p < 0.005$) and from valproate semisodium ($p < 0.005$). Transition between high and low response occurred at 10.2 episodes (SD 0.6) for lithium, 11.9 (SD 0.6) for placebo and 11.4 (SD 4.6) for valproate semisodium (no differences among treatments). Mean asymptotic response for many episodes was 2.5 (SD 0.6) for lithium, 1.2 (SD 0.4) for placebo and 9.3 (SD 3.7) for valproate semisodium. Response to valproate semisodium was significantly different from the response to placebo ($p < 0.005$) and response to lithium ($p < 0.005$). There was no significant relationship between many episodes and mixed states: 38 of 97 patients with 10 episodes or fewer, versus 27 of 67 patients with 11 or more, met previously described criteria for depressive mania ($p > 0.9$). There was a significant increase in current rapid cycling with many episodes (2/84 with 10 or fewer versus 16/56 with 11 or more, $p < 0.0005$). Reduced response to lithium occurred among patients without rapid cycling

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Bowden (1997)[52] **Trial ID** Bowden 1994[49]	See Bowden 1994[49] for description of interventions and participants	This is an effect size analysis of previous data. Rationale seems to be that they only gave *p* values in the Bowden 1994 publication and now they want to look at magnitude of effect size. Analysis not of much interest to this report but extra information is given on outcomes	Not reported	Not reported	**Authors' conclusions**: Using an effect size statistic provides a clear index of the magnitude of the difference which is fundamentally important in physicians' decision-making **Comments**: Have not reported the results of the effect size analysis as we are doing our own analysis

RESULTS

General comments	Outcome 1	Outcome 2
	Outcome: Mania rating scale change scores: total; manic syndrome subscale; behaviour–ideation subscale; elevated mood subscale; increased activity subscale; motor hyperactivity subscale; less need for sleep subscale **Intervention**: 9.4 (12.0); 5.9 (6.6); 3.1 (5.4); 1.27 (1.95); 1.09 (1.57); 0.82 (1.56); 1.46 (1.65) **Control 1**: 9.6 (16.9); 5.7 (8.8); 3.5 (6.6); 1.20 (1.92); 1.34 (1.89); 0.94 (1.64); 0.97 (2.50) **Control 2**: (11.3); 2.4 (6.7); 1.3 (4.9); 0.69 (1.51); 0.33 (1.86); 0.19 (1.60); 0.10 (1.91)	**Outcome**: ADRS change scores: mania; elated or grandiose; psychosis **Intervention**: 4.9 (10.0); 2.6 (4.14); 2.7 (5.94) **Control 1**: 5.9 (11.1); 2.3 (4.88); 1.5 (5.98) **Control 2**: 0.2 (11.1); 0.7 (4.41); 0.6 (6.29)

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Hirschfeld (1999)[53,148] Trial ID M95-305	**Intervention 1**: Valproate semisodium loading ***N***: 20 **Dose**: 30 mg/kg/day on days 1 and 2, 20 mg/kg/day on days 3–10 **Route**: Oral **Intervention 2**: Valproate semisodium non-loading (standard titration) ***N***: 20 **Dose**: 250 mg t.d.s. days 1 and 2 followed by standard dose titration for remaining 8 days **Route**: Oral **Control**: Lithium carbonate ***N***: 20 **Dose**: 30 mg/kg/day on days 1 and 2, 20 mg/kg/day on days 3–10. **Route**: Oral **Duration**: 10 days **Washout**: ≤ 72 hours **Concomitant medications**: Lorazepam was allowed for agitation, insomnia, restlessness, irritability and hostility (4 mg on days 1–4, 2 mg on days 5–7) **Comments**: After washout, subtherapeutic serum concentrations of valproate and lithium were confirmed	**Age**: Range 18–60 years, mean 32.4 (I2), 36.0 (I1), 36.4 (C) **Sex**: 34 M, 25 F **Illness**: Bipolar disorder (manic or mixed), acute manic episode **Diagnosis**: DSM-IV ***N***: 59 **Duration of illness**: Years since first manic episode: I1 19.5 (SD 23.4); I2 19.9 (SD 28.9); C 8.7 (SD 7.3) **Length of follow-up**: 10 days, no extra follow-up **Special characteristics**: Baseline YMRS score: I1 24.5, I2 26.2, C 25.1. Baseline GAS score: I1 36.2, I2 35.7, C 33.0 **Inclusion/exclusion criteria**: Hospitalised for acute manic episode. YMRS score ≥ 14 (assessed by SADS-C). Usual exclusion criteria: substance abuse, pregnancy, serious risk of suicide, depot antipsychotics or any experimental drug within previous 4 weeks **Further details**: People in the lithium group had considerable shorter duration of illness since first manic episode (8.7 years) than people in the 2 intervention groups (19.5 and 19.9 years)	**Intervention group 1 *n***: 7 discontinued medication: 2 due to lack of efficacy, 1 due to non-compliance, remainder miscellaneous (discharge, recovery, other). No adverse event-related withdrawals. **Intervention group 2 *n***: 7 discontinued medication: 4 due to lack of efficacy, remainder miscellaneous (discharge, recovery, other). No adverse event-related withdrawals. **Control group *n***: 9 discontinued medication: 3 due to lack of efficacy, 2 due to non-compliance, remainder miscellaneous (discharge, recovery, other). No adverse event-related withdrawals	Any adverse event: I1 12/20, I2 15/20, C 14/19. None serious. Most common: dyspepsia, nausea, headache, constipation. No statistically significant differences between groups in number and type of adverse effect	**Authors' conclusions**: Accelerated oral loading with divalproex sodium is a feasible and safe method to bring serum valproate concentrations to effective levels rapidly **Comments**: The authors state that the study was not designed to evaluate the relative efficacy of rapid loading compared with non-loading strategies. Sponsored by Abbott Laboratories

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
The authors state that the study was not designed to evaluate the relative efficacy of rapid loading compared with non-loading strategies. Sponsored by Abbott Laboratories	**Outcome**: YMRS mean change **Intervention 1**: –10.3 **Intervention 2**: –8.1 ($p = 0.467$ vs intervention 1) **Control**: –6.1 ($p = 0.152$ vs intervention 1) Similar improvements were seen in all 3 groups on YMRS (including subscales)	**Outcome**: GAS scores Similar improvements were seen in all 3 groups. Results presented on a graph but numbers and SDs not given **Control**: –8.1 ($p = 0.467$ vs intervention 1)	**Outcome**: Received adjunctive lorazepam **Intervention 1**: 14/20 **Intervention 2**: 15/20 **Control**: 15/19	**Outcome**: Serum concentration within therapeutic range on day 3 **Intervention 1**: 16/19 **Intervention 2**: 6/20 **Control**: Not applicable

