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The research reported in this monograph was commissioned by the HTA Programme as project number 05/35/01. The contractual start date was in September 2005. The draft report began editorial review in May 2006 and was accepted for publication in February 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder

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Objectives: To determine the clinical effectiveness and cost-effectiveness of pharmacological and/or psychosocial interventions for the prevention of relapse in people with bipolar disorder.
Data sources: Major electronic databases were searched up to September 2005.
Review methods: Systematic reviews were undertaken on the clinical and economic effectiveness of treatments. An analysis was performed using the methods of mixed treatment comparison (MTC) to enable indirect comparisons to be made between the treatments. An economic model of treatments for the prevention of relapse in bipolar disorder was developed.
Results: Forty-five trials were included in the clinical effectiveness review; all but one studied adults. This review found that for the prevention of all relapses, lithium, valproate, lamotrigine and olanzapine performed better than placebo, with lithium and lamotrigine having the strongest evidence. For depressive relapse prevention, valproate, lamotrigine and imipramine performed better than placebo, with evidence strongest for lamotrigine and weakest for imipramine. For manic relapses, lithium and olanzapine performed significantly better than placebo. The MTC found that the best treatment for bipolar I patients with mainly depressive symptoms was valproate, followed by lithium plus imipramine. For bipolar I patients with mainly manic symptoms, olanzapine was the best treatment. From the studies investigating psychosocial interventions, there were few data for each comparison and outcome. The evidence suggests that cognitive behaviour therapy (CBT), in combination with usual treatment, is effective for the prevention of relapse. Group psychoeducation and possibly family therapy may also have roles as adjunctive therapy for preventing relapse. The results from the decision analytic model developed on the cost-effectiveness of long-term maintenance treatments of bipolar I patients suggest that the choice of treatment is dependent upon a number of factors: the previous episode history of a patient and the mortality benefit assumed for lithium strategies. The results from the base-case analysis for patients with a recent history of depression suggest that valproate, lithium and the combination of lithium and imipramine are potentially cost-effective depending upon the amount that a decision-maker is willing to pay for additional health gain. Using conventional amounts that the NHS is prepared to pay for health gain, then the lithium-based strategies appear to be potentially cost-effective for this group. For patients with a recent history of mania, the choice of pharmacological intervention appears to be between olanzapine and lithium monotherapy. Again using conventional threshold as a reference point, the results suggest that lithium is the most cost-effective therapy. Excluding the additional mortality benefit associated with lithium-based strategies resulted in all treatments for patients with a recent history of a depressive episode being dominated by valproate and, in the case of patients with a recent history of a manic episode, by olanzapine.
Conclusions: Lithium, valproate, lamotrigine and olanzapine are effective as maintenance therapy for the prevention of relapse in bipolar disorder. Olanzapine and lithium are efficacious for the prevention of manic relapses and valproate, lamotrigine and imipramine for

the prevention of depressive relapse. There is some evidence that CBT, group psychoeducation and family therapy might be beneficial as adjuncts to pharmacological maintenance treatments. Insufficient information is available regarding the relative tolerability of the treatments or their relative effects on suicide rate and mortality. For patients with a recent depressive episode, valproate, lithium monotherapy and the combination of lithium and imipramine are potentially cost-effective. For patients with a recent manic episode, olanzapine and lithium monotherapy are potentially cost-effective. The cost-effectiveness estimates in both groups of patients were shown to be sensitive to the assumption of a reduced suicidal risk associated with lithium-based strategies. Further research is needed into the adverse effects of all treatments and the differential effects of agents. Good-quality trials of valproate, of combination therapy, e.g. lithium plus a selective serotonin reuptake inhibitor antidepressant, of psychosocial interventions and of the disorder in children are also required.

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

Akathisia A feeling of 'inner restlessness' and disquiet, manifest in the inability to remain still. A side-effect of antipsychotic (neuroleptic) drugs.

Bipolar I A type of bipolar disorder, usually defined as the occurrence of one or more manic or mixed episodes, often accompanied by one or more major depressive episodes.

Bipolar II A type of bipolar disorder, usually defined as the occurrence of one or more major depressive episodes, accompanied by at least one hypomanic episode.

Credible intervals In Bayesian statistics, a credible interval is a posterior probability interval, used for purposes similar to those of confidence intervals in frequentist statistics.

Depressive episode A period of abnormally depressed mood or loss of interest or pleasure. Symptoms may include persistent feelings of sadness or emptiness, fatigue, insomnia, weight loss, feelings of worthlessness and suicidal ideation.

Dyskinesia A disruption of voluntary movements, resulting in poor or abnormal movement. Can be a side-effect of taking antipsychotic drugs.

Euthymic In a stable mood state, that is, not actively manic or depressed.

Hypomanic episode A period of uncharacteristic elevated mood or irritability, which is distinct from normal non-depressed mood. Less severe than a manic episode and not associated with significant functional impairment.

Manic episode A period of abnormally elevated or irritable mood. Symptoms may include feelings of increased self-esteem, increased talking, restlessness, insomnia or hypersomnia, distractibility and engaging in risky behaviours.

Mixed episode A period of at least 1 week in which both manic and depressive episodes are repeatedly experienced.

Mixed treatment comparison Mixed treatment comparison is a form of Bayesian meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A versus B and B versus C trials) and indirect comparisons (A versus C trials) also, facilitating the simultaneous inference of all treatments in order to select the best option.

Parkinsonism A collection of symptoms similar to those seen with Parkinson's disease, including tremor, muscle rigidity and difficulties in moving. Can result from use of antipsychotic drugs.

Quality-adjusted life-year (QALY) An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Rapid cycling Seen in some individuals with bipolar disorder who experience episodes or mood switching more frequently than others with bipolar disorder. Often defined as four or more episodes in a year.

continued

List of abbreviations *continued*

BAP	British Association for Psychopharmacology
BNF	British National Formulary
BRMRS	Bech–Rafaelsen Mania Rating Scale
CBT	cognitive behaviour therapy
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CPN	community psychiatric nurse
CrI	credible interval
CRT	crisis resolution team
CT	cognitive therapy
DALY	disability-adjusted life-year
DSM-III	*Diagnostic and statistical manual of mental disorders*, 3rd ed.
DSM-III-R	*Diagnostic and statistical manual of mental disorders*, 3rd ed., revised
DSM-IV	*Diagnostic and statistical manual of mental disorders*, 4th ed.
ECG	electrocardiogram
GDG	Guideline Development Group
HAM-D	Hamilton Rating Scale for Depression
HEED	Health Economic Evaluation Database
HES	Hospital Episode Statistics
I$	international dollars
ICD-9	International Classification of Diseases 9
ICD-10	International Classification of Diseases 10
ICER	incremental cost-effectiveness ratio
ISS	Internal State Scale
ITT	intention-to-treat
MAO	monoamine oxidase inhibitor
MeSH	MEDLINE Thesaurus
M–H	Mantel–Haenszel
MRS	Mania Rating Scale
MTC	mixed treatment comparison
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NOS	not otherwise specified
OR	odds ratio
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RDC	research diagnostic criteria
SD	standard deviation
SG	standard gamble
SHO	Senior House Officer
SMR	standardised mortality ratio
SSRI	selective serotonin reuptake inhibitor
TAU	treatment as usual
TTO	time trade-off
VAS	visual analogue scale
WHO	World Health Organization
WTP	willingness to pay
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 recurrent mood disorder associated with significant morbidity and mortality that places a considerable economic burden on UK society. Long-term treatment of bipolar disorder is necessary to prevent recurrence and reduce the loss of productivity and increased medical costs associated with this illness. Lithium has been the mainstay treatment for bipolar disorder for many years, but more recently, anticonvulsants, antidepressants, antipsychotics and adjunctive psychosocial therapies have been used in the maintenance treatment of bipolar disorder. However, the evidence for the effectiveness of these treatments is unclear.

Objective

The aims of this review were to determine the clinical effectiveness and cost-effectiveness of pharmacological and/or psychosocial interventions for the prevention of relapse in people with bipolar disorder.

Methods

This technology assessment comprised the following research.

- A systematic review of the clinical effectiveness of pharmacological and psychosocial interventions for the prevention of relapse in bipolar disorder. Randomised or quasi-randomised controlled trials of maintenance therapy that provided data on rate of relapse were reviewed.
- An analysis using the methods of mixed treatment comparison (MTC) to enable indirect comparisons to be made between the treatments for the prevention of relapse in bipolar disorder.
- A systematic review of existing economic evaluations of treatments for the prevention of relapse in bipolar disorder.
- Development of an economic model of treatments for the prevention of relapse in bipolar disorder.

Results

Clinical effectiveness

The review of clinical effectiveness included 45 trials; all but one tested the intervention or comparator in adults. They were placebo- or active controlled trials of lithium, valproate, lamotrigine, carbamazepine, olanzapine, imipramine, quetiapine, amitriptyline, perphenazine, flupenthixol and psychosocial interventions [cognitive behaviour therapy (CBT); psychoeducation; family intervention; care management; and integrated group therapy].

For the prevention of all relapses, lithium, valproate, lamotrigine and olanzapine were statistically significantly better than placebo. The evidence was strongest for lithium and lamotrigine; that for olanzapine may be unreliable as only responders to olanzapine were studied.

For the prevention of depressive relapses, valproate, lamotrigine and imipramine were statistically significantly better than placebo. The evidence is probably strongest for lamotrigine; the evidence base for imipramine is very weak (two very small trials). For manic relapses, lithium and olanzapine were statistically significantly better than placebo, but again for olanzapine only responders to olanzapine were studied.

Only olanzapine demonstrated greater efficacy than lithium, and then for all relapses and manic relapse, but not for depressive relapse.

In order to investigate the relative efficacy of the treatments, an MTC was performed. The purpose of an MTC is to bring together the clinical evidence regarding the efficacy of all treatments for a specified indication in a 'network of evidence' linked by common comparators. Of all the treatments included in the systematic review, lithium, valproate, lamotrigine, carbamazepine, olanzapine, imipramine and lithium plus imipramine could be linked in a network of evidence. None of the psychosocial interventions could be linked into the network of evidence.

The results of the MTC indicate that carbamazepine is not an effective maintenance treatment for bipolar I disorder. In patients with mainly depressive symptoms the treatment with the highest probability of being the best for the prevention of all relapses appears to be valproate, followed by lithium plus imipramine. In patients with mainly manic symptoms, olanzapine is by far the best option for the prevention of all relapses, followed by valproate and lithium.

From the studies investigating psychosocial interventions, there were few data for each comparison and outcome. The evidence suggests that CBT, in combination with usual treatment, is effective for the prevention of relapse. Group psychoeducation and possibly family therapy may also have roles as adjunctive therapy for preventing relapse.

Cost-effectiveness

Following the review of economic evidence from the literature, a new decision analytic model was developed. This focused on the cost-effectiveness of long-term maintenance treatments of bipolar I patients with a range of alternative pharmacological treatments.

The results from the model suggest that the choice between alternative pharmacological treatments based on cost-effectiveness considerations is dependent upon a number of factors: the previous episode history of a patient (i.e. whether manic or depressive) and the mortality benefit assumed for lithium strategies.

The results from the base-case analysis for patients with a recent history of depression suggest that valproate, lithium and the combination of lithium and imipramine are potentially cost-effective depending upon the amount that a decision-maker is willing to pay for additional health gain [assessed here using quality-adjusted life-years (QALYs)]. Using conventional amounts that the NHS is prepared to pay for health gain (£20,000–40,000 per QALY), the lithium-based strategies appear to be potentially cost-effective for this group.

For patients with a recent history of mania, the choice of pharmacological intervention appears to be between olanzapine and lithium monotherapy. Again using conventional threshold as a reference point, the results suggest that lithium is the most cost-effective therapy.

Excluding the additional mortality benefit associated with lithium-based strategies resulted in all treatments for patients with a recent history of a depressive episode being dominated by valproate and, in the case of patients with a recent history of a manic episode, by olanzapine.

Conclusions

Lithium, valproate, lamotrigine and olanzapine are effective as maintenance therapy for the prevention of relapse in bipolar disorder. Olanzapine and lithium are efficacious for the prevention of manic relapses and valproate, lamotrigine and imipramine for the prevention of depressive relapse. Carbamazepine is not an effective maintenance treatment. There is no trials evidence for the efficacy of combination therapy.

Psychosocial therapies have not been investigated thoroughly. There is some evidence that CBT, group psychoeducation and family therapy might be beneficial as adjuncts to pharmacological maintenance treatments.

There is insufficient information to permit any meaningful assessment of the relative tolerability of the treatments or their relative effects on suicide rate and mortality.

For patients with a recent depressive episode, valproate, lithium monotherapy and the combination of lithium and imipramine are potentially cost-effective. For patients with a recent manic episode, olanzapine and lithium monotherapy are potentially cost-effective.

The cost-effectiveness estimates in both groups of patients were shown to be sensitive to the assumption of a reduced suicidal risk associated with lithium-based strategies.

Research recommendations

The following areas are recommended for further research:

- A comprehensive review of, and further primary research into, the adverse effects of all treatments is required.
- Further investigation is needed of the differential effects in bipolar I, bipolar II and in rapid cycling and of the effects of treatments on suicide rates.

- A trial of a combination of lithium plus a selective serotonin reuptake inhibitor antidepressant is warranted.
- Good-quality trials of valproate are needed.
- Better and larger trials of psychosocial interventions, particularly CBT, are needed.
- Good-quality trials in children are required.

It is very important that future trials should be good-quality randomised controlled trials, involving an adequate number of participants and have sufficient duration of follow-up. Ideally, this research should be conducted via a properly resourced trial network.

Chapter 1

Aim of the review

The aim of this review was to determine the clinical effectiveness and cost-effectiveness of pharmacological and/or psychosocial interventions, given as monotherapy or in combination, for the prevention of relapse in people with bipolar disorders (manic or depressive phases).

In order to achieve this aim, we undertook the following research:

- a systematic review of the clinical effectiveness of pharmacological and psychosocial interventions for the prevention of relapse in bipolar disorder
- an analysis to enable comparisons to be made between the efficacy of all pharmacological treatments for the prevention of relapse in bipolar disorder
- a systematic review of existing economic evaluations of treatments for the prevention of relapse in bipolar disorder
- development of an economic model of treatments for the prevention of relapse in bipolar disorder.

Chapter 2
Background

Description of the disorder

Overview

Bipolar disorder (manic depression) is a complex, recurrent mood disorder associated with significant morbidity and mortality.[1] The lifetime prevalence of bipolar disorder is 1.3–1.6%[1] and it is one of the leading causes of worldwide disability.[2] The severity of the disease is variable, ranging from mild hypomania or mild depression to severe forms of mania or depression accompanied by psychotic symptoms such as delusions and hallucinations. The mortality rate of the disease is two to three times higher than that of the general population.[1,3]

Diagnosis

The diagnosis of bipolar disorder is not straightforward and has been refined over time. In the past, the term 'manic depressive disorder' was used to include both severe unipolar and bipolar disorder.[4] In more recent years, unipolar and bipolar disorders have been recognised as distinct diagnoses, and bipolar disorder is now most commonly used to describe repeated elevations of mood, often interspersed with depressions of mood.[5] The *Diagnostic and statistical manual of mental disorders*, 4th ed. (DSM-IV) diagnostic classification of bipolar disorder distinguishes between two main subtypes: bipolar I and bipolar II disorder. Bipolar I disorder is defined as one or more manic or mixed episodes, often accompanied by one or more major depressive episodes. Conversely, bipolar II disorder requires the occurrence of one or more major depressive episodes, accompanied by at least one hypomanic episode.[6] The mood disturbance with hypomanic episodes is not as severe as the mood elevation seen during manic episodes, and may manifest itself as a period of elevated or irritable mood; it is not associated with significant functional impairment.[6] Further types of bipolar disorder are cyclothymic disorder, characterised by many periods of hypomanic and depressive symptoms that do not meet criteria for full manic or depressive episodes, and bipolar disorder not otherwise specified (NOS), used to describe disorders with bipolar characteristics that do not meet criteria for a specific bipolar disorder.