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Kowatch (2000)[54]	**Intervention**: Divalproex sodium ***N***: 15 **Dose**: Starting dose ~20 mg/kg per day in 3 divided doses. After 1 week, dosage titrated until serum level 85–110 μg/l **Route**: Oral **Control 1**: Lithium ***N***: 14 **Dose**: Starting dose ~20 mg/kg per day in 3 divided doses. After 1 week, dosage titrated until serum level: 85–110 μg/l **Route**: Oral **Control 2**: Carbamazepine ***N***: 13 **Dose**: 15 mg/kg/day **Route**: Oral **Duration**: 8 weeks max. (mean: I1 5.8, C1 6.0, C2 5.6 weeks) **Concomitant medications**: All three: chlorpromazine, 10 to 50 mg/day, was allowed as a 'rescue medication' 2 or 3 times per week for sleep or agitation during the first 2 weeks of treatment. Three responders (one in each group) required low dose of chlorpromazine, typically 10–25 mg **Comments**: Dose and serum level ranges were monitored with levels after 1, 2 and 4 weeks of treatment	**Age**: 11.4 years (SD: 3.0) **Sex**: 16/42 (38%) female **Illness**: Bipolar I or II disorder, mixed or manic episode **Diagnosis**: DSM-IV ***N***: 42 **Duration of illness**: Duration of bipolar symptoms: 4.6 years (SD: 2.8) **Length of follow-up**: 6–8 weeks **Special characteristics**: Bipolar I, $n = 20$; II, $n = 22$. Current comorbid DSM-IV non-mood disorders: attention deficit hyperactivity disorder (71%), obsessive compulsive disorder (38%), anxiety disorder (17%), conduct disorder (7%), enuresis (2%), substance use (2%) **Inclusion/exclusion criteria**: Meet DSM-IV inclusion criteria. For bipolar I or II disorder during a mixed or manic episode; 6–18 year; YMRS score: ≥ 14; no current medical illnesses requiring medication and normal intelligence. Exclusion diagnosis of schizophrenia, obsessive–compulsive disorder or autistic disorder, substance abuse/dependence, history of organic brain disease, current use of psychotropic agents (including neuroleptics, monoamine oxidase inhibitors, stimulants and antidepressants) within 2 weeks of randomisation. Responders receiving depot neuroleptics or fluoxetine had to be medication free for previous month **Further details**: Respondents who missed more than 3 consecutive days of medications were discontinued from the protocol	**Total**: 6/42 completed less than 4 weeks of treatment, 10/42 completed 5 weeks, 13/42 completed 6 weeks, 10/42 completed 7 weeks and 3/42 completed 8 weeks **Intervention group *n***: Divalproex sodium: 2 completed less than 4 weeks **Control group *n***: Lithium: 2 completed less than 4 weeks **Control group 2 *n***: Carbamazepine: 2 completed less than 4 weeks. One responder developed a rash after 1 week	Nausea was most common side-effect (I1 3/15, C1 3/14, C2 6/13). One responder (C2) developed a rash and elected to stop. Majority of side-effects were mild to moderate and tolerated by most. There were no serious adverse events necessitating hospitalisation	**Authors' conclusions**: Valproate semisodium sodium, lithium and carbamazepine all showed a large effect size in the open treatment of children and adolescents with bipolar I or II disorder in a mixed or manic episode **Comments**: Modified ITT sample: completed at least 1 week of treatment. Adequate treatment sample: completed at least 5 weeks of treatment. Responder: weekly CGI-I score of 1 or 2, 'much' or 'very much improved' at end-point; or weekly YMRS scores: ≥ 50% improvement from baseline YMRS at end-point

RESULTS		
General comments	**Outcome 1**	**Outcome 2**
Modified ITT sample: completed at least 1 week of treatment. Adequate treatment sample: completed at least 5 weeks of treatment. Responder: weekly CGI-I score of 1 or 2, 'much' or 'very much improved' at end-point; or weekly YMRS scores: ≥ 50% improvement from baseline YMRS at end-point	**Outcome**: Weekly Clinical Global Impression Improvement score **Intervention**: CGI responders: 6/15 **Control**: Lithium: CGI responders: 6/14 **Control 2**: Carbamazepine: CGI responders: 4/13	**Outcome**: YMRS **Intervention**: YMRS responders: 8/15. YMRS effect size: 1.63. Mean YMRS change (baseline to exit): 14.53 (pooled SD: 12.62) **Control 1**: Lithium: YMRS responders: 5/14. YMRS effect size: 1.06. Mean YMRS change (baseline to exit): 9.46 **Control 2**: Carbamazepine: YMRS responders: 5/13. YMRS effect size: 1.00.Mean YMRS change (baseline to exit): 9.00

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): McElroy (1996)[55]	**Intervention**: Valproate semisodium ***N***: 21 **Dose**: 20 mg/kg/day, usually given in divided doses **Route**: Oral **Control**: Haloperidol ***N***: 15 **Dose**: 20 mg/kg/day, usually given in divided doses **Route**: Oral **Duration**: 6 days **Washout**: 1 day **Concomitant medications**: Lorazepam was allowed up to 4 mg/day for agitation. Benztropine as needed for EPS **Comments**: Valproate semisodium was given by the oral loading strategy	**Age**: 18–65 years (mean I 35.8, C 35.9) **Sex**: I 62% M, C 53% M **Illness**: Bipolar disorder, manic or mixed phase, with psychotic features **Diagnosis**: DSM-III-R ***N***: 36 **Duration of illness**: I 9.3 (SD 9.2) years, C 6.9 years (SD 9.2) years **Length of follow-up**: 6 days, no extra follow-up **Special characteristics**: Patients presented for treatment from the Psychiatric Emergency Service to Psychobiology Research Unit of University of Cincinatti Hospital **Inclusion/exclusion criteria**: Excluded for serious CNS disorders, substance abuse, prior treatment with valproate, unstable medical conditions, history of seizures, could not provide informed consent **Further details**: Clinical evaluations were conducted on washout day. No significant differences between groups in clinical characteristics or in baseline total YMRS, global SAPS or SAPS subscale scores	Not reported	Sedation: I 1, C 4 Indigestion: I 2, C 1 Headache: I 0, C 1 Dry mouth: I 1 C 3 Insomnia: I 1 C 0 EPS: I 0, C 8	**Authors' conclusions**: Valproate semisodium oral loading may produce rapid onset of antimanic and antipsychotic response comparable to that of haloperidol and with minimal side-effects in the initial treatment of acute psychotic mania in a subset of bipolar patients **Comments**: Total lorazepam received, mg/patient/day: I 1.9 (SD 1.1), C 1.9 (SD 1.8). Total benztropine received, mg/patient/day I 0, C 1.3 (SD 0.6)