Course of the disorder/consequences for health

Although the presence of mania is a key feature of bipolar disorder, long-term natural history studies have shown that for both individuals with bipolar I and bipolar II disorder, more time is spent with depressive symptoms than manic, hypomanic or mixed symptoms.[7,8] These studies found that patients with bipolar I disorder were symptomatic 47.3% of weeks of follow-up, changed symptom status an average of six times per year and changed symptom polarity (manic or depressive) more than three times per year.[8] Patients with bipolar II disorder tended to have more depressive than hypomanic or cycling/mixed symptoms, were symptomatic 53.9% of weeks of follow-up and the severity of their symptoms was found to fluctuate frequently, particularly minor or subsyndromal symptoms.[7] About 10–15% of individuals with bipolar disorder exhibit a rapid cycling pattern, in which four or more episodes occur during 1 year.[1] Rapid cycling is said to be associated with poorer prognosis.[6]

Bipolar disorder is recurrent and, as such, its impact on everyday life and functioning can be great. More than 90% of individuals who have a single manic episode will have further episodes,[6] and the intervals between episodes tend to become shorter with time.[9] Patients who have been hospitalised will spend approximately 20% of their lifetime after onset of the disorder in episodes.[9]

Bipolar disorder has been associated with problems of truancy, school or occupational failure, family or marital problems and episodic antisocial behaviour.[6] It has been suggested that these problems are greater for patients experiencing bipolar depression than bipolar mania.[10] Another significant risk in patients with bipolar disorder is suicide[5]. About 10–20% of individuals with bipolar disorder take their own life, and nearly one-third of patients admit to at least one suicide attempt.[1]

Co-morbidity

The difficulties experienced by individuals with bipolar disorder are often compounded by a second co-morbid disorder. Bipolar disorder is

commonly associated with substance abuse, and alcoholism is thought to be the most common significant clinical co-morbidity in Europe.[1,5] In a study of 392 patients hospitalised for a manic or mixed episode of bipolar disorder, almost 60% had a history of some substance abuse over their lifetime, 48.5% had a history of alcohol abuse and 43.9% had a history of drug abuse. Individuals with a history of co-morbid lifetime substance abuse had more psychiatric hospitalisations than individuals without such a history.[11] Other co-morbid psychiatric disorders are common in individuals with bipolar disorder, including anxiety disorders and eating disorders, which can increase the difficulties experienced by the individual, their family and their carers.[10]

Non-compliance

A lack of adherence to medication is another serious problem among individuals with bipolar disorder. For some patients, the perceived costs of adhering to their treatment regimen, such as adverse effects, or missing the feelings of elation produced by manic episodes, may outweigh the benefits.[12] One study has estimated that approximately one in three patients with a mood disorder will not take 30% or more of their medication, and that individuals who do not comply with medication show higher hospitalisation rates and have a poorer prognosis.[13]

Economic cost

Bipolar disorder, due to its recurrent nature and high morbidity and mortality, places a considerable economic burden on UK society. The total annual cost to the UK resulting from bipolar disorder has been estimated as £2 billion at 1999/2000 prices, allowing for 297,000 people with the disorder. The annual cost to the NHS for managing bipolar disorder was estimated to be £199 million, 35% of which was accounted for by hospital admissions. The annual direct non-healthcare cost was estimated at £86 million; however, the greatest contribution to the total cost was indirect costs, resulting from unemployment, absenteeism from work and suicide, estimated at £1770 million per year.[14]

Pharmacological management of bipolar disorder

Because of the great morbidity and mortality associated with bipolar disorder, long-term treatment is necessary to prevent recurrence and reduce the loss of productivity and increased medical costs associated with this illness.[15]

Individuals with bipolar disorder vary considerably, in terms of the type and severity of symptoms, the course of the disease and co-morbidity. As such, it is important that treatments are individualised, to meet the needs of different subgroups of patients.[16] Currently, several pharmacological interventions have been proposed for prevention of relapse in people with bipolar disorders.

Lithium

Lithium salts have been used for the prevention of relapse of bipolar disorder for over 50 years.[3] Lithium is considered a key treatment for the management of bipolar disorder and the British Association for Psychopharmacology (BAP) guidelines recommend lithium monotherapy as the first-line long-term treatment of bipolar disorder.[5] Lithium causes several adverse effects, including excessive thirst, polyuria, weight gain, tremor, nausea, gastrointestinal irritation, subjective memory disturbances and cognitive dulling. If troublesome, these adverse effects can result in patients discontinuing their medication.[12,17] Importantly, lithium salts have a narrow therapeutic index, and the blood levels in patients taking lithium must be monitored.[12] Severe toxic effects and sometimes death can occur when renal excretion is impaired. Progressive renal failure after decades of lithium use has been reported, although some have questioned the specificity of lithium as the causative agent in these cases.[3]

Anticonvulsants

Carbamazepine was the anticonvulsant drug reported to be useful in the treatment of bipolar illness in the 1980s,[3,18] but currently the effectiveness of carbamazepine is unclear. Adverse effects of carbamazepine include sedation, tremor, double vision, weight gain and rash.[17] Other anticonvulsants, valproate (valproic acid, divalproex sodium) and lamotrigine, have been used for maintenance treatment of bipolar disorder.[3,18] BAP guidelines suggest that valproate probably prevents manic and depressive relapse,[5] and recent studies have suggested benefits of lamotrigine in the long-term treatment of bipolar disorder, particularly in preventing depressive symptoms.[5,19]

Antipsychotics

Dopamine receptor-blocking drugs (neuroleptics) that are used in schizophrenia are also used in acute mania, and sometimes also for the prevention of relapse. However, the risk of tardive dyskinesia and other movement disorders has

limited their use.[3] The effectiveness of newer atypical neuroleptic drugs, such as clozapine, olanzapine, risperidone and ziprasidone, for bipolar disorder has also been examined. Evidence suggests that olanzapine may be effective in the long-term treatment of bipolar disorder, particularly in the prevention of manic rather than depressive relapse.[5,20] Some literature suggests that atypical antipsychotics may have more favourable adverse effects than typical antipsychotics.[20] However, agranulocytosis and weight gain leading to an increased risk of diabetes are possible adverse effects of these drugs.[20–23]

Antidepressants

Antidepressants have been used for the treatment of bipolar disorder, and their effectiveness in the short-term treatment of bipolar depression has been demonstrated.[24] Concerns have been raised that antidepressants, particularly tricyclics, may cause a switch to mania or hypomania.[20] As a result, it is often recommended that bipolar depression should be treated with a combination of an antidepressant and a mood stabiliser.[24] However, there is evidence that newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOs), are also effective in the treatment of bipolar depression and appear to carry a lower risk of switching to mania.[17,20]

Non-pharmacological management of bipolar disorder

Although pharmacological treatments are the primary tool in the management of people with bipolar disorder, they cannot control all aspects and consequences of the disorder. Various psychosocial interventions (individual, group, and family) have been used, some of which are specially tailored to bipolar disorder.[19,25] Psychosocial interventions aim to target issues untouched by pharmacological treatments, such as medication adherence, awareness and understanding of the disorder, early identification of prodromal symptoms and improving coping skills. Psychosocial interventions may enable individuals to take a more active role in the management of their disorder, and can improve relations between the patient and carer. When combined with long-term pharmacological treatment, psychosocial interventions may improve mood stability, occupational and social functioning and overall quality of life (QoL).[26]

There is some evidence to suggest that psychosocial interventions, particularly cognitive behaviour therapy (CBT) and psychoeducation, may be useful in reducing the risk of relapse and improving functional status and medication adherence in individuals with bipolar disorder.[5,19,27,28] However, psychosocial interventions do not appear to be equally useful for all aspects of bipolar disorder, and are not as beneficial for some individuals as others.[26]

Clarification of the research question

Although the use of pharmacological interventions and the use of psychosocial interventions as adjunct to pharmacotherapy appear to be accepted, and guidelines have been issued by the National Institute for Health and Clinical Excellence (NICE),[29] the effectiveness of such approaches as maintenance therapy in bipolar disorder is still unclear. In the light of the current uncertainties, this review examined the evidence for the clinical effectiveness and cost-effectiveness of interventions to prevent relapses in people with bipolar disorders.

Chapter 3

Systematic review of clinical effectiveness: methods

The investigation of clinical effectiveness comprised:

- a systematic review of the clinical effectiveness of pharmacological and psychosocial interventions for the prevention of relapse in bipolar disorder
- an analysis to enable comparisons to be made between the efficacy of all pharmacological treatments for the prevention of relapse in bipolar disorder.

Clinical effectiveness: methods

Search strategy

The search strategy was devised to take into account the broad nature of the review question. Rather than trying to include every potential pharmacological, psychotherapeutic and psychosocial intervention for relapsing bipolar disorder, the research team agreed that it would be more sensible to use search terms for 'bipolar disorder' alone. To limit the search results, it was also agreed that a methodological search filter should be used to help identify randomised controlled trials (RCTs). The search was not restricted by language.

The following databases were searched:

- MEDLINE (Ovid), 1966–2005/August week 4
- PreMEDLINE (Ovid), 2 September 2005
- EMBASE (Ovid), 1980–2005/week 36
- CINAHL (Ovid), 1982–2005/August week 4
- BIOSIS (Edina), 1985–2005/08
- PsycINFO (Ovid), 1872–2005/08
- Science Citation Index (SCI) (Web of Science), 1900–2005/08
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library/Wiley), 2005:3
- LILACS (BVS Virtual Health Library), 1982–2005/08.

In addition, information on studies in progress, unpublished research or research reported in the grey literature was sought by searching a range of other databases, including:

- Inside Conferences (DIALOG), 1990–2005/16 September.
- ISI Proceedings: Science and Technology (ISI Proceedings), 1993–2005/September week 3
- National Research Register (Update Software), 2005:3
- National Technical Information Service (NTIS) (Internet), 1990–2005/09.

Internet searches were carried out using the specialist search engine OMNI (http://omni.ac.uk/), the general search engine Google (http://www.google.co.uk/) and the meta-search engine Copernic (http://www.copernic.com/). In addition, specific organisation websites were browsed for further information: American Psychiatric Association (http://www.psych.org/), MIND (http://www.mind.org.uk/), International Society for Bipolar Disorders (http://www.isbd.org/), Stanley Medical Research Institute (http://www.stanleyresearch.org/) and the British Association for Psychopharmacology (http://www.bap.org.uk/). Any potentially relevant information not already retrieved from the database searches was printed, downloaded and added to the database results.

The search strategies, dates and results of all searches are listed in Appendix 1.

Although the search strategy was thought to have identified all relevant articles, the abstracts of the Society of Biological Psychiatry 1999 Annual Meeting, Affective Disorders/European Psychiatry 2005 and the Biennial Schizophrenia Winter Workshop, Davos 2002, to which the first reviewer had easy access, were searched by hand; however, no further relevant papers were detected.

Inclusion and exclusion criteria

The titles and abstracts of all papers identified by the search were screened and the full papers for all potentially relevant studies were obtained and screened according to the criteria described below. A minimum of 30% of the papers was screened in duplicate by at least two independent reviewers. All papers that did not meet the inclusion criteria were excluded and the decisions for exclusion documented. Disagreements were resolved by consensus, or with the decision of a third reviewer.

Where there was insufficient information reported to make a decision, or insufficient data for the study to be included, study authors were contacted for further details. None of the authors contacted provided further information, and the studies were excluded.

Interventions

The following interventions were eligible for inclusion in the review, used as monotherapy, as adjunct therapy or in combination, compared with placebo, no intervention or with another intervention:

1. *Pharmacological interventions*
   (a) lithium salts
   (b) anticonvulsants (valproate/divalproex, carbamazepine, lamotrigine)
   (c) antipsychotics (conventional and/or atypical)
   (d) antidepressants (tricyclics and/or SSRI)
2. *Psychosocial interventions*
   (a) CBT
   (b) psychoeducation
   (c) family intervention
   (d) case management
   (e) integrated group therapy.

Only those therapies that were considered relevant to current clinical practice were included. As such, it was decided that studies evaluating sleep deprivation, omega 3, pindolol and eating advice should be excluded. Only trials of therapy used for maintenance were eligible for the review. In the protocol, this was defined as treatment given for a minimum of 3 months. In the review, a more accurate definition was used. Thus, maintenance treatment was defined as treatment instituted primarily to prevent further episodes of affective illness, after patients were already stabilised, not including treatment of the acute phase of the disease. Nevertheless, we expected that some studies would randomise patients while in the acute treatment phase and continue the medication in the maintenance phase of treatment. It was planned that such studies would be included in the review, but analysed separately.

Participants

All patients suffering from bipolar I disorder or bipolar II disorder diagnosed according to explicit diagnostic criteria [e.g. DSM-IV or International Classification of Diseases 10 (ICD-10)], through the use of a structured interview or otherwise, were included. Patients treated only in an acute manic or depressive phase were excluded; however, studies in which patients were randomised to maintenance treatment while in the acute phase were included. A subgroup analysis was planned for the latter type of studies. Studies which included both unipolar and bipolar patients were included only if the data for bipolar patients could be extracted separately.

Study design

Randomised or quasi-randomised controlled clinical trials with at least 3 months of follow-up that compared pharmacological or psychosocial interventions with placebo, no intervention, or with another intervention were included. Crossover trials in which the length of treatment before first crossover was less than 3 months were excluded. Where the length of treatment before crossover was greater than 3 months, studies were included, but data were extracted only for the period before the first crossover. Discontinuation studies were excluded.

Outcomes

The primary outcome measures were:

1. all relapses of a bipolar episode using the following three definitions:
   (a) defined as the number of hospitalisations in each group
   (b) defined as the number of patients who received an additional intervention to treat a manic or depressive episode
   (c) as defined by the authors.

Although in the review protocol the primary outcome measure was specified as time to next episode, in practice very few included trials reported data on this outcome. Consequently, these data have not been analysed. Where they were available, they have been extracted and are presented in the data extraction tables (Appendix 6).

The secondary outcome measures were:

1. manic relapses using the following three definitions:
   (a) defined as the number of hospitalisations in each group
   (b) defined as the number of patients that received an additional intervention to treat a manic episode
   (c) as defined by the authors
2. depressive relapses using the following three definitions:
   (a) defined as the number of hospitalisations in each group

(b) defined as the number of patients that received an additional intervention to treat a depressive episode
(c) as defined by the authors
3. drop-outs before end of study
4. adverse events leading to discontinuation and other treatment related adverse effects
5. suicide or suicide attempts.

Data extraction strategy

Data were extracted by one reviewer and checked independently by a second reviewer. Disagreements were resolved by consensus, or with the decision of a third reviewer. Data were extracted into a predefined Microsoft Access database. The following data were extracted:

- **Study details and aims**: study identifier (EndNote ID), author, year, setting, number of participants per study and duration of follow-up.
- **Study population**: description of the participants included in the study (age, gender, ethnicity, proportion single or living alone, predefined inclusion and/or exclusion criteria, and other important factors), details of the disease, diagnostic criteria used, and number of previous episodes.
- **Details of the intervention**: name and characteristics of the intervention (dosage, length of treatment, monotherapy or combination), whether co-interventions were permitted.
- **Results**: dichotomous data were extracted as the number of individuals with the outcome of interest and the total numbers of individuals in the intervention and control groups. For continuous data, the mean and standard deviation (SD) were extracted where available. Otherwise, median, standard error or range was extracted.

Where there were multiple publications for the same study, data were extracted primarily from the most recent and complete publication. In cases where the duplicate publications reported additional relevant data, these data were also extracted.

Quality assessment strategy

The methodological design of all included trials was assessed according to the quality criteria defined by CRD Report 4:[30] study design, random assignment, sequence generation, allocation concealment, groups similar at baseline, eligibility criteria specified, assessors blinded, care provided blinded, patient blinded to treatment, point estimates and variability presented for primary outcome, intention-to-treat (ITT) analysis and sample size calculation reported. The quality assessment tool is given in Appendix 2.

Quality assessment was carried out by one reviewer and checked by an independent second reviewer. Disagreements were resolved by consensus, or with the decision of a third reviewer.

Data analysis

The data were taken from the Access database and worked out in a flat Excel table before being exported to Stata (version 8.2) or StatsDirect (version 2.4.1).

Dichotomous data were analysed by calculating the odds ratio (OR) for each trial. Where there was more than one study for a comparison, the ORs were pooled using a fixed-effect model [the Mantel–Haenszel (M–H) method] and the corresponding 95% confidence intervals (CIs) were calculated.[31] Statistical heterogeneity was assessed using the χ^2 test. In studies with more than two treatment arms, data were analysed for different combinations within the same trial. For studies that presented data for more than one length of follow-up, data from the longest follow-up time point were used.

Although the review protocol stated that publication bias would be investigated, the small number of trials for each treatment comparison precluded this.

Primary outcome measure: all relapses

Several forms of ITT analysis have been described.[32] For the base-case analysis, ORs were calculated using the number of patients analysed as the denominator. The potential impact of the missing data was explored via sensitivity analysis:[33] a sensitivity analysis was used to test best-case and worst-case scenarios for the primary outcome (all relapses). For the best-case scenario, the number of patients randomised was used as the denominator (i.e. assuming that all patients who had not been analysed had not had a relapse). For the worst-case scenario, the number of patients randomised was used as the denominator and the difference between the number analysed and number randomised was added to the numerator (i.e. assuming that all patients who were not included in the analysis had relapsed).

Studies that included only patients with bipolar II disorder or in which data for bipolar I and II patients were presented separately were included in the main analysis. However, the effect of data from only bipolar II patients was investigated in subgroup analyses.

Studies in which patients were randomised during the acute phase of bipolar disorder were not included in the main analysis, but were examined in subgroup analyses, using the number randomised as the denominator to calculate ORs. Similarly, studies in which patients were only randomised to treatment after they had shown a positive response to the study drug of interest were not included in the main analysis, but were examined in subgroup analyses. Subgroup analyses were performed for the primary outcome (all relapses) only. Where there was only a single study for a comparison, and that study was one that would have been included in a subgroup analysis only, then results for that study were presented as for the main analysis.

Secondary outcomes

Where provided, data were analysed for manic and depressive relapses separately. For studies where mixed relapse was clearly defined as at least one manic episode (and additional depressive episode), the number of patients experiencing a mixed relapse was added to the number of patients with a manic relapse.

Where available, data for drop-outs before the end of the study, suicide and adverse events leading to discontinuation were analysed for each comparison.

Data on treatment-related adverse effects from comparisons of each treatment with placebo were analysed. Other adverse effects data are presented in the data extraction tables (Appendix 6).

Mixed treatment comparison

In order to facilitate decision-making, we attempted to derive results for the relative effectiveness of the treatments reviewed. As it was expected that there would be no head-to-head trials comparing all the treatments, an analysis using the methods of mixed treatment comparison (MTC) was planned.[34,35] The purpose of an MTC analysis is to bring together the clinical evidence regarding the efficacy of all treatments for a specified indication. In general terms, this consists of identifying a 'network of evidence' between the treatments. In the context of the present review, this would mean that, for example, although carbamazepine and olanzapine have not been directly compared in a trial, they can be compared **indirectly** as both have been assessed against a common comparator. Similarly, other treatments that have been compared with a common comparator can also be included in the analysis and compared with each other. The common comparator need not be placebo and, within an MTC, there can be more than one common comparator. For example, if lithium, valproate and olanzapine have all been compared with placebo but carbamazepine has only been compared with lithium, then carbamazepine can be compared **indirectly** with lithium, valproate and olanzapine because carbamazepine can be linked into the chain of evidence through the comparison with lithium. Within an MTC, **all** the available trials data on a treatment for the specified indication should be included.

The strength of an MTC analysis is that it allows consideration of a more complete evidence base and facilitates a valid comparison of a range of treatment strategies. Although concerns are often raised regarding the use of indirect approaches in establishing the efficacy and cost-effectiveness of particular interventions, it is important to recognise that these approaches are necessary in order to provide a simultaneous assessment of the full range of potential comparators. It is only through such approaches that the potential inconsistencies that could be introduced by a series of separate comparisons can be avoided. As a result, this avoids the inevitable difficulties faced by a decision-maker in making a single recommendation based on multiple sources of evidence.

It is often assumed that in all indirect comparisons randomisation is lost and the resultant comparison comprises an 'observational study' with all its potential confounders. This is not the case in MTC, which uses methods that respect randomisation. Although pooling data across trials in this way does require certain assumptions to be made, these are in fact exactly those applied in standard meta-analysis, with only the additional assumption that relative treatment effects are generalisable across the trials. However, it must also be recognised that when indirect evidence is used as the basis for the assessment of relative treatment effects, it is not possible to rule out the introduction of bias, hence the results should be interpreted accordingly.

The MTC used the outcomes all relapse, manic relapse and depressive relapse, using the definition as 'as stated by author' and the main MTC analysis excluded trials that were purely bipolar II. Exact details of the analysis are dictated by the available data and further details are given in the relevant results section.

Chapter 4

Systematic review of clinical effectiveness: results

Quantity and quality of research available

Description of studies

Eligibility

We identified 1186 potentially relevant and obtainable references through our search strategy. Of these, we included 45 trials (107 references) and excluded 1079 references. Thirty-nine references that could not be obtained are listed in Appendix 3. A summary of the selection of studies for the review is presented in *Figure 1*.

Studies were excluded for one or more of the following reasons: they were not a randomised or quasi-randomised study (308), were not performed on participants with bipolar disorder (152), were not a maintenance study (552), participants were not followed up for at least 3 months (481), inclusion criteria were not clear (223) or no data were available from the current publication (110). Details of the included studies and the analyses in which they could be included can be found in Appendix 5 and in the data extraction tables (Appendix 6). A list of duplicate publications is given in Appendix 4.

Participants

All but one study[36] tested the intervention or comparator in adults. The proportion of females in the studies ranged from 23 to 100%. Twenty-eight studies included participants diagnosed as bipolar I and II or not specified, 14 studies included only participants with bipolar I, and three studies included only bipolar II participants. The percentage of participants with rapid cycling ranged from 2.5 to 100% in the included studies. The sample size of the included studies varied from 12 to 463 participants. Few studies reported ethnicity or the proportion of participants who were single or lived alone.

Interventions

Details of the specific interventions assessed in the included studies can be found in *Figure 1*. Thirty-three studies dealt with pharmacological interventions, comparing them with placebo or other pharmacological interventions, and 12 studies compared a psychosocial intervention, given in addition to pharmacological treatment, with treatment as usual (TAU), waiting list, non-structured group meeting or another psychosocial intervention.

Outcomes

Bipolar disorders were diagnosed using the following diagnostic criteria: DSM-IV (21 studies), *Diagnostic and statistical manual of mental disorders*, 3rd ed., revised (DSM-III-R) (seven studies), *Diagnostic and statistical manual of mental disorders*, 3rd ed. (DSM-III) (six studies), Research Diagnostic Criteria (RDC) (six studies), International Classification of Diseases 9 (ICD-9) (two studies) and Feighner (two studies). Five studies did not use diagnostic criteria or did not state which criteria were used. Symptoms of mania were measured using the Young Mania Rating Scale (YMRS) (14 studies), the Bech–Rafaelsen Mania Rating Scale (BRMRS) (eight studies), the Mania Rating Scale (MRS) (one study) or another scale (18 studies). Four studies did not state which scale(s) they used to measure mania. Symptoms of depression were measured using the Hamilton Rating Scale for Depression (HAM-D) (21 studies), or another scale (19 studies). Five studies did not state which scale(s) they used to measure depression.

Few studies reported continuous data. Therefore, number of relapses (all relapses, manic and depressive) has been used as the primary outcome (see the section 'Outcomes', p. 8).

Study location

Trials were conducted in Australia (one), Austria (one), Germany (one), Italy (three), The Netherlands (one), Spain (two), the UK (nine) and the USA (27).

Methodological quality of included studies

Details of quality assessment of each study are given in *Table 1*.

Of the 45 RCTs in this review, three were quasi-randomised: two studies had no proper random assignment and the method of assignment was unclear in the other.

The generation of allocation sequence was not well reported, being unclear in 30 studies. It was

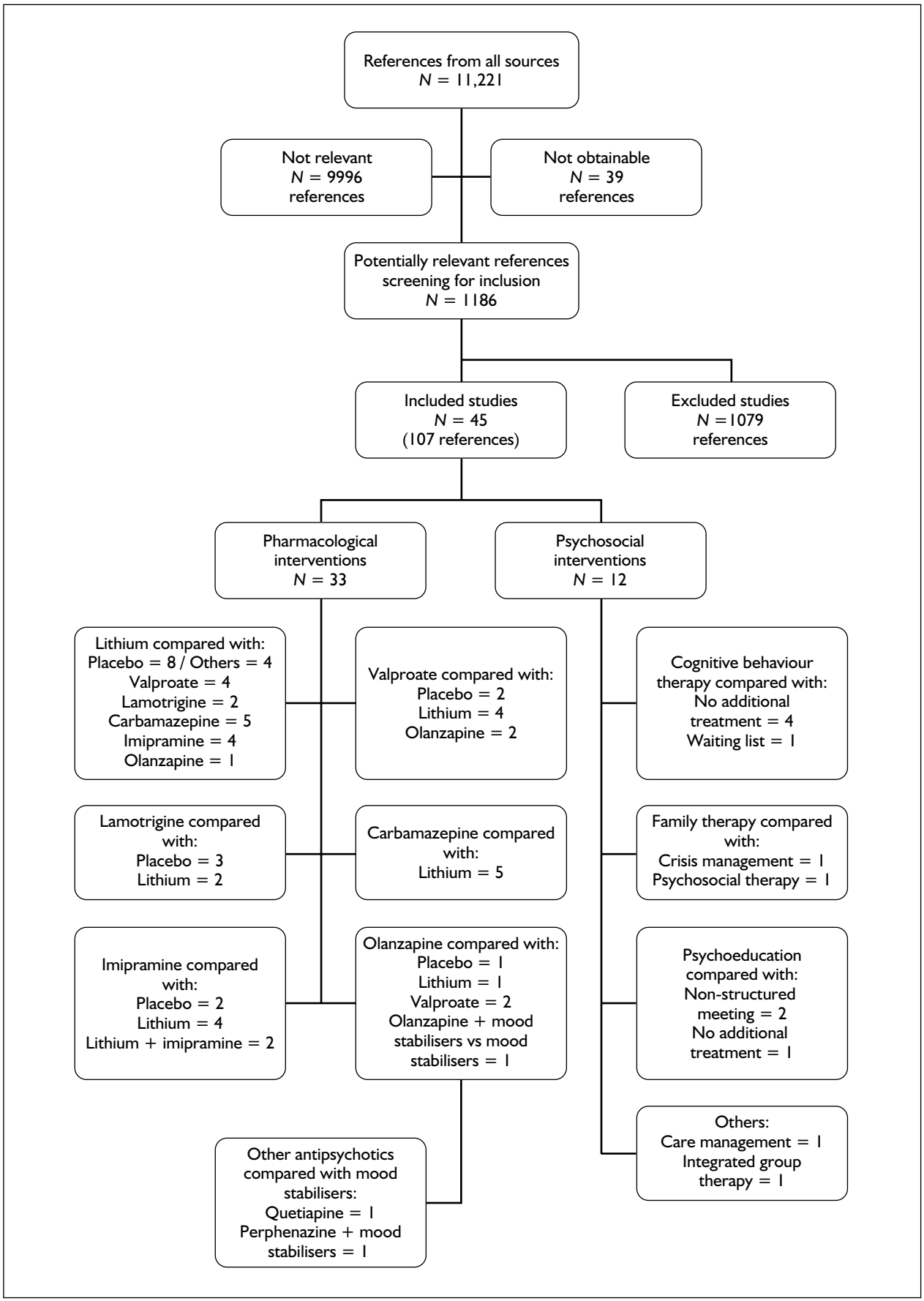

FIGURE 1 *Flow chart of studies included in the efficacy analyses of the review*

TABLE 1 *Quality assessment for each included study*

Study	Sponsored by pharmaceutical company	Random assignment	Sequence generation	Allocation concealed	Concealment	Groups similar at baseline	Eligibility criteria specified	Assessors blinded	Care provided blinded	Patient blinded to treatment	Point estimates and variability presented for primary outcome	Analyses include an ITT analysis	Sample size calculation reported
Altamura, 2003[37]	No	Yes	UC	UC	UC	Yes	Yes	Yes	No	No	Yes	Yes	No
Altamura, 2004[38]	No	Yes	UC	UC	UC	No	Yes	No	No	No	No	Yes	No
Bowden, 2000[39]	Yes	Yes	UC	UC	UC	Yes	Yes	UC	UC	UC	Yes	Yes	Yes
Bowden, 2003[40]	Yes	Yes	UC	UC	UC	Yes	Yes	UC	UC	UC	Yes	Yes	Yes
Calabrese, 2000[41]	Yes	Yes	UC	UC	UC	Yes	Yes	UC	Yes	Yes	Yes	Yes	No
Calabrese, 2003[42]	Yes	Yes	UC	UC	UC	Yes	Yes	UC	UC	Yes	Yes	Yes	Yes
Calabrese, 2005[43]	No	Yes	UC	UC	UC	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Cochran, 1984[44]	No	Yes	UC	UC	UC	Yes	Yes	No	No	No	Yes	Yes	No
Colom, 2003a[45]	No	Yes	AD	Yes	AD	Yes	Yes	Yes	UC	No	Yes	Yes	No
Colom, 2003b[46]	No	Yes	AD	Yes	AD	Yes	Yes	UC	No	No	Yes	Yes	No
Coxhead, 1992[47]	Yes	Yes	UC	UC	UC	Yes	Yes	Yes	Yes	Yes	Yes	UC	No
Dunner, 1976[48]	No	Yes	UC	UC	UC	UC	Yes	Yes	Yes	Yes	UC	Yes	No
Esparon, 1986[49]	Yes	Yes	UC	UC	UC	No	Yes	UC	UC	Yes	Yes	Yes	No
Fieve, 1976[50]	No	Yes	UC	UC	UC	UC	Yes	Yes	Yes	Yes	Yes	UC	No
Findling, 2005[36]	No	Yes	UC	UC	UC	Yes	Yes	Yes	UC	Yes	Yes	Yes	Yes
Frankenburg, 2002[51]	Yes	Yes	AD	Yes	AD	Yes	Yes	Yes	Yes	Yes	Yes	UC	No
Gelenberg, 1989[52]	No	Yes	AD	UC	UC	Yes	Yes	UC	No	Yes	Yes	Yes	No
Hartong, 2003[53]	Yes	Yes	AD	Yes	AD	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Johnstone, 1990[54]	Yes	Yes	UC	UC	UC	UC	Yes	UC	UC	Yes	Yes	UC	No
Kane, 1981[55]	No	Yes	UC	UC	UC	Yes	Yes	UC	Yes	UC	Yes	Yes	No
Kane, 1982[56]	No	Yes	UC	UC	UC	No	Yes	UC	Yes	Yes	Yes	UC	No
Kleindienst, 2000[57]	No	Yes	UC	Yes	UC	Yes	Yes	No	No	No	Yes	No	Yes
Lam, 2000[58]	No	Yes	UC	UC	UC	No	Yes	No	UC	No	Yes	No	No
Lam, 2005[59]	No	Yes	AD	Yes	AD	Yes	Yes	Yes	UC	UC	Yes	Yes	No
Lusznat, 1988[60]	Yes	Yes	UC	UC	UC	No	Yes	Yes	No	Yes	Yes	Yes	No

continued

TABLE I *Quality assessment for each included study (cont'd)*

Study	Sponsored by pharmaceutical company	Random assignment	Sequence generation	Allocation concealed	Concealment	Groups similar at baseline	Eligibility criteria specified	Assessors blinded	Care provided blinded	Patient blinded to treatment	Point estimates and variability presented for primary outcome	Analyses include an ITT analysis	Sample size calculation reported
Maj, 1986[61]	No	No	UC	No	UC	Yes	Yes	No	No	No	Yes	No	No
Miklowitz, 2003[62]	No	Yes	AD	Yes	AD	Yes	Yes	UC	No	No	Yes	Yes	No
Perry, 1999[63]	No	Yes	AD	UC	UC	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Platman, 1970[64]	No	UC	InAD	No	InAD	UC	No	UC	UC	UC	No	UC	No
Prien, 1973[65]	No	Yes	UC	UC	UC	UC	Yes	Yes	No	Yes	Yes	UC	No
Prien, 1974[66]	No	Yes	UC	UC	UC	UC	Yes	Yes	No	Yes	Yes	No	No
Prien, 1984[67]	No	Yes	UC	Yes	UC	UC	Yes	Yes	Yes	Yes	Yes	UC	No
Rea, 2003[68]	No	Yes	UC	UC	UC	Yes	Yes	Yes	No	No	Yes	No	No
Revicki, 2005[69]	Yes	Yes	UC	UC	UC	Yes	Yes	No	No	No	Yes	UC	Yes
Scott, 2001[70]	No	Yes	AD	UC	UC	Yes	Yes	UC	No	No	Yes	UC	No
Scott, 2005[71]	No	Yes	AD	Yes	AD	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Simhandl, 1993[72]	No	Yes	UC	UC	UC	UC	Yes	No	No	No	Yes	No	No
Simon, 2005[73]	No	Yes	AD	Yes	AD	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Solomon, 1997[74]	Yes	Yes	UC	UC	UC	UC	Yes	Yes	No	Yes	Yes	UC	No
Tohen, 2003[75]	Yes	Yes	UC	UC	UC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tohen, 2004[76]	Yes	Yes	AD	Yes	AD	Yes	Yes	UC	UC	Yes	Yes	Yes	Yes
Tohen, 2005[77]	Yes	Yes	AD	Yes	AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tohen, 2006[78]	Yes	Yes	UC	UC	UC	Yes	Yes	UC	UC	Yes	Yes	Yes	No
Weiss, 2000[79]	No	No	InAD	No	InAD	No	Yes	UC	No	No	Yes	Yes	No
Zarate, 2004[80]	No	Yes	UC	UC	UC	Yes	Yes	UC	UC	UC	UC	UC	No

AD, adequate; InAD, inadequate; UC, unclear.

adequate in 13 studies and inadequate in two studies.