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
Total lorazepam received mg/pt/day: I 1.9 (SD 1.1), C 1.9 (SD 1.8). Total benztropine received mg/pt/day 10, C 1.3 (SD 0.6)	**Outcome**: YMRS score **Intervention**: Baseline 36.1 (SD 11.0) End-point 20.7 (11.0) **Control**: Baseline 37.2 (SD 8.8) End-point 24.3 (12.5)	**Outcome**: SAPS score: hallucination; delusion; bizarre thinking; thought disorder **Intervention**: Baseline: 1.7 (SD 1.7); 3.7 (SD 0.9); 2.4 (SD 1.1); 3.3 (SD 0.8) **End-point**: 1.1 (SD 1.7); 2.3 (SD 1.2); 1.2 (SD 1.3); 2.0 (SD 1.1) **Control**: Baseline: 1.8 (SD 1.8); 3.4 (SD 0.6); 2.5 (SD 1.0); 3.1 (SD 0.8) **End-point**: 0.9 (SD 1.5); 2.3 (SD 1.2); 1.3 (SD 1.0); 1.8 (SD 1.2)	**Outcome**: Response **Intervention**: 10 **Control**: 5	**Outcome**: Length of stay (days) **Intervention**: 18.2 (SD 9.0, range 7–42) **Control**: 14.9 (SD 9.0, range 7–34)

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Pope (1991)[48]	**Intervention**: Valproate semisodium ***N***: 20 **Dose**: 3 250-mg tablets per day **Route**: Oral **Control**: Placebo ***N***: 23 **Dose**: 3 250-mg tablets per day **Route**: Oral **Duration**: 7–21 days **Washout**: Unclear **Concomitant medications**: Lorazepam during 1st 10 days, 1 mg up to 4 times daily, if needed to treat agitation or insomnia. Some errors were made **Comments**: Details of tablet blinding are given. One investigator was unblinded and performed dosage adjustments. No communication regarding patient status was permitted between unblinded investigator and other investigators, except that unblinded investigator was informed of adverse effects	**Age**: I, mean 39.7 (SD 11.8); C, mean 34.6 (SD 14.7) years **Sex**: 26 M, 10 F **Illness**: Bipolar disorder, manic phase **Diagnosis**: DSM-III-R ***N***: 43 **Duration of illness**: I, mean 12.2 (SD 10.9); C, mean 11.2 (SD 9.7) years **Length of follow-up**: 21 days **Special characteristics**: Lithium resistant or intolerant **Inclusion/exclusion criteria**: Aged 18–65 years. Failure to respond adequately to a trial of lithium or intolerance of lithium side-effects. Excluded for serious medical disorders, previous dose of valproate >250 mg, substance dependence (including more than 3 alcoholic drinks per day). Other neurological exclusions, paroxysmal activity on any EEG. At 4th month criterion was added requiring female patients to be postmenopausal or surgically sterilised. **Further details**: Only 36 reported in analysis. 7 withdrew before day 7. Groups did not differ significantly at baseline in age, sex distribution, duration of illness, days in the study or baseline scores on YMRS or GAS	**Intervention group *n***: 13 terminated between days 7 and 21 (4 withdrawn by trial investigators for failure to improve). 3 withdrew before day 7 and are not included in the analysis (one signed themselves out of hospital, one due to nausea and vomiting, one for clinical deterioration) **Control group *n***: 15 terminated between days 7 and 21 (12 withdrawn by trial investigators for failure to improve). 4 withdrew before day 7 and are not included in data analysis (1 ineligible, 2 clinical deterioration, 1 nausea and projectile vomiting)	***N*** = 43 GI discomfort or nausea without vomiting I 5/20, C 5/23 GI discomfort or nausea with vomiting: I 1/20, C 2/23 Headache: I 4/20, C 6/23 Sedation or fatigue: I 4/20, C 1/23 Constipation: I 0/20, C 3/23 Local swelling or pain: I 1/20, C 2/23 Ataxia: I 2/20, C 0/23 Dysuria: I 0/20, C 2/23 Palpitations: I 1/20, C 1/23 Diplopia: I 1/20, C 1/23 Tightness in chest: I 1/20, C 0 Dry eyes: I 1/20, C 0 Sinus pressure: I 1/20, C 0 Dysarthria: I 1/20, C 0 Depression: I 1/20, C 0 Diarrhoea: I 1/20, C 0 Anorexia: I 1/20, C 0 Agitation: I 1/20, C 0 Bruising: I 0, C 1/23 Lump in throat: I 0, C 1/23 Panic attacks: I 0, C 1/23	**Authors' conclusions**: The data suggest that valproate semisodium is a useful new agent for the treatment of manic patients who have failed to respond to lithium or who cannot tolerate it **Comments**: BPRS subscale data: on 4 of the 18 subscales (conceptual disorganisation, tension, hostility and excitement), patients receiving valproate improved significantly more than those receiving placebo ($p < 0.005$). No subscale produced significant change in favour of placebo. Using ANCOVA, patients randomised to valproate improved significantly more than those randomised to placebo on the MRS ($p = 0.005$), GAS ($p = 0.001$) and BPRS-A ($p = 0.001$)

RESULTS				
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**	**Outcome 4**
BPRS subscale data: on 4 of the 18 subscales (conceptual disorganisation, tension, hostility and excitement), patients receiving valproate improved significantly more than those receiving placebo ($p < 0.005$). No subscale produced significant change in favour of placebo. Using ANCOVA, patients randomised to valproate improved significantly more than those randomised to placebo on the MRS ($p = 0.005$), GAS ($p = 0.001$) and BPRS-A ($p = 0.001$)	**Outcome**: YMRS scores **Intervention**: Baseline 28.2 (5.8) End-point 16.8 (12.9) **Control**: Baseline 28.6 (6.9) End-point 28.1 (12.1)	**Outcome**: GAS scores **Intervention**: Baseline 30.0 (5.9) End-point 50.6 (19.9) **Control**: Baseline 31.6 (5.5) End-point 32.6 (14.5)	**Outcome**: BPRS-A total score **Intervention**: Baseline 75 (SD not reported) End-point median 17-point improvement **Control**: Baseline 75 (SD not reported) End-point median 3-point improvement ($p = 0.001$)	**Outcome**: Received lorazepam (mean total dose) **Intervention**: 5.8 (7.0) mg **Control**: 13.9 (10.3) ($p = 0.010$)
	Outcome 5			
	Outcome: YMRS response (at least 50% improvement) **Intervention**: 9/20 **Control**: 2/23			
CI, gastrointestinal; ANCOVA, analysis of covariance.				