Similarly, the methods used to conceal allocation were unclear in 33 studies. Less than one-quarter of all studies (10 of 45 trials) used an adequate method to conceal allocation. It was inadequate in two studies.

Information about who was blinded, such as the participants, care providers or outcome assessors, was provided in most studies. Assessors were blinded in 21 studies, care was provided blind in 11 studies and participants were blinded in 22 studies. Information was unclear for 17, 13 and six studies regarding blinding of assessors, care providers or participants, respectively. In addition, seven studies did not blind outcome assessors, 21 did not blind care providers and 17 did not blind participants.

An ITT analysis was reported in more than half of the studies (26 out of 45 studies). It was unclear in 12 studies and not performed in another seven studies.

In 30 studies, intervention and comparison groups were described as similar on the baseline measurements. Almost all studies clearly identified eligibility criteria and presented point estimates with variability for the primary outcome. Only 14 studies reported a sample size calculation.

Sixteen out of 45 studies were sponsored by the pharmaceutical industry.

Efficacy of pharmaceutical interventions

Lithium

A total of 25 randomised or quasi-randomised trials that investigated the efficacy of lithium were identified for the review.[36,39,40,42,43,47–50,52–57,60,61,64–67,69,72,74,77] Two of these studies compared only different doses of lithium and are not considered in the analyses.[52,61] Trial details are summarised in *Table 2* and presented in the data extraction tables (Appendix 6).

All but one study[36] tested the intervention or comparator in adults. The proportion of females in the study ranged from 23 to 77%. Fourteen studies included participants diagnosed as bipolar I and II or not specified, nine studies included only participants with bipolar I and two studies included only bipolar II participants. The proportion of participants with rapid cycling ranged from 2.5 to 100% in the included studies. The sample size of the included studies varied from 12 to 463 participants.

The reported quality of the included lithium studies was limited. In 23 out of 25 studies, participants were randomly assigned; however, the sequence generation was adequate in only three of them.[52,53,77] Four studies used allocation concealment, but only two of them described an adequate procedure.[53,77] Assessors were blinded in 12 studies, care providers in eight studies and participants in 17 studies. In 13 studies, intervention and comparison groups were described as similar on the baseline measurements. Almost all studies clearly identified eligibility criteria and presented point estimates with variability for the primary outcome, and nine studies reported a sample size calculation. Details of the quality assessment of individual studies are given in *Table 1*. Eleven studies were sponsored by the pharmaceutical industry

In the available trials, lithium was compared with placebo and/or valproate, lamotrigine, olanzapine, imipramine, imipramine plus lithium, carbamazepine, flupenthixol plus lithium, valproate plus lithium or amitriptyline plus lithium.

Lithium compared with placebo

Eight studies compared lithium with placebo.[39,40,42,48,50,56,65,66]

All relapses

Seven trials provided data for all relapses and were included in both the base-case analysis and the best-case/worst-case sensitivity analysis. One trial[48] did not provide data for all relapses and could only be included in separate analyses for manic and depressive relapses.

The results for all relapses are given in *Table 3*. The pooled fixed-effect M–H ORs were statistically significant in favour of lithium for all definitions of relapse, and there was no indication of significant statistical heterogeneity for relapse defined as admission to hospital or institution of additional treatment. However, statistical heterogeneity was detected for relapses as stated by authors. This heterogeneity appears to arise from the different results seen in the more recent trials compared with the older ones. It may suggest that the pooled estimate for all relapses as stated by authors overestimates the efficacy of lithium. However, this difference is not reflected in the findings for the other definitions of relapse.

TABLE 2 *Characteristics of included studies comparing lithium with placebo or other active treatments*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Bowden, 2000[39]	Mainly adults	372	51.20		Caucasian	Yes	Bipolar I	Mania + depression		Lithium: 0.8–1.2 mmol/l	Divalproex: 71–125 μg/ml	Placebo	
Bowden, 2003[40]	Mainly adults	175	53.00			Yes	Bipolar I	Mainly mania		Lithium: 0.8–1.1 mEq/l	Lamotrigine: 100–400 mg/day	Placebo	
Calabrese, 2003[42]	Mainly adults	463	56.00			Yes	Bipolar I	Mainly depression		Lithium: median 900 mg/day (0.8–1.1 mEq/l	Lamotrigine: 50, 200, 400 mg/day	Placebo	
Calabrese, 2005[43]	Mainly adults	60	51.67			Yes	Bipolar I and II	All	100.00	Lithium: 750–2750 mg/day (mean 77 μg/ml)	Divalproex: 900–1200 mg/day (mean 0.92 mEq/l)		
Coxhead, 1992[47]	Mainly adults	31	67.74			Yes	Bipolar – not specified	Mania + depression		Lithium: 400 mg twice daily (0.6–1.0 mmol/l)	Carbamazepine: 200 mg twice daily (38–51mmol/l)		
Dunner, 1976[48]	Mainly adults	40	57.50			Yes	Bipolar II	Hypomania + depression	15.00	Lithium: 0.8–1.2 mEq/l	Placebo		
Esparon, 1986[49]	Mainly adults	15	73.00			Unclear	Bipolar – not specified	Mania + depression		Lithium: 0.6–1.2 mmol/l	Lithium + flupenthixol: 0.6–1.2 mmol/l + 20-mg injections every 4 weeks		
Fieve, 1976[50]	Mainly adults	53	51.00			Yes	Bipolar I and II	Mania + depression	7.50	Lithium: 0.7–1.3 mEq/l	Placebo		
Findling, 2005[36]	Mainly children	60	35.00			Yes	Bipolar I and II	All	50.00	Lithium: 0.6–1.2 mmol/l	Valproate: 50–100 μg/ml		
Gelenberg, 1989[52]	Mainly adults	94	55.30			Yes	Bipolar – not specified	Mania + depression		Lithium: 600–2100 mg/day (0.8–1.0 mmol/l)	Lithium: 450–1350 mg/day (04-0.6 mmol/l)		
Hartong, 2003[53]	Mainly adults	53	54.30	44.70		Yes	Bipolar I and II	All		Lithium: 800 mg/day (0.6–1.0 mmol/l)	Carbamazepine: 400 mg/day (6–10 mg/l)		

continued

TABLE 2 *Characteristics of included studies comparing lithium with placebo or other active treatments (cont'd)*

Study	Age	N	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Johnstone, 1990[54]	Mainly adults	13	69.23			Unclear	Bipolar I and II	All		Lithium: 0.5–0.9 mEq/l	Lithium + amitriptyline: 0.5–0.9 mEq/l + 50–225 mg/day		
Kane, 1981[55]	Mainly adults	75	52.00			Yes	Bipolar I	Mania + depression		Lithium: 300 mg 2–4 times per day (0.8–1.2 mEq/l)	Lithium + imipramine: 300 mg 2–4 times per day (0.8–1.2 mEq/l) + 100–150 mg/day		
Kane, 1982[56]	Mainly adults	22	77.27		Caucasian	Yes	Bipolar II	Hypomania + depression		Lithium: 0.8–1.2 mEq/l	Lithium + imipramine: 0.8–1.2 mEq/l + 100–150 mg/day	Imipramine: 100–150 mg/day	Placebo
Kleindienst, 2000[57]	Mainly adults	171	56.14	50.00		Yes	Bipolar I and II	Mania + depression		Lithium: 0.6–0.8 mmol/l	Carbamazepine: 4–12 μg/ml		
Lusznat, 1988[60]	Mainly adults	54	53.70			No	Bipolar I	Mainly mania		Lithium: tablets of 400 mg (0.6–1.4 mmol/l)	Carbamazepine: tablets of 200 mg (0.6–1.2 mg per 100 ml)		
Maj, 1986[61]	Mainly adults	80	56.25			Unclear	Bipolar – not specified	Not stated		Lithium: plasma lithium level 0.30–0.45 mEq/l	Lithium: plasma lithium level 0.46–0.60 mEq/l	Lithium: plasma lithium level 0.61–0.75 mEq/l	Lithium: plasma lithium level 0.76–0.90 mEq/l
Platman, 1970[64]		79	51.90			Unclear	Bipolar – not specified	Mania + depression		Lithium	Imipramine		
Prien, 1973[65]	Mainly adults	44	23.00			Yes	Bipolar – not specified	Mainly depression		Lithium: 500–2250 mg/day (median 0.8 mEq/l)	Imipramine: 50–200 mg/day	Placebo	
Prien, 1974[66]	Mainly adults	205	35.00			Yes	Bipolar – not specified	Mainly mania		Lithium: 0.5–1.4 mEq/l	Placebo		

continued

TABLE 2 *Characteristics of included studies comparing lithium with placebo or other active treatments (cont'd)*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Prien, 1984[67]	Mainly adults	117	58.00			Yes	Bipolar I	Mania + depression	2.50	Lithium: mean 0.75 mEq/l (0.45–1.10 mEq/l)	Lithium + imipramine: mean 0.75 mEq/l + mean 132 mg/day	Imipramine: mean 132 mg/day (75–150 mg/day)	
Revicki, 2005[69]	Mainly adults	221	51.20		Caucasian	No	Bipolar I	Mania + mixed	12.25	Lithium: 900–1200 mg/day	Divalproex: 15–20 mg/kg/day or usual psychiatric practice		
Simhandl, 1993[72]	Mainly adults	52	69.05			Unclear	Bipolar – not specified	Not stated		Lithium: 12-h serum level 0.6–0.8 mmol/l	Carbamazepine: 12-h serum level 15–25 μmol/l	Carbamazepine: 12-h serum level 28–40 μmol/l	
Solomon, 1997[74]	Mainly adults	12	33.33	50.00		Unclear	Bipolar I	Mania + depression		Lithium: 0.8–1.0mmol/l	Lithium + divalproex: 0.8–1.0 mmol/l + twice daily 50–125 μg/ml		
Tohen, 2005[77]	Mainly adults	431	52.90		Caucasian	Yes	Bipolar I	Mania + mixed	3.02	Lithium: 300–1800 mg/day (0.6–1.2 mEq/l)	Olanzapine: 5–20 mg/day		

TABLE 3 *All relapses (manic, depressive or mixed episodes)*

Study	Lithium	Placebo	OR (95% CI), % weight
All relapses: admission to hospital			
Fieve BPI, 1976[50]	3/17	9/18	0.21 (0.04 to 1.01), 12.78
Fieve BPII, 1976[50]	1/7	2/11	0.75 (0.05 to 10.23), 2.36
Prien, 1974[66]	31/101	70/104	0.21 (0.12 to 0.39), 84.85
M–H pooled OR	$\chi^2 = 0.84$ (df = 2), $p = 0.66$		0.23 (0.13 to 0.39)
Test of OR = 1: $z = 5.38$, $p = 0.000$			
All relapses: institution of additional treatment			
Bowden, 2003[39]	18/44	49/69	0.28 (0.12 to 0.67), 32.18
Calabrese, 2003[42]	56/120	66/119	0.7 (0.41 to 1.21), 50.46
Prien, 1974[66]	12/101	14/104	0.87 (0.35 to 2.15), 17.36
M–H pooled OR	$\chi^2 = 4.58$ (df = 2), $p = 0.1012$		0.6 (0.41 to 0.87)
Test of OR = 1: $z = 2.62$, $p = 0.0089$			
All relapses: as stated by authors			
Bowden, 2000[39]	28/91	36/94	0.71 (0.37 to 1.38), 24.42
Calabrese, 2003[42]	99/120	107/119	0.53 (0.23 to 1.2), 18.72
Kane, 1982[56]	1/4	5/7	0.13 (0.01 to 3.5), 2.71
Prien, 1973[65]	9/18	12/13	0.08 (0.01 to 0.85), 6.93
Prien, 1974[66]	47/101	90/104	0.13 (0.06 to 0.28), 47.22
M–H pooled OR	$\chi^2 = 15.86$ (df = 4), $p = 0.0032$		0.35 (0.24 to 0.5)
Test of OR = 1: $z = 5.75$, $p = 0.000$			

BPI, bipolar I; BPII, bipolar II; df, degrees of freedom.

TABLE 4 *Subgroup analysis: studies where all participants were bipolar II analysed separately from studies described as bipolar I or II or not specified*

Study	Lithium	Placebo	OR (95% CI), % weight
All relapses: admission to hospital (bipolar II)			
Fieve BPII, 1976[50]	1/7	2/11	0.75 (0.05 to 10.23), 100
All relapses: admission to hospital (bipolar I)			
Fieve BPI, 1976[50]	3/17	9/18	0.21 (0.04 to 1.01), 13.09
Prien, 1974[66]	31/101	70/104	0.21 (0.12 to 0.39), 86.91
M–H pooled OR	$\chi^2 = 0.00$ (df = 1), $p = 0.996$		0.21 (0.12 to 0.37)
Test of OR = 1: $z = 5.47$, $p = 0.000$			
All relapses: as stated by authors (bipolar II)			
Kane, 1982[56]	1/4	5/7	0.13 (0.01 to 2.18), 100
All relapses: as stated by authors (bipolar I)			
Bowden, 2000[39]	28/91	36/94	0.72 (0.39 to 1.32), 25.09
Calabrese, 2003[42]	99/120	107/119	0.53 (0.25 to 1.13), 19.24
Prien, 1973[65]	9/18	12/13	0.08 (0.01 to 0.78), 7.13
Prien, 1974[66]	47/101	90/104	0.13 (0.07 to 0.27), 48.53
M–H pooled OR	$\chi^2 = 15.37$ (df = 3), $p = 0.002$		0.35 (0.24 to 0.51)
Test of OR = 1: $z = 5.52$, $p = 0.000$			

Results for the sensitivity analysis are presented in Appendix 7, *Tables 93* and *94*, and showed no differences when compared with the main results.