Valproate semisodium versus olanzapine

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Tohen (2002)[56]	**Intervention**: Olanzapine ***N***: 125 **Dose**: 5–20 mg/day (initial daily dose 15 mg/day) **Route**: Oral **Control**: Valproate semisodium ***N***: 126 **Dose**: 5–20 mg/day (initial daily dose 15 mg/day) **Route**: Oral **Duration**: 3 weeks **Concomitant medications**: Lorazepam up to a max. dose of 2 mg/day, not allowed within 8 hours of administration of a symptom rating scale. Benztropine permitted to treat EPS up to a max. of 2 mg/day throughout the study but not as prophylaxis for EPS **Comments**: Investigators made dose adjustments primarily on basis of clinical response but also on plasma levels and adverse events. Double-blind continuation phase of 44 weeks not reported here	**Age**: 18–75 years **Sex**: 107 M, 144 F **Illness**: Bipolar I disorder manic or mixed episode, **Diagnosis**: DSM-IV ***N***: 251 **Duration of illness**: Not stated **Length of follow-up**: Not reported here **Special characteristics**: With or without psychotic features **Inclusion/exclusion criteria**: Minimum total score of 20 on YMRS required on screening visit and on day of random assignment to study groups. Exclusions: serious and unstable medical illness, DSM-IV substance dependence (except nicotine or caffeine), documented history of intolerance to olanzapine or valproate semisodium and treatment with lithium, an anticonvulsant or an antipsychotic medication within 24 hours of random assignment to study groups **Further details**: Patients hospitalised at baseline and for at least the first week of double-blind treatment. Patients who did not tolerate the minimum dose level for treatment were discontinued from participation in study	**Intervention group *n***: 39 (31%) did not complete (12 adverse effects, 11 lack of efficacy) **Control group *n***: 45 (36%) did not complete (9 adverse events, 12 lack of efficacy)	Somnolence: I 49, C 26, $p = 0.002$ Dry mouth: I 42, C 8, $p < 0.001$ Headache: I 28, C 29, $p = 1.00$ Asthenia: I 20, C 17, $p = 0.60$ Dizziness: I 20, C 15, $p = 0.37$ Constipation: I 18, C 15, $p = 0.58$ Dyspepsia: I 18, C 14, $p = 0.46$ Pain: I 17, C 18, $p = 1.00$ Increased appetite: I 15, C 3, $p = 0.003$ Weight gain: I 15, C 10, $p = 0.3$ Agitation: I 14, C 14, $p = 1.0$ Nausea: I 13, C 36, $p < 0.001$ Nervousness: I 13, C 21, $p = 0.2$ Tremor: I 12, C 4, $p = 0.05$ Vomiting: I 10, C 18, $p = 0.16$ Speech disorder: I 10, C 1, $p = 0.005$ Neck rigidity: I 9, C 2, $p = 0.04$ Diarrhoea: I 8, C 17, $p = 0.09$ Sleep disorder: I 7, C 1, $p = 0.04$ Tongue oedema: I 6, C 0, $p = 0.02$	**Authors' conclusions**: Olanzapine group had significantly greater mean improvement of mania ratings and a significantly greater proportion of patients achieving remission compared with the valproate semisodium group. More adverse events, including weight gain, occurred significantly more frequently during treatment with olanzapine than with valproate semisodium **Comments**: Among patients without psychotic features, improvement with olanzapine was 5.4 points greater than with divaploex. In the subgroup with psychotic features, there was no statistically significant difference in improvement between the treatment groups.

RESULTS			
General comments	**Outcome 1**	**Outcome 2**	**Outcome 3**
Among patients without psychotic features, improvement with olanzapine was 5.4 points greater than with valproate semisodium. In the subgroup with psychotic features, there was no statistically significant difference in improvement between the treatment groups.	**Outcome**: YMRS Mean Total Score **Intervention**: Baseline: 27.4 Mean change: 13.4 **Control**: Baseline: 27.9 Mean change: –10.4	**Outcome**: Response rate, YMRS > 50% reduction **Intervention**: 68 patients (54.4%) **Control**: 52 patients (42.3%)	**Outcome**: Remission, YMRS ≤ 12 **Intervention**: 59 patients (47.2%) **Control**: 42 patients (34.1%)

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Tohen (2002)[232]	**Comments**: 44-week follow-up of 3-week trial described in 1158	–	–	Adverse events and laboratory abnormalities more frequent with olanzapine ($p < 0.05$) were somnolence, dry mouth, increased appetite, weight gain, akathisia and liver function test (increased ALT) and for valproate semisodium ($p < 0.05$) nausea, nervousness, manic reaction, rectal disorder and decreased platelets	**Authors' conclusions**: Olanzapine-treated patients had significantly greater mania improvement than valproate semisodium-treated patients over a period of 47-weeks. Relapse rates were higher and time to relapse shorter for valproate semisodium, although not statistically significant **Comments**:

RESULTS

General comments	Outcome 1	Outcome 2	Outcome 3
	Outcome: Mania relapse rates **Intervention**: 24/49, 40.7% **Control**: 21/42, 50%	**Outcome**: Median time to mania relapse **Intervention**: 270 days **Control**: 74 days	**Outcome**: Mean YMRS improvement **Intervention**: Significantly greater by 1.98 ($p < 0.001$)

Study details	Intervention details	Participant details	Withdrawals	Adverse events	Comments
Author (year): Zajecka (2000)[57]	**Intervention**: Valproate semisodium ***N***: 63 **Dose**: 20 mg/kg/day. Mean max. daily dosage: 2115 mg (range: 750–3250) **Control**: Olanzapine ***N***: 57 **Dose**: 20 mg/kg/day. Mean max. daily dosage: 2115 mg (range: 750–3250) **Duration**: 12-week treatment period **Washout**: Screening period 1–3 days **Concomitant medications**: Not stated	**Age**: Mean 38.1–38.9 years **Sex**: 46% F **Illness**: Bipolar disorder, acute mania **Diagnosis**: Not stated ***N***: 120 **Duration of illness**: Not stated **Length of follow-up**: 12 weeks **Special characteristics**: Not stated **Inclusion/exclusion criteria**: Not stated **Further details**: Bipolar patients hospitalised for mania (up to 21 days). Participants were later followed as outpatients	**Intervention group *n***: Participants who met improvement criteria at or before day 21 were discharged from hospital; others were discontinued from study	Changes in body weight sign greater in C (+8.8 lb) than I (+5.5 lb; $p = 0.049$). Adverse events occurring in significantly greater proportion in C: somnolence (I 29%, C 47%), weight gain (I 10%, C 25%), rhinitis (I 3%, C 14%), oedema (I 0%, C 14%) and speech disorder (I 0%, C 7%). No adverse events sign more often in I. One death in C (diabetic ketoacidosis)	**Authors' conclusions**: Results suggest that I and C are equally efficacious in treating mania and have similar effects on QoL. However, I appears to exhibit a superior adverse event profile and is associated with sign less weight gain and lower outpatient costs than C **Comments**: Total 12-week outpatient costs of I, US$554, were statistically significantly lower ($p = 0.0028$) than C (US$1109). Ref. 233 reports detailed effects on weight gain and related outcomes for 118 (I 61, C 57) respondents with weight measurements available. No relevant extra data

RESULTS

General comments	Outcome 1	Outcome 2	Outcome 3
Total 12-week outpatient costs of I, US$554, were statistically significantly lower ($p = 0.0028$) than C ($1109). Ref. 233 reports detailed effects on weight gain and related outcomes for 118 (I 61, C 57) respondents with weight measurements available. No relevant extra data	**Outcome**: MRS **Intervention**: Mean change from baseline to day 21: –14.8 **Control**: Mean change to day 21: –17.2; difference not significant ($p = 0.210$)	**Outcome**: CGI, BPRS, HAM-D Mean change from baseline to day 21: no significant difference between groups	**Outcome**: QoL, Q-LES-Q No statistically significant difference between groups, but trend favouring I for physical portion ($p = 0.09$)

Appendix 7

Quality assessment – clinical effectiveness

Study	Random procedure adequate	Allocation concealed	No. randomised stated	Baseline comparison achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of administrators	Participants blinded	Success of blinding checked	Follow-up adequate	Outcome of withdrawals	Appropriate dose of comparator?	ITT	Comments
AstraZeneca, Study 99 (2002)[26–28]	Yes	Unclear	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	No	Yes	Yes	Yes	Partially	Only ITT analysis for safety data
AstraZeneca, Study 100 (2002)[27]													Yes	Partially	Only ITT analysis for safety data
AstraZeneca, Study 104 (2002)[30]													Yes	Partially	Only ITT analysis for safety data
AstraZeneca, Study 105 (2002)[31,34]													Yes	partially	Only ITT analysis for safety data
Berk, 1999[40]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	Not stated	Yes	Yes	Unclear	No	
Bowden, 1994[49]	Computer-generated random numbers	Yes (centralised/ pharmacy controlled/ other)	Yes	No	Yes	Yes	Unclear	Yes	Yes	Not stated	Yes	Yes	Yes	No	Lithium dose perhaps slightly high (up to 1200 mg). ITT analysis was carried out on fewer patients than were randomised. Block randomisation size 5, patient numbers sent to centres in blocks of 10. Possible to break code? Refs. 50–52 are subgroup analyses of this study so do not need a separate quality assessment
Delbello, 2002[33]	Yes: random number generator	Unclear	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	
Hirschfeld 1999[53]	Not stated	Not stated	Yes	No	Yes	Yes	Yes	Unclear	Yes	Not stated	No	Yes	Yes	Unclear	Lithium dose possibly slightly low (initial 900 mg/day, BNF advises 1–1.5 g/day). Results poorly reported
Kowatch 2000[54]	Not stated	Not stated	Yes	Not stated	Yes	Yes	No	No	No	Not stated	Yes	Yes	Unclear	Yes	
McElroy 1996[55]	Not stated	Not stated	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Not stated	No	Yes	Yes	Yes	

continued

Study	Random procedure adequate	Allocation concealed	No. randomised stated	Baseline comparison achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of administrators	Participants blinded	Success of blinding checked	Follow-up adequate	Outcome of withdrawals	Appropriate dose of comparator?	ITT	Comments
Meehan 2001[42]	Not stated	Not stated	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Not stated	Yes	No	Yes	No	Authors state that ITT analysis was used, but this is not apparent from data presented. Ref. 43 is an abstract of this trial – no separate quality assessment necessary
Pope 1991[48]	Random number tables	Yes (centralised/ pharmacy controlled/ other)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	Yes	No	7 withdrawals were described but not included in the analysis of results
Tohen 1999[35]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	Not stated	Unclear	No	Yes	No	ITT analysis for adverse events but not for effectiveness
Tohen 2002[56,232]	Not stated	Not stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	
Tohen 2002[41]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	
Tohen 2000[36]	Computer-generated random numbers	No (sealed envelopes/ quasi-random methods)	Yes	No	Yes	Unclear	Not stated	Unclear	Yes	Not stated	Yes	Yes	Yes	Yes	
Tohen 2001[37]	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	Not stated		Yes	No	No	No	Yes	Yes
Zajecka 2000[57]	Not stated	Not stated	Unclear	Not stated	No	Yes	Not stated	Yes	Yes	Not stated	Not stated	No	Unclear	Not stated	Abstract

Appendix 8

Data extraction tables for economic evaluations

Primary source	Database
Author	Keck PE, Jr, Nabulsi AA, *et al*. A pharmacoeconomic model of valproate semisodium vs. lithium in the acute and prophylactic treatment of bipolar I disorder. *J Clin Psychiatry* 1996; **57**:213–22[58]
Date	1996
Type of economic evaluation	Cost-effectiveness analysis
Currency used	US$
Year to which costs apply	1994
Perspective used	Unclear but can infer perspective of third-party payer
Timeframe	1 year
Comparators	Valproate semisodium, lithium
Source(s) of effectiveness data	University of Cincinnati Mania Project database, and studies published since 1980: Freeman (1992),[118] Bowden (1994),[49] Calabrese (1992)[95] and Pope (1991)[48]
Source(s) of resource use data	A panel of five psychiatrists was assembled to provide data about the resources utilised. Also from University of Cincinnati Mania Project database
Source(s) of unit cost data	Physicians Fee and Coding Guide, Medicare Physician Fee Schedule, Medicare Laboratory Fee Schedule, California Office of Statewide Health Planning and Development database of hospital discharges for 1992 and the Red Book of wholesale drug prices
Modelling approach used	Decision-analytic model. Treatment was modelled as resulting in either response or non-response. Those who were non-responders to either drug were assumed to have had the alternative drug added, and then to have had a pattern of relapse that did not differ by initial treatment. The relapses were separated by whether or not they required hospitalisation
Summary of effectiveness results	Initial hospital length of stay is 18.4 days (L) and 14.3 days (V). Initial response rate is 0.49 (L), and 0.59 (V). Relapse rate is 0.56 (L), 0.56 (V). Number of relapses is 1.7 (L), 1.7 (V). Probability of hospitalisation is 0.43 (L) and 0.43 (V). Rate of reported side-effects is 1.1 (L) and 0.55 (V)
Summary of cost results	Mean total costs were $43,400 and $39,643, respectively, for lithium and valproate semisodium. Cost savings for patients with classic mania were greater for lithium, whereas cost savings for patients with mixed mania and rapid cycling were greater for valproate semisodium. Considering all types of illness together, beginning treatment with valproate semisodium led to costs that were 9% lower than the estimated costs when lithium was the initial treatment
Summary of cost-effectiveness results	Not reported since the focus of the model was on the costs of treatment. Can infer that valproate semisodium is cost-effective (i.e. has higher response and lower costs) from the results reported
Sensitivity analysis	Univariate sensitivity analysis. The variations tested included the length of stay of the initial hospitalisation, the response rate to the initial therapy during this hospitalisation, the relapse rate, the number of relapses, the probability of hospitalisation during a relapse, the cost of treating side-effects, the cost of prophylactic treatment, the use of Medicare prices and the prevalence of the illness subtype. These variations made only a small change in overall costs
Main conclusions	Valproate semisodium is a less costly treatment than lithium in the acute and prophylactic treatment of patients with bipolar I disorder