Subgroup analyses

Subgroup analysis by whether the population was bipolar I or bipolar II involved two analyses: all relapses defined as admission to hospital and all relapses as stated by authors (*Table 4*). When the bipolar II trials were removed from the meta-analysis (a subset of the Fieve[50] and Kane[56] studies), the effect of lithium was not changed; the statistical heterogeneity on all relapses as stated by authors was maintained. One further bipolar II study[48] could not be included in the main analysis or the subgroup analyses because it did not provide data for all relapses.

TABLE 5 *Manic relapses*

Study	Lithium	Placebo	OR (95% CI), % weight
Admission to hospital			
Dunner, 1976[48]	0/16	1/24	0.47 (0.02 to 12.39), 15.55
Fieve BPI, 1976[50]	1/17	7/18	0.10 (0.01 to 0.91), 84.45
M–H pooled OR	$\chi^2 = 0.61$ (df = 1), $p = 0.43$		0.16 (0.02 to 0.96)
Test of OR = 1: $z = 2.01$, $p = 0.045$			
Institution of additional treatment			
Bowden, 2003[40]	8/44	28/69	0.32 (0.13 to 0.80), 61.22
Dunner, 1976[48]	1/16	6/24	0.20 (0.02 to 1.85), 15.44
Fieve BPI, 1976[50]	10/17	17/18	0.08 (0.01 to 0.78), 23.33
M–H pooled OR	$\chi^2 = 1.28$ (df = 2), $p = 0.53$		0.25 (0.11 to 0.54)
Test of OR = 1: $z = 3.52$, $p = 0.000$			
As stated by authors			
Bowden, 2000[39]	19/91	21/94	0.92 (0.45 to 1.85), 75.98
Prien, 1973[65]	2/18	4/13	0.28 (0.04 to 1.85), 19.19
Kane, 1982[56]	0/4	1/7	0.48 (0.01 to 14.70), 4.82
M–H pooled OR	$\chi^2 = 1.41$ (df = 2), $p = 0.49$		0.77 (0.41 to 1.46)
Test of OR = 1: $z = 0.79$, $p = 0.43$			

TABLE 6 *Depressive relapses*

Study	Lithium	Placebo	OR (95% CI), % weight
Admission to hospital			
Bowden, 2000[39]	2/91	6/94	0.33 (0.06 to 1.68), 48.83
Dunner, 1976[48]	1/16	4/24	0.33 (0.03 to 3.29), 25.38
Fieve BPI, 1976[50]	2/17	2/18	1.07 (0.13 to 8.56), 14.50
Fieve BPII, 1976[50]	1/7	2/11	0.75 (0.05 to 10.23), 11.28
M–H pooled OR	$\chi^2 = 0.98$ (df = 3), $p = 0.81$		0.48 (0.18 to 1.32)
Test of OR = 1: $z = 1.42$, $p = 0.16$			
Institution of additional treatment			
Bowden, 2003[40]	10/44	21/69	0.67 (0.28 to 1.61), 51.25
Dunner, 1976[48]	9/16	12/24	1.28 (0.36 to 4.58), 17.03
Fieve BPI, 1976[50]	5/17	8/18	0.52 (0.13 to 2.11), 22.25
Fieve BPII, 1976[50]	4/7	7/11	0.76 (0.11 to 5.28), 9.46
M–H pooled OR	$\chi^2 = 1.01$ (df = 3), $p = 0.80$		0.75 (0.41 to 1.37)
Test of OR = 1: $z = 0.93$, $p = 0.35$			
As stated by authors			
Bowden, 2000[39]	9/91	15/94	0.62 (0.26 to 1.48), 61.14
Prien, 1973[65]	2/18	7/13	0.21 (0.04 to 1.16), 29.49
Kane, 1982[56]	1/4	4/7	0.43 (0.03 to 5.39), 9.36
M–H pooled OR	$\chi^2 = 1.25$ (df = 2), $p = 0.53$		0.48 (0.23 to 1.00)
Test of OR = 1: $z = 1.95$, $p = 0.05$			

Manic and depressive relapse

Six studies provided data on manic relapses and six on depressive relapses (*Tables 5* and *6*). The pooled ORs revealed a statistically significant benefit of lithium for manic relapses, defined as admission to hospital and institution of additional treatment. However, there was no statistically significant difference between lithium and placebo for manic relapses as stated by authors. Pooled ORs for depressive relapses favoured lithium over placebo for all definitions of relapse, but were not statistically significant. However, this lack of statistical significance may be due to the different effects of lithium in bipolar I and bipolar II patients. No statistical heterogeneity was detected for any of the pooled estimates.

Drop-outs, suicide and adverse events leading to discontinuation (*Table 7*)

All eight studies provided data on drop-outs before the end of the study. The pooled OR showed significantly fewer drop-outs in the participants

TABLE 7 *Drop-outs, suicide attempts and adverse events leading to discontinuation*

Study	Lithium	Placebo	OR (95% CI), % weight
Drop-outs before the end of study			
Bowden, 2000[39]	41/91	35/94	1.38 (0.77 to 2.49), 14.40
Bowden, 2003[40]	27/46	21/70	3.31 (1.52 to 7.22), 5.23
Calabrese, 2003[42]	45/121	43/121	1.07 (0.64 to 1.81), 20.54
Dunner, 1976[48]	8/16	20/24	0.20 (0.05 to 0.85), 6.08
Fieve BPI, 1976[50]	2/17	18/18	0.00 (0.00 to 0.10), 11.78
Fieve BPII, 1976[50]	1/7	7/11	0.09 (0.01 to 1.10), 3.55
Kane, 1982[56]	3/4	2/7	7.50 (0.46 to 122.70), 0.28
Prien, 1973[65]	5/18	9/13	0.17 (0.03 to 0.82), 5.74
Prien, 1974[66]	27/101	59/104	0.28 (0.15 to 0.50), 32.40
M–H pooled OR	$\chi^2 = 53.60$ (df = 8), $p = 0.000$		0.73 (0.56 to 0.95)
Test of OR = 1: $z = 2.36$, $p = 0.018$			
Suicide attempts			
Bowden, 2000[39]	2/91	2/94	1.03 (0.14 to 7.50), 100
Adverse events leading to discontinuation			
Bowden, 2003[40]	11/46	3/70	7.02 (1.84 to 26.81), 15.18
Calabrese, 2003[42]	19/121	12/121	1.69 (0.78 to 3.65), 84.82
M–H pooled OR	$\chi^2 = 3.26$ (df = 1), $p = 0.07$		2.50 (1.30 to 4.79)
Test of OR = 1: $z = 2.76$, $p = 0.006$			

receiving lithium than those receiving placebo. However, significant statistical heterogeneity was detected. This reflected the very variable results reported for the individual trials. One study[39] presented data on suicide attempts. The numbers of suicide attempts in the lithium and placebo groups were not significantly different. However, numbers of events were too small to make a meaningful comparison. Data for adverse events leading to discontinuation were presented in two studies.[40,42] Numbers of participants leaving the study early due to adverse events were significantly higher in participants receiving lithium than participants receiving placebo. Statistical heterogeneity was detected, one trial finding a much larger treatment difference than the other.

Adverse events with lithium identified in placebo-controlled trials

The limited available data (*Table 8*) indicate that fine tremor and gastrointestinal disturbances are statistically and clinically significantly more common with lithium than with placebo. Other adverse effects identified, sedation, headache, weight gain and rash, do not appear to occur more frequently with lithium than with placebo.

Summary of results: lithium compared with placebo

All the analyses for lithium versus placebo demonstrate that lithium is more effective than placebo in reducing relapses (all relapses using all definitions). The size of the treatment effect for all relapses ranged from a pooled OR of 0.23–0.6. Although the findings appear to be robust, poor reporting of methodology makes it difficult to judge accurately the internal validity of the studies. There is a suggestion that lithium is slightly less effective in bipolar II patients; however, the data are very sparse and from trials of limited quality, and may not be reliable. The results for manic and depressive episodes were less clear cut, with a suggestion that lithium is less effective at preventing depressive episodes than manic episodes: results for prevention of depressive relapses were not statistically significant. However, again, the limited amount of data makes it difficult to draw firm conclusions. Heterogeneity among studies was observed only for all relapses as stated by authors. It is possible that this heterogeneity may in part be attributable to participant differences between the studies. Several of the studies are relatively old, and used different diagnostic criteria to the more recent studies: three studies used RDC or Feighner criteria,[48,50,56] which exclude atypical bipolar disorders, and, as a consequence, might favour lithium more than do recent studies using DSM diagnostic criteria.[39,40,42] This may have resulted in different populations across the studies, each showing a different response to lithium.

Few placebo-controlled trials reported suicide attempts as an outcome and the review failed to demonstrate any impact of lithium on suicide attempts. Although the pooled estimate for

TABLE 8 *Adverse events with lithium identified in placebo-controlled trials*

Study	Lithium	Placebo	OR (95% CI), % weight
Adverse events leading to discontinuation			
Bowden, 2003[40]	11/46	3/70	7.02 (1.84 to 26.81), 15.18
Calabrese, 2003[42]	19/121	12/121	1.69 (0.78 to 3.65), 84.82
M–H pooled OR	$\chi^2 = 3.26$ (df = 1), $p = 0.07$		2.50 (1.30 to 4.79)
Test of OR = 1: $z = 2.76$, $p = 0.006$			
Adverse events: rash			
Calabrese, 2003[42]	5/121	3/121	1.69 (0.40 to 7.26), 100
Adverse events: fine tremor			
Bowden, 2000[39]	38/91	12/94	4.90 (2.35 to 10.21), 57.86
Calabrese, 2003[42]	20/121	6/121	3.79 (1.47 to 9.82), 42.14
M–H pooled OR	$\chi^2 = 0.17$ (df = 1), $p = 0.68$		4.34 (2.48 to 7.94)
Test of OR = 1: $z = 5.01$, $p = 0.000$			
Adverse events: gastrointestinal disturbances			
Bowden, 2000[39]	42/91	28/94	2.02 (1.10 to 3.70), 55.60
Bowden, 2003[40]	13/46	6/70	4.20 (1.46 to 12.06), 12.79
Calabrese, 2003[42]	19/121	10/121	2.06 (0.92 to 4.65), 31.60
M–H pooled OR	$\chi^2 = 1.50$ (df = 2), $p = 0.47$		2.31 (1.49 to 3.59)
Test of OR = 1: $z = 3.75$, $p = 0.000$			
Adverse events: headache			
Bowden, 2003[40]	2/46	11/70	0.24 (0.05 to 1.16), 29.18
Calabrese, 2003[42]	23/121	25/121	0.90 (0.48 to 1.70), 70.81
M–H pooled OR	$\chi^2 = 2.36$ (df = 1), $p = 0.12$		0.71 (0.40 to 1.25)
Test of OR = 1: $z = 1.18$, $p = 0.24$			
Adverse events: sedation			
Bowden, 2000[39]	24/91	33/94	0.66 (0.35 to 1.24), 79.74
Calabrese, 2003[42]	16/121	7/121	2.48 (0.98 to 6.27), 20.26
M–H pooled OR	$\chi^2 = 5.35$ (df = 1), $p = 0.02$		1.03 (0.62 to 1.70)
Test of OR = 1: $z = 0.12$, $p = 0.91$			
Adverse events: weight gain			
Bowden, 2000[39]	12/91	7/94	1.89 (0.73 to 4.89), 100

drop-outs was statistically significant in favour of lithium, this was subject to enormous statistical heterogeneity, reflecting the highly variable results reported for this outcome across the trials. Adverse events leading to discontinuation were much more common among those taking lithium. The main adverse effects seen with lithium were tremor and gastrointestinal disturbance.

Lithium compared with valproate

Four studies compared lithium with valproate (divalproex).[36,39,43,69] One trial did not provide any dichotomous relapse data and was not included in the analyses.[69] Another trial included only paediatric participants and is considered separately.[36] Both remaining trials provided data for all relapses and were included in the main analysis.

All relapses

The results for all relapses are presented in *Table 9*. The ORs favoured the use of valproate over lithium for prevention of relapses as stated by authors, but were not statistically significant. Significant statistical heterogeneity was not detected. No best-case/worst-case sensitivity analysis was carried out because the number of participants randomised and the number of participants analysed were the same for all studies. No study investigated only participants with bipolar II disorder.

Manic and depressive relapse

Both studies provided data on manic and depressive relapses (*Tables 9*). The numbers of manic relapses as stated by authors and depressive relapses defined as admission to hospital and as stated by authors were not significantly different between participants receiving lithium and participants receiving valproate. No statistical heterogeneity was detected.

Drop-outs, suicide and adverse events leading to discontinuation

The pooled OR showed no statistically significant difference in the number of drop-outs between

TABLE 9 *Relapses (manic, depressive or mixed episodes)*

Study	Lithium	Valproate	OR (95% CI), % weight
All relapses: as stated by authors			
Bowden, 2000[39]	28/91	45/187	1.40 (0.80 to 2.44), 75.74
Calabrese, 2005[43]	18/32	14/28	1.28 (0.46 to 3.56), 24.26
M–H pooled OR	$\chi^2 = 0.02$ (df = 1), $p = 0.88$		1.37 (0.84 to 2.24)
Test of OR = 1: $z = 1.27$, $p = 0.20$			
Manic relapses: as stated by authors			
Bowden, 2000[39]	19/91	33/187	1.23 (0.65 to 2.31), 77.37
Calabrese, 2005[43]	7/32	6/28	1.03 (0.30 to 3.52), 22.63
M–H pooled OR	$\chi^2 = 0.07$ (df = 1), $p = 0.80$		1.18 (0.67 to 2.08)
Test of OR = 1: $z = 0.59$, $p = 0.55$			
Depressive relapses: admission to hospital			
Bowden, 2000[39]	2/91	3/187	1.38 (0.23 to 8.40), 100
Depressive relapses: as stated by authors			
Bowden, 2000[39]	9/91	12/187	1.60 (0.65 to 3.94), 55.83
Calabrese, 2005[43]	11/32	8/28	1.31 (0.44 to 3.92), 44.17
M–H pooled OR	$\chi^2 = 0.08$ (df = 1), $p = 0.78$		1.47 (0.73 to 2.96)
Test of OR = 1: $z = 1.08$, $p = 0.28$			

TABLE 10 *Drop-outs and suicide attempts*

Study	Lithium	Valproate	OR (95% CI), % weight
Drop-outs before the end of study			
Bowden, 2000[39]	41/91	71/187	1.34 (0.80 to 2.22), 88.45
Calabrese, 2005[43]	27/32	20/28	2.16 (0.61 to 7.60), 11.54
M–H pooled OR	$\chi^2 = 0.48$ (df = 1), $p = 0.49$		1.43 (0.90 to 2.29)
Test of OR = 1: $z = 1.51$, $p = 0.13$			
Suicide attempts			
Bowden, 2000[39]	2/91	2/187	2.08 (0.29 to 15.00), 100

TABLE 11 *Relapses (manic, depressive or mixed episodes)*

Study	Lithium	Valproate	OR (95% CI), % weight
All relapses: institution of additional treatment			
Findling, 2005[36]	18/30	20/30	0.75 (0.27 to 2.12), 100
Manic relapses: institution of additional treatment			
Findling, 2005[36]	15/30	19/30	0.58 (0.21 to 1.61), 100
Depressive relapses: institution of additional treatment			
Findling, 2005[36]	3/30	1/30	3.22 (0.43 to 23.62), 100

the lithium and valproate groups (*Table 10*). One study presented data for attempted suicides.[39] There were a greater proportion of suicide attempts in the lithium group than the valproate group. However, the number of events in both groups was too small to make a meaningful comparison. Neither of the studies provided data for adverse events leading to discontinuation from the study.