Primary source	Database
Author	Zajecka J, Weisler R, Sommerville KW, *et al*. Divalproex sodium vs olanzapine for the treatment of mania in bipolar disorder. In *39th Annual Meeting of the American College of Neuropsychopharmacology*, 10–14 December 2000, San Juan, Puerto Rico. Vanderbilt University Medical Center, American College of Neuropsychopharmacology[57]
Date	2000
Type of economic evaluation	Cost-effectiveness analysis
Currency used	US$
Year to which costs apply	Not stated
Perspective used	Not stated
Timeframe	12 weeks
Comparators	Valproate semisodium and olanzapine
Source(s) of effectiveness data	Randomized, double-blind, parallel group, multicentre study
Source(s) of resource use data	Not stated
Source(s) of unit cost data	Not stated
Modelling approach used	Not stated
Summary of effectiveness results	Changes in mean MRS, CGI scale, BPRS and HAM-D scores did not reveal any statistically significant difference between the two groups
Summary of cost results	Total 12-week outpatient cost of the valproate semisodium group (US$554) were statistically significant lower than the olanzapine group (US$1109)
Summary of cost-effectiveness results	Total 12-week outpatient cost of the valproate semisodium group (US$554) were statistically significant lower than the olanzapine group (US$1109). Changes in effectiveness did not reveal any statistically significant difference between the two groups
Sensitivity analysis	Not stated
Main conclusions	Valproate semisodium and olanzapine are equally efficacious in treating mania. Valproate semisodium appears to exhibit a superior adverse event profile and is associated with significant less weight gain and lower outpatient cost than olanzapine

Primary source	Company submission
Author	Eli Lilly and Company Limited
Date	21 October 2002
Type of economic evaluation	Cost-effectiveness analysis
Currency used	£ Sterling
Year to which costs apply	2000–01
Perspective used	NHS
Timeframe	1 year
Comparators	Separate pairwise comparisons made across 3 separate scenarios. Scenario 1 evaluated olanzapine co-therapy (olanzapine in combination with either lithium or valproate semisodium) in comparison with a mixed group of patients receiving either lithium or valproate semisodium alone. Scenario 2 evaluated olanzapine monotherapy in comparison with valproate semisodium. Scenario 3 evaluated olanzapine monotherapy in comparison with haloperidol
Source(s) of effectiveness data	• Shi L, Namjoshi MA, Zhang F, *et al*. Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *Int Clin Psychopharmacol*. 2002;**17**:227–37[38]

continued

Primary source	Company submission
	• Tohen M, Chengappa KNR, Suppes T, *et al*. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry* 2002;**59**:62–9[41] • Tohen M, Chengappa KNR, Suppes T, *et al*. Olanzapine combined with lithium or valproate in prevention of recurrence in bipolar disorder: an 18 month study. Poster presented at the 11th Biennial Winter Workshop in Schizophrenia, February–March 2002, Davos • Tohen M, Baker RW, Altshuler LL, *et al*. Olanzapine versus divalproex in the treatment of acute mania. *Am J Psychiatry* 2002;**159**:1011–17[56] • Tohen M, Baker RW, Altshuler L, *et al*. Olanzapine versus divalproex for bipolar mania: a 47-week study. Poster presented at the 11th Biennial Winter Workshop in Schizophrenia, February–March 2002, Davos
Source(s) of resource use data	BNF, Maudsley Guidelines, UKPPG website
Source(s) of unit cost data	PSSRU Health and Social Care Unit Costs, NHS Trust data, BNF
Modelling approach used	The model was based on a deterministic decision-analytic model which included the use of drugs on both the acute treatment period and as part of maintenance therapy. The model assessed costs and outcomes for five patient subgroups (newly diagnosed, no episode, classic, mixed and rapid cycling) and across all patient groups. Each manic episode type is analysed using the decision model; initial patient response to first-line therapy is evaluated. Patients who respond to first-line therapy move to maintenance therapy, and are treated as such until another episode occurs. Unresponsive patients switch to a second-line treatment, and proceed similarly to first line. Patients unresponsive to second-line treatment proceed to a third-line treatment, to which all patients are assumed responsive. Remission end-points reported in the clinical trials are used as an indicator of treatment response. The treatment used for acute treatment is also assumed for maintenance. The model assumes that the recurrence rate and time to recurrence for all patients are the same as those experienced by the respective mania patients. Resource use data in the model consist of all medications, hospitalisations, laboratory equipment and other specialist services used for the treatment of bipolar disorder
Summary of effectiveness results	For the combined analysis for all patients, the average number of acute symptoms days was 4.63 (olanzapine + lithium/divalproex) and 8.2 (lithium/divalproex) in scenario 1, 6.49 (olanzapine) and 6.38 (divalproex) in scenario 2 and 12.65 (haloperidol) and 10.38 (olanzapine) in scenario 3. For the classic group, the average number of acute symptoms days was 18.78 (olanzapine + lithium/divalproex) and 32.77 (lithium/divalproex) in scenario 1, 26.13 (olanzapine) and 25.61 (divalproex) in scenario 2 and 50.68 (haloperidol) and 41.88 (olanzapine) in scenario 3
Summary of cost results	For the combined analysis for all patients, the average cost per patient is £5908 (olanzapine + lithium/divalproex) and £6752 (lithium/divalproex) in scenario 1, £6427 (olanzapine) and £6465 (divalproex) in scenario 2 and £6873 (haloperidol) and £6198 (olanzapine) in scenario 3 For the classic group, the average cost per patient is £15,365 (olanzapine + lithium/divalproex) and £17,661 (lithium/divalproex) in scenario 1, £16,789 (olanzapine) and £17,039 (divalproex) in scenario 2 and £18,316 (haloperidol) and £16,187 (olanzapine) in scenario 3
Summary of cost-effectiveness results	In both the total population and in the classic group, the olanzapine group dominated the comparator in both scenarios 1 and 3. In scenario 2 the incremental cost-effectiveness in terms of cost per day in remission was £321 (all patients) and £467 (classic patients) more per symptom-free day for the divalproex treatment strategy compared with the olanzapine strategy
Sensitivity analysis	Univariate and multivariate sensitivity analysis. Parameters used in the sensitivity analysis are remission rate, time to remission, recurrence rate and time to recurrence
Main conclusions	The results demonstrate the cost-effectiveness of olanzapine as part of a combination therapy regimen with other commonly used treatments. Olanzapine as monotherapy is also cost-effective in comparison with haloperidol. Olanzapine compared with divalproex as monotherapy has an ICER of £321 for all patients and £467 for classic mania patients

Primary source	Company submission
Author	Sanofi-Synthelabo Ltd
Date	21 October 2002
Type of economic evaluation	Cost-effectiveness analysis
Currency used	£ Sterling
Year to which costs apply	2001–02
Perspective used	NHS
Timeframe	90-day period
Comparators	Valproate semisodium, lithium and olanzapine
Source(s) of effectiveness data	Keck PE, Jr, Nabulsi AA, Taylor JL, *et al*. A pharmacoeconomic model of divalproex semisodium vs. lithium in the acute and prophylactic treatment of bipolar I disorder. *J Clin Psychiatry* 1996;**57**:213–22[58]
Source(s) of resource use data	• Keck PE, Jr, Nabulsi AA, Taylor JL, *et al*. A pharmacoeconomic model of divalproex semisodium vs. lithium in the acute and prophylactic treatment of bipolar I disorder. *J Clin Psychiatry* 1996;**57**:213–22[58] • Department of Health. Hospital Episode Statistics (HES) 2000–01. http://www.doh.gov.uk/hes/standard_data/available_tables/index.html 2002 • Das Gupta R, Guest JF. Annual cost of bipolar disorder to UK society. *Br J Psychiatry* 2002;**180**:227–33[16] • Expert opinion
Source(s) of unit cost data	• British Medical Association and the Royal Pharmaceutical Society of Great Britain. *British National Formulary*. London: British Medical Association; 2002. • Netten A, Curtis L. *Unit costs of health and social care 2001*. Canterbury: Personal Social Services Research Unit; 2001.
Modelling approach used	A decision-analytic model is presented, which estimates the costs and benefits of treating 1000 patients presenting to hospital with an acute manic episode. The model uses clinical data from the published pharmacoeconomic study by Keck and colleagues[58] and applies costs and resource-use patterns taken from available UK sources. An assumption was made that valproate semisodium and olanzapine are equally effective
Summary of effectiveness results	Number of responders per 1000 patients was 590 for divalproex, 490 for lithium and 590 for olanzapine
Summary of cost results	Total costs for 1000 patients initiated on divalproex were £7,223,327, lithium £8,090,355 and olanzapine £7,381,225
Summary of cost-effectiveness results	Average costs per patient and per responder for divalproex are £7223 and £12,243, respectively, for lithium £8090 and £16,511, respectively and for olanzapine, £7381 and £12,510, respectively
Sensitivity analysis	Univariate and multivariate sensitivity analysis. Increased daily dose of divalproex by 25%; decreased daily dose of comparators by 25%. Decreased daily dose of divalproex by 25%; increased daily dose of comparators by 25%. Increased length of initial phase to 31 days. Decreased length of time horizon to 70 days. Increased adjunct duration by 7 days. Increased cost of hospitalisations by 5%. Increased cost of other resource use by 5%. Increased length of stay for divalproex by 10%; decreased length of stay for comparators by 10%. Decreased length of stay for divalproex by 10%; increased length of stay for comparators by 10%. Decreased response rate for divalproex by 10%; increased response rate for comparator by 10%. Increased response rate for divalproex by 10%; decreased response rate for comparators by 10%. Decreased duration of hospitalisation for non responders to 40 days. The model was relatively insensitive to changes in the majority of the model inputs
Main conclusions	Average costs per patient and per responder were lower for divalproex than for lithium (£7223 vs £8090 and £12,243 vs £16,511, respectively). When compared with olanzapine, average costs per patient and per responder are lower for divalproex than for olanzapine (£7223 vs £7381 and £12,243 vs £12,510, respectively)

Appendix 9

Details of quality assessment for economic studies

All items are graded as either ✓ yes (item adequately addressed), ✗ no (item not adequately addressed), **?** unclear or not enough information, NA not applicable or NS not stated.

Keck PE, Jr, Nabulsi AA, *et al*. A pharmacoeconomic model of divalproex semisodium vs lithium in the acute and prophylactic treatment of bipolar I disorder. *J Clin Psychiatry* 1996;57(5):213–22[58]

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✗	Can infer third-party payer
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✗	The study only considers two active substances in monotherapy
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✗	There is no justification of selected alternatives
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	**?**	Effectiveness data derived from RCTs and observational data
11. Potential biases identified (especially if data not from RCTs)	✗	Insufficient details provided regarding the generalisability of the observational data source
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	**?**	Resource utilisation derived from expert opinion and hospitalisation data from a single US centre
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource-use data	✗	
17. Productivity costs treated separately from other costs	NA	Productivity costs not considered
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	

continued

Study question		Comments
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	NA	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves)	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	
35. The choice of variables for sensitivity analysis is justified	✗	
36. The ranges over which the variables are varied are stated	✗	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✗	Incremental analysis is not reported. Only cost per patient is stated
38. Major outcomes are presented in both a disaggregated and an aggregated form	✓	
39. Applicable to the NHS setting	?	Insufficient details provided regarding the generalisability of the observational data source to determine applicability to a UK setting

Zajecka J, Weisler R, Sommerville KW, *et al*. Divalproex sodium vs olanzapine for the treatment of mania in bipolar disorder. In *39th Annual Meeting of the American College of Neuropsychopharmacology*, 10–14 December 2000, San Juan, Puerto Rico. Vanderbilt University Medical Center, American College of Neuropsychopharmacology[57]

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✗	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✗	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✗	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✗	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	Effectiveness comes from an RCT
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✗	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	
Costs		
13. All the important and relevant resource use included	✗	
14. All the important and relevant resource use measured accurately (with methodology)	✗	
15. Appropriate unit costs estimated (with methodology)	✗	
16. Unit costs reported separately from resource-use data	✗	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✗	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✗	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	NA	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	NA	
24. All model outputs described adequately	NA	

continued

Study question		Comments
Discounting		
25. Discount rate used for both costs and benefits	NA	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	?	Statistical comparison limited to outpatient costs only
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves)	✗	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✗	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✗	Not reported
35. The choice of variables for sensitivity analysis is justified	✗	
36. The ranges over which the variables are varied are stated	✗	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✗	No ratio is reported.
38. Major outcomes are presented in both a disaggregated and an aggregated form	✗	
39. Applicable to the NHS setting	?	Does not provide enough information

Eli Lilly and Company Limited submission

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	?	A series of separate pairwise comparisons is made between the different drug treatments. No scenario considers the full range of treatment alternatives
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	Based on direct comparisons made in the trials

continued

Study question		Comments
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✗	Clinical effectiveness not established for second- and third-line therapies
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	No formal synthesis undertaken. Results from separate studies reporting on the effectiveness of a single drug treatment are analysed using separate scenarios
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	**?**	Combination of retrospective UK chart review and expert opinion
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource-use data	✓	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	NA	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves)	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	

continued

Study question		Comments
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	Univariate and multivariate
35. The choice of variables for sensitivity analysis is justified	✗	No justification for remission rate, time to remission, recurrence rate and time to recurrence
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in both a disaggregated and an aggregated form	✓	
39. Applicable to the NHS setting	✓	

Sanofi-Synthelabo Ltd submission

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	?	Source of effectiveness data is Keck (1996).[58] See comments there
11. Potential biases identified (especially if data not from RCTs)	?	Source of effectiveness data is Keck (1996).[58] See comments there

continued

Study question		Comments
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	Effectiveness comes from a single study; Keck (1996)[58]
Costs		
13. All the important and relevant resource use included	✗	Laboratory and diagnostic costs not considered. Justified on the basis that their exclusion will be conservative
14. All the important and relevant resource use measured accurately (with methodology)	**?**	Expert opinion is used to establish primary and adjunctive medication. The length of stay is based on median value rather than mean value. Unclear how reliable the assumptions derived from a single US centre are to a UK setting. Reduction in length of stay of divalproax in comparison with lithium is based on a rapid loading strategy
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource-use data	✓	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	NA	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	Deterministic analysis
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves)	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order uncertainty (uncertainty between patients)?	NA	

continued

Study question		Comments
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	
35. The choice of variables for sensitivity analysis is justified	✗	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in both a disaggregated and an aggregated form	✓	
39. Applicable to the NHS setting	**?**	Assumptions for key cost components taken from a single US centre. It is unclear how generalisable these results are to a UK setting