Paediatric bipolar disorder

One study[36] compared lithium and valproate for the treatment of bipolar disorder in a paediatric population. The data for all relapses are presented in *Table 11*, and show no statistically significant difference in the number of relapses, defined as the institution of additional treatment, between the lithium and valproate groups. No best-case/worst-case sensitivity analysis was performed

TABLE 12 *Drop-outs and adverse events leading to discontinuation*

Study	Lithium	Valproate	OR (95% CI), % weight
Drop-outs before the end of study			
Findling, 2005[36]	27/30	27/30	1.00 (0.21 to 4.76), 100
Adverse events: leading to discontinuation			
Findling, 2005[36]	2/30	3/30	0.64 (0.12 to 3.52), 100

because all randomised participants were analysed. Data for manic and depressive episodes are presented in *Table 11*. There were slightly more manic relapses, defined as institution of additional treatment, in the valproate group than the lithium group. However, this difference was not statistically significant. There was no significant difference in the number of depressive relapses, defined as institution of additional treatment, between the lithium and valproate groups. However, there were very few events in either group.

Drop-outs, suicide and adverse events leading to discontinuation

The number of drop-outs before the end of the study was equally high in both treatment groups (*Table 12*). Very few adverse events were reported, and there was no significant difference between treatment groups. The study did not provide any data for suicide.

Summary of results: lithium compared with valproate

Although there was a tendency favouring the efficacy of valproate over lithium, the pooled analyses found no statistically significant treatment difference for any of the outcomes. Some limitations in the reporting of study methodology make it difficult to judge the validity of these findings. In addition, it should be noted that all the participants in one of these studies had rapid cycling variant of bipolar disorder.[43] Although there was little difference in the results of the two studies, there are insufficient data to draw a meaningful comparison between individuals with and without rapid cycling disorder. The single study in children indicated a different finding, with the ORs for all relapse and manic relapse favouring lithium, although again, they were not statistically significant. However, this was a small study, with a high rate of drop-outs, and it is possible that real treatment differences may have gone undetected.

No statistically significant difference was observed between lithium and valproate for number of drop-outs. No information was provided regarding adverse events leading to discontinuation. Only one trial reported on suicide and the number of events was too small to demonstrate any treatment difference.

Overall, there is a lack of data to demonstrate clearly whether there is any real treatment difference between lithium and valproate.

Lithium compared with lamotrigine

Two studies compared lithium with lamotrigine.[40,42] One of these studies had three separate lamotrigine treatment arms, each with a different dosage: 50, 200 and 400 mg. For the purposes of the analysis, participants receiving 50 mg were excluded, because the dosage was considered to be sub-therapeutic. Data for participants receiving either 200 or 400 mg of lamotrigine were pooled and analysed as one lamotrigine treatment arm,[42] because the two doses were thought to be similar enough to be considered as one treatment. Furthermore, an investigation of different dosage effects was beyond the scope of this review.

All relapses

Both trials provided data for all relapses and were included in the base-case analysis and the best-case/worst-case sensitivity analysis. Data for all relapses are summarised in *Table 13*. The pooled ORs showed no statistically significant difference in the number of relapses as defined by institution of additional treatment or as stated by authors between lithium and lamotrigine groups. No statistical heterogeneity was detected. Results of the best-case/worst-case sensitivity analysis are given in Appendix 7, *Tables 95* and *96*, and show no difference when compared with the main results.

Manic and depressive relapses

One trial provided data for manic and depressive relapses defined as institution of additional treatment;[40] these are presented in *Tables 13*. The ORs favoured lithium for the prevention of manic relapses and lamotrigine for the prevention of depressive relapses. However, differences were not statistically significant.

TABLE 13 *Relapses (manic, depressive or mixed episodes)*

Study	Lithium	Lamotrigine	OR (95% CI), % weight
All relapses: institution of additional treatment			
Bowden, 2003[40]	18/44	28/58	0.74 (0.34 to 1.64), 27.69
Calabrese, 2003[42]	56/120	83/165	0.86 (0.54 to 1.38), 72.31
M–H pooled OR	$\chi^2 = 0.11$ (df = 1), $p = 0.74$		0.83 (0.55 to 1.24)
Test of OR = 1: $z = 0.90$, $p = 0.37$			
All relapses: as stated by authors			
Calabrese, 2003[42]	99/120	134/165	1.09 (0.59 to 2.01), 100
Manic relapses: institution of additional treatment			
Bowden, 2003[40]	8/44	20/58	0.42 (0.16 to 1.07), 100
Depressive relapses: institution of additional treatment			
Bowden, 2003[40]	10/44	8/58	1.84 (0.66 to 5.13), 100

TABLE 14 *Drop-outs and adverse events leading to discontinuation*

Study	Lithium	Lamotrigine	OR (95% CI), % weight
Drop-outs before the end of study			
Bowden, 2003[40]	27/46	28/59	1.57 (0.72 to 3.43), 100
Adverse events leading to discontinuation			
Bowden, 2003[40]	11/46	3/59	5.87 (1.53 to 22.51), 100

Drop-outs, suicide and adverse events leading to discontinuation

Data for drop-outs before the end of the study and adverse events leading to discontinuation were provided by one study[40] (*Table 14*). The OR favoured lamotrigine regarding drop-outs before the end of the study, but was not statistically significant. The OR showed a statistically significant greater number of adverse events leading to discontinuation in the lithium group than in the lamotrigine group. There were no data on suicide.

Summary of results: lithium compared with lamotrigine

The pooled analysis did not show a statistically significant difference favouring either lithium or lamotrigine in the prevention of all relapses, or episodes of mania or depression. Although the results were based on only two studies, each had a reasonable sample size. Inadequacies in the description of treatment allocation and blinding make it difficult to make a full assessment of the studies' validity. In the single study where data were reported, there was a tendency favouring lithium in the prevention of manic relapses and lamotrigine in the prevention of depressive relapses. Data from a single study suggest that although there is no statistically significant difference in the number of drop-outs from lithium or lamotrigine, lithium significantly increases the presence of adverse events leading to discontinuation. However, only participants who had tolerated lamotrigine were randomised into the study, so this finding may not be generalisable.

Lithium compared with carbamazepine

Five studies compared lithium with carbamazepine.[47,53,57,60,72]

All relapses

Four trials provided data for all relapses and were included in both the base-case analysis and the best-case/worst-case sensitivity analysis. One trial[60] was excluded from the main analysis because participants were randomised while still in an acute phase of bipolar disorder.

Data for all relapses are presented in *Tables 15*. The pooled ORs favoured lithium over carbamazepine, but only the result for relapses as stated by authors was statistically significant in favour of lithium. No statistical heterogeneity was detected.

The results of the best-case sensitivity analysis did not differ from the base-case analysis for admission to hospital. However, for relapse as stated by authors, the differences between lithium and carbamazepine were no longer statistically significant, OR 0.68 (95% CI 0.41 to 1.12)

TABLE 15 *All relapses (manic, depressive or mixed episodes)*

Study	Lithium	Carbamazepine	OR (95% CI), % weight
All relapses: admission to hospital			
Kleindienst BPI, 2000[57]	20/54	21/38	0.48 (0.19 to 1.2), 68.01
Kleindienst BPII, 2000[57]	7/21	3/18	2.50 (0.44 to 17.57), 9.47
Simhandl, 1993[72]	3/21	5/14	0.3 (0.04 to 2.02), 22.52
M–H pooled OR	$\chi^2 = 4.3$ (df = 2), $p = 0.1166$		0.63 (0.33 to 1.2)
Test of OR = 1: $z = 1.25$, $p = 0.2111$			
All relapses: as stated by authors			
Coxhead, 1992[47]	8/15	6/13	1.33 (0.30 to 5.91), 8.28
Hartong, 2003[53]	3/22	14/30	0.18 (0.04 to 0.74), 28.23
Kleindienst BPI, 2000[57]	24/54	28/42	0.40 (0.17 to 0.92), 48.30
Kleindienst BPII, 2000[57]	10/21	10/19	0.82 (0.24 to 2.83), 15.18
M–H pooled OR	$\chi^2 = 4.54$ (df = 3), $p = 0.21$		0.48 (0.27 to 0.84)
Test of OR = 1: $z = 2.59$, $p = 0.01$			

TABLE 16 *Subgroup analyses 1: studies in which all participants were bipolar II analysed separately from studies in which participants were bipolar I or II or not specified*

Study	Lithium	Carbamazepine	OR (95% CI), % weight
All relapses: admission to hospital			
Kleindienst BPII, 2000[57]	7/21	3/18	2.50 (0.54 to 11.62), 100
All relapses: admission to hospital			
Kleindienst BPI, 2000[57]	20/54	21/38	0.48 (0.19 to 1.2), 75.12
Simhandl, 1993[72]	3/21	5/14	0.3 (0.04 to 2.02), 24.88
M–H pooled OR	$\chi^2 = 0.24$ (df = 1), $p = 0.6235$		0.43 (0.2 to 0.91)
Test of OR = 1: $z = 2.01$, $p = 0.044$			
All relapses: as stated by authors			
Kleindienst BPII, 2000[57]	10/21	10/19	0.82 (0.24 to 2.83), 100
All relapses: as stated by authors			
Coxhead, 1992[47]	8/15	6/13	1.33 (0.30 to 5.91), 9.76
Hartong, 2003[53]	3/22	14/30	0.18 (0.04 to 0.74), 33.29
Kleindienst BPI, 2000[57]	24/54	28/42	0.40 (0.17 to 0.92), 56.95
M–H pooled OR	$\chi^2 = 3.70$ (df = 2), $p = 0.16$		0.42 (0.22 to 0.78)
Test of OR = 1: $z = 2.72$, $p = 0.007$			

(Appendix 7, *Table 97*). The results of the worst-case sensitivity analysis also differed from the base-case analysis, with the OR for relapse admission to hospital reaching statistical significance, OR 0.46 (95% CI 0.26 to 0.8) (Appendix 7, *Table 98*).

Subgroup analyses

One trial[57] presented data for bipolar II participants separately from data for bipolar I participants. When the bipolar II data were removed from the meta-analysis, the results for all relapses as stated by authors remained statistically significant in favour of lithium (*Table 16*) and the result for all relapses defined as admission to hospital became statistically significant in favour of lithium.

When the trial[60] that randomised participants while they were in the acute phase of bipolar disorder was included in the analyses, the results were reversed to favour carbamazepine for relapse defined as admission to hospital (*Table 17*), but again, the pooled OR was not statistically significant.

Manic or depressive relapses

One study provided data on manic and depressive relapses, as stated by authors (*Table 18*). Although the ORs favoured lithium over carbamazepine for the prevention of manic and depressive relapses, the results were not statistically significant.

Drop-outs, suicide and adverse events leading to discontinuation (*Table 19*)

Two studies provided data for drop-outs before the end of the study. One study strongly favoured carbamazepine and the other lithium. The pooled ORs revealed no significant difference between the

TABLE 17 *Subgroup analyses 2: studies in which participants randomised during an acute episode were included in the analysis*

Study	Lithium	Carbamazepine	OR (95% CI), % weight
All relapses: admission to hospital			
Kleindienst BPI, 2000[57]	20/58	21/56	0.88 (0.38 to 2.02), 57.14
Kleindienst BPII, 2000[57]	7/28	3/29	2.89 (0.56 to 19.09), 9.06
Lusznat, 1988[60]	10/27	5/27	2.59 (0.64 to 11.38), 12.82
Simhandl, 1993[72]	3/21	5/14	0.3 (0.04 to 2.02), 20.98
M–H pooled OR	$\chi^2 = 6.2$ (df = 3), $p = 0.1024$		1.16 (0.67 to 1.99)
Test of OR = 1: $z = 0.4$, $p = 0.6921$			

TABLE 18 *Manic and depressive relapses*

Study	Lithium	Carbamazepine	OR (95% CI), % weight
Manic relapses: as stated by authors			
Hartong, 2003[53]	1/22	5/30	0.24 (0.02 to 2.20), 100
Depressive relapses: as stated by authors			
Hartong, 2003[53]	2/22	9/30	0.23 (0.05 to 1.21), 100

TABLE 19 *Drop-outs, suicide attempts and adverse events leading to discontinuation*

Study	Lithium	Carbamazepine	OR (95% CI), % weight
Drop-outs before the end of study			
Hartong, 2003[53]	12/23	6/30	4.36 (1.30 to 14.67), 9.43
Kleindienst BPI, 2000[57]	5/58	17/56	0.22 (0.07 to 0.63), 59.87
Kleindienst BPII, 2000[57]	7/28	11/29	0.54 (0.17 to 1.70), 30.70
M–H pooled OR	$\chi^2 = 13.48$ (df = 2), $p = 0.001$		0.71 (0.39 to 1.28)
Test of OR = 1: $z = 1.14$, $p = 0.25$			
Suicide attempts			
Kleindienst, 2000[57]	0/86	4/85	0.10 (0.00 to 1.97), 100
Adverse events leading to discontinuation			
Coxhead, 1992[47]	0/16	2/15	0.16 (0.01 to 2.17), 21.37
Hartong, 2003[53]	4/23	2/30	2.95 (0.37 to 34.94), 12.31
Kleindienst, 2000[57]	3/86	8/85	0.35 (0.06 to 1.53), 66.32
M–H pooled OR	$\chi^2 = 4.29$ (df = 2), $p = 0.1169$		0.63 (0.25 to 1.58)
Test of OR = 1: $z = 0.78$, $p = 0.4337$			

two treatment groups; not surprisingly, there was significant statistical heterogeneity. Three studies provided data for adverse events leading to discontinuation, and showed no significant difference between lithium and carbamazepine, but again there was significant statistical heterogeneity. One study provided data for suicide attempts and found no significant difference in the number of suicide attempts in the carbamazepine and lithium groups.

Summary of results: lithium compared with carbamazepine

The pooled analyses showed a tendency for a greater level of efficacy with lithium compared with carbamazepine in the prevention of relapses, but this was not always statistically significant, varying with definition of relapse and type of analysis. The studies were of mixed quality; all but one failed to provide an adequate description of methods of randomisation and treatment allocation. However, the findings of the better quality study[53] did not differ from those of the pooled analysis. After removal of data on bipolar II patients from the analysis, the results were significantly in favour of lithium. The results for bipolar II patients showed a tendency for a greater level of efficacy with carbamazepine compared with lithium. However, this finding was not significant and was based on a very small number

TABLE 20 *Relapses (manic, depressive or mixed episodes)*

Study	Lithium	Olanzapine	OR (95% CI), % weight
All relapses: admission to hospital Tohen, 2005[77]	49/214	31/217	1.78 (1.08 to 2.93), 100
All relapses: as stated by authors Tohen, 2005[77]	69/193	53/202	1.56 (1.02 to 2.40), 100
Manic relapses: as stated by authors Tohen, 2005[77]	53/193	25/202	2.68 (1.59 to 4.53), 100
Depressive relapses: as stated by authors Tohen, 2005[77]	16/193	28/202	0.56 (0.29 to 1.07), 100

TABLE 21 *Drop-outs, suicide and adverse events leading to discontinuation*

Study	Lithium	Olanzapine	OR (95% CI), % weight
Drop-outs before the end of study Tohen, 2005[77]	113/214	147/217	0.53 (0.36 to 0.79), 100
Suicides Tohen, 2005[77]	1/214	0/217	3.06 (0.12 to 75.44), 100
Adverse events leading to discontinuation Tohen, 2005[77]	55/214	41/217	1.48 (0.94 to 2.35), 100

of participants, and so may not be reliable. Few data were available on manic and depressive episodes and no significant differences between groups were seen. The variable results regarding drop-outs and adverse effects leading to discontinuation make it difficult to reach conclusions. Also, as with other comparisons, there were insufficient data on suicide.

Lithium compared with olanzapine

One study compared lithium with olanzapine.[77] This trial provided data for all relapses and manic and depressive relapses.

All relapses

The ORs for all relapses were statistically significant and favoured olanzapine over lithium for admission to hospital and all relapses as stated by authors (*Table 20*). Best-case/worst-case sensitivity analysis was performed. Although the results of the best-case analysis still favoured olanzapine, the results were no longer statistically significant for all relapses as stated by authors, OR.1.47 (95% CI 0.96 to 2.24). However, the results of the worst-case analysis did not differ from the results of the base-case analysis (Appendix 7, *Tables 99* and *100*).

Manic or depressive relapses

The OR for manic relapses as stated by authors was statistically significant in favour of olanzapine. However, the OR for depressive relapses as stated by authors favoured lithium, but was not statistically significant (*Table 20*).

Drop-outs, suicide and adverse events leading to discontinuation

The data for drop-outs before the end of the study were significantly in favour of lithium (*Table 21*). There was no significant difference in the number of suicides between the two treatment groups: only one in the lithium group and none in the olanzapine group. There were fewer adverse events leading to discontinuation in the olanzapine group than the lithium group. However, this difference was not statistically significant.

Summary of results: lithium compared with olanzapine

The results showed a marginally significant efficacy favouring olanzapine in the prevention of all relapses and manic episodes, but not depressive episodes. All results, however, were based on a single study, albeit of good quality and with an adequate sample size. Significantly more participants dropped out of the olanzapine group than the lithium group before the end of the study. However, no statistically significant difference between groups was observed for those who presented with adverse events leading to discontinuation. The study failed to demonstrate

TABLE 22 *All relapses (manic, depressive or mixed episodes)*

Study	Lithium	Imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	1/4	3/5	0.22 (0.01 to 3.98), 8.88
Prien, 1973[65]	9/18	11/13	0.18 (0.03 to 1.06), 28.37
Prien, 1984[66]	23/42	29/36	0.29 (0.10 to 0.81), 62.75
M–H pooled OR	$\chi^2 = 0.22$ (df = 2), $p = 0.90$		0.25 (0.11 to 0.59)
Test of OR = 1: $z = 3.17$, $p = 0.002$			

TABLE 23 *Subgroup analyses 1: studies in which all participants were bipolar II analysed separately from studies in which participants were bipolar I or II or not specified*

Study	Lithium	Imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	1/4	3/5	0.22 (0.01 to 3.98), 100
All relapses: as stated by authors			
Prien, 1973[65]	9/18	11/13	0.18 (0.03 to 1.06), 31.13
Prien, 1984[66]	23/42	29/36	0.29 (0.10 to 0.81), 68.87
M–H pooled OR	$\chi^2 = 0.21$ (df = 1), $p = 0.65$		0.26 (0.11 to 0.62)
Test of OR = 1: $z = 3.01$, $p = 0.003$			

any impact of lithium or olanzapine on suicide attempts: despite a relatively large sample size, there was only one suicide.

Lithium compared with imipramine

Four studies compared lithium with imipramine.[56,64,65,67] One poor-quality trial[64] was excluded from all statistical analyses because it did not provide any dichotomous data. Of the studies included in the analysis, two compared three treatment arms: lithium, imipramine and placebo,[65] and lithium, lithium + imipramine, imipramine.[67] Another very small study compared four treatment arms: lithium, lithium + imipramine, imipramine and placebo.[56] For the purposes of the analyses in the current review, results were reported for each comparison separately: lithium compared with a combination of lithium and imipramine is reported in the section 'Lithium alone compared with a combination of lithium and imipramine' (p. 30).

All relapses

Three trials provided data for all relapses and were included in both the base-case analysis (*Table 22*) and the best-case/worst-case sensitivity analysis (Appendix 7, *Tables 101* and *102*). The pooled OR was statistically significant in favour of lithium for all relapses as stated by authors. The results of the sensitivity analysis did not differ from the base-case analysis. No statistical heterogeneity was detected.

Subgroup analysis

One very small trial[56] included only participants with bipolar II participants. When this study was removed from the meta-analysis, the results were not significantly different from the main analysis (*Table 23*).

Manic or depressive relapses

All three trials provided data on both manic and depressive relapses as stated by authors (*Table 24*). The pooled OR was statistically significant in favour of lithium for the prevention of manic relapses. In contrast, the pooled OR for depressive relapses favoured imipramine, although it was not statistically significant.

Drop-outs, suicide and adverse events leading to discontinuation

The results for drop-outs were not consistent across studies, and the pooled OR showed no statistically significant treatment difference and was subject to heterogeneity (*Table 25*). In the one study that reported them, no adverse events leading to discontinuation occurred in either the lithium or the imipramine group. No data for suicide were reported.

Summary of results: lithium compared with imipramine

The pooled analysis found lithium to be more efficacious than imipramine in the prevention of all relapses as stated by authors, and in the

TABLE 24 *Manic and depressive relapses*

Study	Lithium	Imipramine	OR (95% CI), % weight
Manic relapses: as stated by authors			
Kane, 1982[56]	0/4	1/5	0.33 (0.01 to 10.57), 4.79
Prien, 1973[65]	2/18	9/13	0.05 (0.01 to 0.36), 36.26
Prien, 1984[66]	11/42	19/36	0.32 (0.12 to 0.82), 58.95
M–H pooled OR	$\chi^2 = 2.67$ (df = 2), $p = 0.26$		0.22 (0.10 to 0.50)
Test of OR = 1: $z = 3.67$, $p = 0.000$			
Depressive relapses: as stated by authors			
Kane, 1982[56]	1/4	2/5	0.50 (0.03 to 8.95), 14.00
Prien, 1973[65]	2/18	0/13	4.09 (0.18 to 92.68), 5.25
Prien, 1984[66]	12/42	10/36	1.04 (0.39 to 2.80), 80.75
M–H pooled OR	$\chi^2 = 0.99$ (df = 2), $p = 0.61$		1.12 (0.47 to 2.69)
Test of OR = 1: $z = 0.26$, $p = 0.79$			

TABLE 25 *Drop-outs and adverse events leading to discontinuation*

Study	Lithium	Imipramine	OR (95% CI), % weight
Drop-outs before the end of study			
Kane, 1982[56]	3/4	2/5	4.50 (0.25 to 80.56), 3.55
Prien, 1973[65]	5/18	10/13	0.11 (0.02 to 0.60), 66.93
Prien, 1984[66]	7/44	4/36	1.51 (0.40 to 5.64), 29.52
M–H pooled OR	$\chi^2 = 7.50$ (df = 2), $p = 0.02$		0.68 (0.29 to 1.61)
Test of OR = 1: $z = 0.87$, $p = 0.38$			
Adverse events leading to discontinuation			
Prien, 1984[66]	0/42	0/42	Not calculable

prevention of episodes of mania as stated by authors. In contrast, the pooled analyses for the prevention of depressive episodes as stated by authors tended to favour imipramine but did not reach statistical significance. These results are based on three very small studies, with a total of less than 120 patients in the relevant treatment arms. In particular, the results of the Kane study ($n = 9$) cannot be considered reliable.[56] The results for bipolar II patients tended to favour lithium compared with imipramine for all relapses; however, this was not statistically significant and the number of participants was too few to make the comparison meaningful. Given the variable results for drop-outs across the three studies, the pooled result is unlikely to be reliable. Similarly, no reliable data on adverse events leading to discontinuation were available and no study reported on suicides for this comparison.

Lithium alone compared with a combination of lithium and imipramine

Three studies compared lithium with a combination of imipramine and lithium.[55,56,67] From the studies included in the analysis, one compared two treatment arms (lithium plus imipramine and lithium),[55] one study compared three treatment arms (lithium, lithium + imipramine and imipramine)[67] and another very small study compared four treatment arms (lithium, lithium + imipramine, imipramine and placebo).[56] For the purposes of the analyses in the current review, results were reported for each comparison separately: lithium compared with imipramine is reported in the section 'Lithium compared with imipramine' (p. 29).

All relapses

All three trials provided data for all relapses and were included in both the base-case analysis and the best-case/worst-case sensitivity analysis.

Data for all relapses are summarised in *Table 26*. The results of the studies were inconsistent, and the pooled OR did not reveal a significant difference between lithium alone and a combination of lithium and imipramine for the prevention of relapse, as stated by authors. The results of the sensitivity analysis did not significantly differ from the base-case analysis (Appendix 7, *Tables 103* and *104*). Only one of the included studies did not analyse all participants that had been randomised.[67] No statistical heterogeneity was detected.

TABLE 26 *All relapses (manic, depressive or mixed episodes)*

Study	Lithium	Lithium + imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1981[55]	8/38	12/37	0.55 (0.20 to 1.57), 50.61
Kane, 1982[56]	1/4	1/6	1.67 (0.07 to 37.72), 3.16
Prien, 1984[67]	23/42	18/36	1.21 (0.50 to 2.95), 46.23
M–H pooled OR	$\chi^2 = 1.40$ (df = 2), $p = 0.50$		0.89 (0.46 to 1.72)
Test of OR = 1: $z = 0.34$, $p = 0.74$			

TABLE 27 *Subgroup analyses 1: studies in which all participants were bipolar II analysed separately from studies in which participants were bipolar I or II or not specified*

Study	Lithium	Lithium + imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	1/4	1/6	1.50 (0.07 to 31.57), 100
All relapses: as stated by authors			
Kane, 1981[55]	8/38	12/37	0.55 (0.20 to 1.57), 52.26
Prien, 1984[67]	23/42	18/36	1.21 (0.50 to 2.95), 47.74
M–H pooled OR	$\chi^2 = 1.24$ (df = 1), $p = 0.26$		0.87 (0.44 to 1.70)
Test of OR = 1: $z = 0.41$, $p = 0.68$			

TABLE 28 *Manic and depressive relapses*

Study	Lithium	Lithium + imipramine	OR (95% CI), % weight
Manic relapses: as stated by authors			
Kane, 1981[55]	4/38	9/37	0.37 (0.10 to 1.31), 50.68
Kane, 1982[56]	0/4	0/6	Excluded
Prien, 1984[67]	11/42	10/36	0.92 (0.34 to 1.31), 49.32
M–H pooled OR	$\chi^2 = 1.24$ (df = 1), $p = 0.26$		0.64 (0.29 to 1.39)
Test of OR = 1: $z = 1.13$, $p = 0.26$			
Depressive relapses: as stated by authors			
Kane, 1981[55]	4/38	3/37	1.33 (0.28 to 6.41), 28.71
Kane, 1982[56]	1/4	1/6	1.67 (0.07 to 37.72), 6.33
Prien, 1984[67]	12/42	8/36	1.40 (0.50 to 3.93), 64.95
M–H pooled OR	$\chi^2 = 0.02$ (df = 2), $p = 0.99$		1.40 (0.61 to 3.21)
Test of OR = 1: $z = 0.79$, $p = 0.43$			

Subgroup analysis

One very small trial[56] included only participants with bipolar II disorder and was compared with the other studies in a subgroup analysis (*Table 27*). Removing this study from the meta-analysis did not significantly affect the results.

Manic or depressive relapses

All three studies provided data on manic relapses and depressive relapses (*Table 28*). One study reported no manic relapses in either treatment group, and so was excluded from the analysis. The pooled OR for the remaining studies favoured lithium for manic relapses as stated by authors, but was not statistically significant. No statistical heterogeneity was detected. All studies favoured the combination of lithium and imipramine over lithium alone for the prevention of depressive relapses as stated by authors, but this was not statistically significant.

Drop-outs, suicide and adverse events leading to discontinuation

The results of the studies were not consistent, and the pooled OR revealed no significant difference in the number of drop-outs in each of the treatment groups (*Table 29*). One study[67] provided data for adverse events leading to discontinuation. The results revealed no significant difference between the two treatment groups, but the number of events in both treatment groups was very small. There were no data on suicide.

TABLE 29 *Drop-outs and adverse events leading to discontinuation*

Study	Lithium	Lithium + imipramine	OR (95% CI), % weight
Drop-outs before the end of study			
Kane, 1981[55]	21/38	18/37	1.30 (0.52 to 3.23), 56.50
Kane, 1982[56]	3/4	4/6	1.50 (0.09 to 25.39), 5.54
Prien, 1984[67]	7/44	6/37	0.98 (0.30 to 3.21), 37.96
M–H pooled OR	$\chi^2 = 0.17$ (df = 2), $p = 0.92$		1.19 (0.59 to 2.39)
Test of OR = 1: $z = 0.49$, $p = 0.62$			
Adverse events leading to discontinuation			
Prien, 1984[67]	0/42	1/36	0.28 (0.02 to 3.53), 100

Summary of results: lithium compared with a combination of lithium and imipramine

The pooled analysis for the prevention of all relapses as stated by authors and the prevention of episodes of mania or depression as stated by authors did not show a statistically significant difference favouring either lithium or a combination of lithium + imipramine. Similarly, no statistically significant difference was observed among those who dropped out before the end of the study. Although there were three studies with relevant data, the total sample size was small. In addition, all three studies failed to report sufficient methodological details to allow full assessment of the studies' validity. The data for bipolar II patients were insufficient to draw any conclusions. The one trial that reported data on adverse events leading to discontinuation found no significant difference. There were no data on suicide attempts.

Lithium alone compared with a combination of lithium and another drug

Three studies compared lithium alone with a combination of lithium and another drug: lithium plus flupenthixol, lithium plus amitriptyline and lithium plus valproate.[49,54,74] These studies were of poor quality and had insufficient reliable data to be included in any statistical analyses. Their details are given in the table of included studies (Appendix 5) and in the data extraction tables (Appendix 6). Their quality assessment details are given in *Table 1*.

For the comparison of lithium with lithium plus flupenthixol ($n = 15$),[49] the results showed a non-statistically significant difference favouring lithium (OR 0.5, 95% CI 0.03 to 7.10) for prevention of all relapses, defined as the number of participants needing hospitalisation. For the comparison of lithium with lithium plus amitriptyline ($n = 13$),[54] the OR of 0.4 (95% CI 0.04 to 3.95) tended to favour lithium alone to prevent relapse of depressive episodes; however, the results were not statistically significant. None of the participants had a manic relapse. For the comparison of lithium with lithium plus divalproex and lithium,[74] the 12 participants were in acute phase at recruitment. Hence the findings are not directly relevant to the prevention of relapse

Overall, there are only very limited data on the efficacy of lithium combination therapy, none of which can be used to draw conclusions regarding its place in maintenance treatment for bipolar disorder.

Conclusions regarding the effectiveness of lithium

In summary, overall the placebo-controlled trial data indicate that lithium is an efficacious treatment for the management of bipolar disorder. There is a suggestion that lithium is not as effective at preventing depressive relapses as manic relapses and may be less efficacious in bipolar II patients. However, the evidence for this is very weak and further controlled trials are required. The main adverse effects seen with lithium were tremor and gastrointestinal disturbance.

When compared with other pharmacological treatments, lithium was shown to be statistically significantly more effective than carbamazepine and imipramine, but statistically significantly less effective than olanzapine, particularly for the prevention of manic episodes. The evidence for the comparison with carbamazepine was reasonable; however, evidence for that with imipramine was somewhat weaker, based on small studies with few data. The results for the comparison with olanzapine came from just one good-quality study. No statistically significant treatment difference was found for the comparisons of lithium with valproate, lamotrigine or the combination of lithium plus imipramine. These results were based on few studies for each

comparison and, in the case of imipramine and lithium combination therapy, few data. There were insufficient reliable data to draw any firm conclusion regarding prevention of relapse in bipolar I compared with bipolar II patients.

The review failed to demonstrate any impact of lithium compared with placebo, carbamazepine, valproate, lamotrigine, olanzapine, imipramine or lithium plus imipramine on suicide or suicide attempts, because the included trials did not provide the relevant information. The review also failed to provide any evidence on the relative impact of possible troublesome adverse events with lithium and the comparator interventions.

In the trials, tremor and gastrointestinal disturbances are the adverse effects associated with lithium. The small amount of data in the trials reviewed here do not indicate that lithium is tolerated any less well than the other treatments for bipolar disorder, with the exception of lamotrigine. However, as most of the data relate to relatively short follow-up periods, their relevance to clinical practice is limited.

Valproate

A total of seven randomised or quasi-randomised trials that investigated the efficacy of valproate (or divalproex) were identified for the review.[36,38,39,43,51,69,75] Trial details are summarised in *Table 30* and presented in the data extraction tables (Appendix 6).

All but one study[36] tested the intervention or comparator in adults. The proportion of females in the studies ranged from 35 to 100%. Four studies included participants diagnosed as bipolar I and II or not specified, two studies included only participants with bipolar I and one study only included bipolar II participants. The proportion of participants with rapid cycling ranged from 12 to 100% in the included studies. The sample size of the included studies varied from 23 to 372 participants.