Appendix 10
WinBUGS model

```
model{

for (j in 1:5) { delta[j] ~ dnorm(0.0,0.0001) }
m.r~dnorm(0.0,0.001)
t.r~dgamma(0.01,0.01)
for (j in 1:7){ mu.r[j]~dnorm(m.r,t.r) }

for (i in 1:17){ logit(p[i])<-mu.r[study[i]] + equals(treat[i],2) * delta[1] + equals(treat[i],3) * delta[2] +
equals(treat[i],4) * delta[3] + equals(treat[i],5) * delta[4] + equals(treat[i],6 )* delta[5]}

for (i in 1:17){ r[i]~dbin(p[i],n[i]) }

logit(t[1]) <- m.r
for (j in 2: 6) { logit(t[j]) <- m.r + delta[j-1] }
}

# data
list( r=c(34,16,30,19,32,17,18,68,52,55,43,35,57,51,27,5,10),
n=c(70,66,54,56,67,35,72,125,123,98,101,100,107,98,97,15,21),
study=c(1,1,2,2,3,3,3,4,4,5,5,5,6,6,6,7,7),
treat=c(5,1,5,1,3,2,1,5,3,6,4,1,4,2,1,6,3))

# initial
list(
m.r=0,
t.r=1)
```

Node	Mean	SD	MC error	2.5%	Median	97.5%	Start	Sample
delta[1]	0.9057	0.2178	0.005356	0.4763	0.9039	1.334	100001	10000
delta[2]	0.7169	0.2013	0.005949	0.3262	0.7129	1.12	100001	10000
delta[3]	0.7645	0.1892	0.004861	0.3934	0.7659	1.136	100001	10000
delta[4]	1.057	0.1907	0.00595	0.6858	1.054	1.436	100001	10000
delta[5]	1.023	0.2319	0.004929	0.564	1.023	1.487	100001	10000
m.r	–0.9088	0.1363	0.005013	–1.181	–0.9057	–0.6519	100001	10000
t[1]	0.288	0.02775	0.001026	0.2348	0.2879	0.3426	100001	10000
t[2]	0.4992	0.05095	6.271E-4	0.3988	0.4999	0.5969	100001	10000
t[3]	0.4525	0.04158	5.529E-4	0.3718	0.4514	0.5382	100001	10000
t[4]	0.4643	0.04371	7.04E-4	0.3757	0.4652	0.5477	100001	10000
t[5]	0.5368	0.03887	5.026E-4	0.4615	0.5361	0.6144	100001	10000
t[6]	0.5283	0.05411	7.299E-4	0.4204	0.5288	0.6331	100001	10000
t.r	70.5	68.49	1.349	6.661	49.27	256.3	100001	10000

Appendix 11

Cost assumptions applied to sensitivity analysis

Scenario A costs for responders and non-responders

Drug	Parameter	Cost for responders	Cost for non-responders
Olanzapine	Inpatient days	21	62
	Inpatient costs (£)	3040.13	8999.21
	Drug cost (£)	118.75	118.75
	Diagnostic cost (£)	2.23	2.23
	Total (£)	3161.11	9120.19
Valproate semisodium	Inpatient days	21	62
	Inpatient costs (£)	3040.13	8999.21
	Drug cost (£)	50.99	50.99
	Diagnostic cost (£)	48.13	48.13
	Total (£)	3139.24	9098.33
Quetiapine	Inpatient days (£)	21	62
	Inpatient costs (£)	3040.13	8999.21
	Drug cost (£)	122.55	122.55
	Diagnostic cost (£)	2.23	2.23
	Total (£)	3164.91	9123.99
Lithium	Inpatient days (£)	21	62
	Inpatient costs (£)	3040.13	8999.21
	Drug cost (£)	2.35	2.35
	Diagnostic cost (£)	119.52	119.52
	Total (£)	3161.99	9121.07
Haloperidol	Inpatient days (£)	21	62
	Inpatient costs (£)	3040.13	8999.21
	Drug cost (£)	4.61	4.61
	Diagnostic cost (£)	2.23	2.23
	Total (£)	3046.96	9006.05

Scenario B costs for responders and non-responders

Drug	Parameter	Cost for responders	Cost for non-responders
Olanzapine	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	118.75	118.75
	1st-line diagnostic cost (£)	2.23	2.23
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	Total (£)	9120.19	9369.75
Valproate semisodium	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	50.99	50.99
	1st-line diagnostic cost (£)	48.13	48.13
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	Total (£)	9098.33	9347.89
Quetiapine	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	122.55	122.55
	1st-line diagnostic cost (£)	2.23	2.23
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	Total (£)	9123.99	9373.55
Lithium	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	2.35	2.35
	1st-line diagnostic cost (£)	119.52	119.52
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	Total (£)	9121.07	9370.63
Haloperidol	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	4.61	4.61
	1st-line diagnostic cost (£)	2.23	2.23
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	124.78
	Total (£)	9006.05	9255.61

Scenario C costs for responders and non-responders

Drug	Parameter	Cost for responders	Cost for non-responders
Olanzapine	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	118.75	118.75
	1st-line diagnostic cost (£)	2.23	2.23
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	Total (£)	9120.19	9133.86
Valproate semisodium	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	50.99	50.99
	1st-line diagnostic cost (£)	48.13	48.13
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	Total (£)	9098.33	9112.00
Quetiapine	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	122.55	122.55
	1st-line diagnostic cost (£)	2.23	2.23
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	Total (£)	9123.99	9137.66
Lithium	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st-line drug cost (£)	2.35	2.35
	1st-line diagnostic cost (£)	119.52	119.52
	2nd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	3rd-line drug cost (including laboratory/diagnostics) (£)	0	6.84
	Total (£)	9121.07	9134.75
Haloperidol	Inpatient days	62	62
	Inpatient costs (£)	8999.21	8999.21
	1st Line drug cost (£)	4.61	4.61
	1st Line diagnostic cost (£)	2.23	2.23
	2nd Line drug cost (including laboratory/diagnostics) (£)	0	6.84
	3rd Line drug cost (including laboratory/diagnostics) (£)	0	6.84
	Total (£)	9006.05	9019.72

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine

Dr Jeffrey Aronson
Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London

Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen

Professor Stuart Logan, Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter & Plymouth

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, Institute for Research in the Social Services, University of York

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Birmingham

Ms Kate Thomas, Deputy Director, Medical Care Research Unit, University of Sheffield

Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke, Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, Institute of Community Health Sciences, Queen Mary, University of London

Mr Matthew William Cooke, Senior Clinical Lecturer and Honorary Consultant, Emergency Department, University of Warwick, Coventry & Warwickshire NHS Trust, Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery, South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson, Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology, University of Liverpool, Liverpool Women's Hospital

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma, Consultant Psychiatrist & Hon Snr Lecturer, Mental Health Resource Centre, Victoria Central Hospital, Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278