The quality of the included studies comparing valproate with placebo or other interventions was limited. In all the studies participants were randomly assigned; however, only one study had an adequate sequence generation.[51] This study was also the only one to have described an adequate procedure of allocation concealment. Assessors and participants were blinded in four studies and care providers were blinded in two studies. In almost all studies the intervention and comparison groups were described as similar on the baseline measurements. Eligibility criteria were clearly identified and point estimates with variability were presented for the primary outcome in all but one study. Five studies reported a sample size calculation. Details of the individual study quality are presented in *Table 1*. Of the seven valproate studies, four were sponsored by the pharmaceutical industry.

Trial data were available for comparisons of valproate with placebo, lithium and olanzapine.

Valproate compared with placebo

Two studies compared valproate with placebo.[39,51] The smaller of the two trials[51] only included participants with bipolar II disorder and provided data for relapses of depressive episodes only.

All relapses

One trial[39] provided data for all relapses, but a best-case/worst-case sensitivity analysis was not performed because all participants who were randomised were analysed. The data for all relapses as stated by authors are presented in *Table 31* and show a statistically significant benefit of valproate compared with placebo.

Manic or depressive relapses

One study provided data for manic relapses and found no significant difference between valproate and placebo for the prevention of relapses as stated by authors (*Table 31*). Data for depressive relapses were provided by both studies, and are presented in *Table 31*. The OR for depressive relapses admission to hospital, and the pooled OR for depressive relapses as stated by authors were both statistically significant, in favour of valproate. Statistical heterogeneity was not detected.

Drop-outs, suicide and adverse events leading to discontinuation

Both studies showed a higher proportion of drop-outs in the valproate group than the placebo group (*Table 32*). However, this difference was not statistically significant. One study provided data for adverse events leading to discontinuation, which showed no significant difference between treatment groups. However, it should be noted that the number of events in both treatment groups was very small. Neither of the studies provided data for suicide.

Adverse events with valproate identified in placebo-controlled trials

Most of the placebo-controlled trial data on adverse effects for valproate are derived from a single trial[39] (*Table 33*). These data suggest that

TABLE 30 *Characteristics of included studies comparing valproate with placebo or other active treatments*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2
Altamura, 2004[38]	Mainly adults	23	50.00			Yes	Bipolar I and II	Mania + depression		Valproate: final: 415 ± 16.39 mg (62.7 ± 19.5 μg/ml)	Olanzapine: final: 9 ± 3.2 mg	
Bowden, 2000[39]	Mainly adults	372	51.20		Caucasian	Yes	Bipolar I	Mania + depression		Divalproex: 71–125 μg/ml	Lithium: 0.8–1.2 mmol/l	Placebo
Calabrese, 2005[43]	Mainly adults	60	51.67			Yes	Bipolar I and II	All	100.00	Divalproex: 900–1200 mg/day (mean 0.92 mEq/l)	Lithium: 750–2750 mg/day (mean 77 μg/ml)	
Findling, 2005[36]	Mainly children	60	35.00			Yes	Bipolar I and II	All	50.00	Valproate: 50–100 μg/ml	Lithium: 0.6–1.2 mmol/l	
Frankenburg, 2002[51]	Mainly adults	30	100.00		Caucasian	Yes	Bipolar II	Hypomania + depression		Valproate: 50–100 mg/l	Placebo	
Revicki, 2005[69]	Mainly adults	221	51.20		Caucasian	No	Bipolar I	Mania + mixed	12.25	Divalproex: 15–20 mg/kg/day or usual psychiatric practice	Lithium: 900–1200 mg/day	
Tohen, 2003[75]	Mainly adults	251	57.37		Caucasian	No	Bipolar – not specified	Mania + mixed	57.40	Divalproex: 500–2500 mg/day (50–125 μg/ml)	Olanzapine: 5–20 mg/day	

TABLE 31 *Relapses (manic, depressive or mixed episodes)*

Study	Valproate	Placebo	OR (95% CI), % weight
All relapses: as stated by authors			
Bowden, 2000[39]	45/187	36/94	0.51 (0.30 to 0.87), 100
Manic relapses: as stated by authors			
Bowden, 2000[39]	33/187	21/94	0.74 (0.40 to 1.38), 100
Depressive relapses: admission to hospital			
Bowden, 2000[39]	3/187	6/94	0.24 (0.06 to 0.98), 100
Depressive relapses: as stated by authors			
Bowden, 2000[39]	12/187	15/94	0.36 (0.16 to 0.81), 85.36
Frankenburg, 2002[51]	0/20	2/10	0.08 (0.00 to 1.91), 14.64
M–H pooled OR	$\chi^2 = 0.80$ (df = 1), $p = 0.37$		0.32 (0.15 to 0.69)
Test of OR = 1: $z = 2.91$, $p = 0.004$			

TABLE 32 *Drop-outs and adverse events leading to discontinuation*

Study	Valproate	Placebo	OR (95% CI), % weight
Drop-outs before end of study			
Bowden, 2000[39]	71/187	35/94	1.03 (0.62 to 1.72), 91.17
Frankenburg, 2002[51]	13/20	6/10	1.24 (0.26 to 5.91), 8.33
M–H pooled OR	$\chi^2 = 0.05$ (df = 1), $p = 0.83$		1.05 (0.64 to 1.71)
Test of OR = 1: $z = 0.20$, $p = 0.84$			
Adverse events leading to discontinuation			
Frankenburg, 2002[51]	1/20	1/10	0.47 (0.03 to 8.46), 100

TABLE 33 *Adverse events with valproate identified in placebo-controlled trials*

Study	Valproate	Placebo	OR (95% CI), % weight
Adverse events leading to discontinuation			
Frankenburg, 2002[51]	1/20	1/10	0.47 (0.03 to 8.46), 100
Adverse events: fine tremor			
Bowden, 2000[39]	77/187	12/94	4.78 (2.44 to 9.37), 100
Adverse events: gastrointestinal disturbances			
Bowden, 2000[39]	65/187	28/94	1.25 (0.73 to 2.14), 100
Adverse events: sedation			
Bowden, 2000[39]	78/187	33/94	1.32 (0.79 to 2.21), 100
Adverse events: weight gain			
Bowden, 2000[39]	39/187	7/94	3.27 (1.40 to 7.64), 100

fine tremor and weight gain are associated with valproate, being statistically and clinically significantly more common than with placebo.

Summary of results: valproate compared with placebo

The results of one large placebo-controlled study showed valproate to be efficacious in the prevention of all relapses. However, limitations in the reporting of study methodology make it difficult to fully assess the quality of this study. This beneficial effect of valproate on all relapses was reflected in the effect on depressive relapse, but the results for the prevention of episodes of mania did not reach statistical significance. Results for bipolar II patients favoured placebo over valproate; however, this difference was not significant and, although the study was of reasonable quality, there were insufficient participants to make a reliable comparison. No statistically significant increase in drop-out rate was associated with valproate. The data on adverse events leading to discontinuation

TABLE 34 *All relapses (manic, depressive or mixed episodes)*

Study	Valproate	Olanzapine	OR (95% CI), % weight
All relapses: as stated by authors			
Tohen, 2003[75]	13/20	20/31	1.02 (0.32 to 3.23), 100

TABLE 35 *Manic and depressive relapses*

Study	Valproate	Olanzapine	OR (95% CI), % weight
Manic relapses: as stated by authors			
Altamura, 2004[38]	2/10	1/10	2.25 (0.17 to 29.78), 100
Depressive relapses: as stated by authors			
Altamura, 2004[38]	2/10	6/10	0.17 (0.02 to 1.23), 100

TABLE 36 *Drop-outs and adverse events leading to discontinuation*

Study	Valproate	Olanzapine	OR (95% CI), % weight
Drop outs before end of study			
Altamura, 2004[38]	0/10	3/13	0.14 (0.00 to 3.12), 100
Tohen, 2003[75]	106/126	106/125	0.95 (0.48 to 1.88), 100
Adverse events leading to discontinuation			
Altamura, 2004[38]	0/10	3/13	0.14 (0.00 to 3.12), 100
Tohen, 2003[75]	25/126	31/125	0.75 (0.41 to 1.36), 100

were very limited and there were no data on suicide or suicide attempts. Based on the limited data available, tremor and weight gain are the main adverse effects seen with valproate.

Valproate compared with olanzapine

Two studies compared valproate with olanzapine.[38,75]

All relapses

Only one trial[75] provided data for all relapses and this study randomised participants while in the acute phase of bipolar disorder. The affects of this acute randomisation could not be investigated with a subgroup analysis, because no other study provided data for the main outcome. The results for all relapses, taking the number who entered the maintenance phase (although not randomised to it), are summarised in *Table 34* and show no significant difference between valproate and olanzapine for rate of relapse. Results of the sensitivity analysis are presented in Appendix 7, *Tables 105* and *106*, and did not differ from the results of the base-case analysis.

Manic or depressive relapses

One small study provided data on manic relapses and depressive relapses (*Table 35*).[38] The results revealed no statistically significant difference between valproate and olanzapine for the prevention of manic or depressive relapses as stated by authors.

Drop-outs, suicide and adverse events leading to discontinuation

Both studies provided data on number of drop-outs before the end of the study and for adverse events leading to discontinuation (*Table 36*). The majority of participants in the Tohen study[75] dropped out before entering the maintenance phase so the data for the two were not pooled. Neither trial revealed a statistically significant treatment difference between valproate and olanzapine for the number of drop-outs or for discontinuations due to adverse events. No suicide data were reported.

Summary of results: valproate compared with olanzapine

Only very limited data were available for the comparison of valproate with olanzapine. Results for all relapses are based on a single study in which the participants were not randomised to treatment in the maintenance phase. A single, very small, poor-quality study provided data for

episodes of mania or depressive relapses. No statistically significant differences favouring either valproate or olanzapine were found. However, the inadequate design of one trial and the inadequate sample size in the other renders these results unreliable.

No statistically significant difference was observed among those who dropped out before the end of the study or for adverse events leading to discontinuation. Data on suicide and suicide attempts were not available.

Valproate compared with lithium

See the section 'Lithium compared with valproate' (p. 22) for the comparison of lithium and valproate.

Conclusions regarding the effectiveness of valproate

The efficacy of valproate for the prevention of relapse has not been well studied. Results of just one placebo-controlled study suggest that valproate is efficacious in the prevention of all relapses, particularly depressive relapse. When compared with lithium, there was a tendency in favour of valproate for all relapses, and manic and depressive episodes, but the pooled analyses found no statistically significant difference between the treatments for any of the outcomes. The very limited data comparing valproate with olanzapine found no treatment difference.

The numbers of suicides or suicide attempts were not available in any of the included studies comparing valproate with placebo, olanzapine or lithium.There was no real evidence relating to drop-outs or adverse events leading to discontinuation with valproate. Once again, data were scarce and not reliable enough to be combined. Limited data suggested that tremor and weight gain may be the main adverse effects of valproate.

Lamotrigine

Three randomised trials that investigated the efficacy of lamotrigine were identified for the review.[40–42] Trial details are summarised in *Table 37* and presented in the data extraction tables (Appendix 6).

All studies tested the intervention or comparator in adults. All lamotrigine trials included participants who could tolerate lamotrigine. The proportion of females in the study ranged from 53 to 57%. One study included participants diagnosed as bipolar I and II and two studies included only participants with bipolar I disorder. All participants in one study[41] had rapid cycling bipolar disorder, but the percentage of participants with rapid cycling in the other two studies was not reported. The sample size of the included studies varied from 175 to 463 participants.

The quality of the included studies revealed that although in all studies participants were randomly assigned, the sequence generation was not stated and no study used allocation concealment. Assessors were not blinded in any trial, care providers were blinded in one study and participants were blinded in two studies. In all studies, intervention and comparison groups were described as similar on the baseline measurements, eligibility criteria was clearly identified and point estimates with variability were presented for the primary outcome. Two studies reported a sample size calculation. Details of the quality assessment for each trial are presented in *Table 1*.

All three studies were sponsored by the pharmaceutical industry.

The available trials provided data comparing lamotrigine with placebo and lithium. Two trials included comparisons with both placebo and lithium; the third trial was just placebo controlled.

Lamotrigine compared with placebo

Three studies compared lamotrigine with placebo.[40–42] One of these studies had three separate lamotrigine treatment arms, each with a different dosage: 50, 200 and 400 mg. For the purposes of the analysis, participants receiving 50 mg were excluded, because the dosage was considered to be sub-therapeutic. Data for participants receiving either 200 or 400 mg of lamotrigine were pooled and analysed as one lamotrigine treatment arm[42] because the two doses were thought to be similar enough to be considered as one treatment. Furthermore, an investigation of different dosage effects was beyond the scope of this review.

All relapses

All three trials provided data for all relapses and were included in both the base-case analysis and the best-case/worst-case sensitivity analysis. The results for all relapses are summarised in *Table 38*. The pooled OR was statistically significant in favour of lamotrigine for all relapses by institution of additional treatment. The results of one study revealed lamotrigine to be significantly better than placebo for the prevention of all relapses as stated

TABLE 37 *Characteristics of included studies comparing lamotrigine with placebo or lithium*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2
Bowden, 2003[40]	Mainly adults	175	53.00			Yes	Bipolar I	Mainly mania		Lamotrigine: 100–400 mg/day	Lithium: 0.8–1.1 mEq/l	Placebo
Calabrese, 2000,[41]	Mainly adults	182	57.00			Yes	Bipolar I and II	All	100.00	Lamotrigine: 100–500 mg orally once daily	Placebo: matching to lamotrigine	
Calabrese, 2003[42]	Mainly adults	463	56.00			Yes	Bipolar I	Mainly depression		Lamotrigine: 50, 200, 400 mg/day	Lithium: median 900 mg/day (0.8–1.1 mEq/l)	Placebo

TABLE 38 *Relapses (manic, depressive or mixed episodes)*

Study	Lamotrigine	Placebo	OR (95% CI), % weight
All relapses: institution of additional treatment			
Bowden, 2003[40]	28/58	49/69	0.38 (0.18 to 0.79), 26.86
Calabrese, 2000[41]	45/90	49/87	0.77 (0.43 to 1.40), 28.91
Calabrese, 2003[42]	83/165	66/119	0.81 (0.51 to 1.30), 44.22
M–H pooled OR	$\chi^2 = 3.14$ (df = 2), $p = 0.21$		0.69 (0.49 to 0.95)
Test of OR = 1: $z = 2.25$, $p = 0.02$			
All relapses: as stated by authors			
Calabrese, 2003[42]	134/165	107/119	0.48 (0.24 to 0.99), 100
Manic relapses: institution of additional treatment			
Bowden, 2003[40]	20/58	28/69	0.77 (0.37 to 1.59), 100
Depressive relapses: Institution of additional treatment			
Bowden, 2003[40]	8/58	21/69	0.36 (0.15 to 0.90), 100

TABLE 39 *Drop-outs and adverse events leading to discontinuation*

Study	Lamotrigine	Placebo	OR (95% CI), % weight
Drop-outs before the end of study			
Bowden, 2003[40]	28/59	21/70	2.11 (1.02 to 4.34), 39.73
Calabrese, 2000[41]	11/93	17/89	0.57 (0.25 to 1.29), 60.27
M–H pooled OR	$\chi^2 = 5.51$ (df = 1), $p = 0.02$		1.18 (0.7 to 2.00)
Test of OR = 1: $z = 0.48$, $p = 0.6285$			
Adverse events leading to discontinuation			
Bowden, 2003[40]	3/59	3/70	1.19 (0.15 to 9.28), 56.52
Calabrese, 2000[41]	2/93	2/89	0.96 (0.07 to 13.46), 43.48
M–H pooled OR	$\chi^2 = 0.03$ (df = 1), $p = 0.86$		1.09 (0.31 to 3.86)
Test of OR = 1: $z = 0.17$, $p = 0.8529$			

by authors. No significant statistical heterogeneity was detected.

The results for the sensitivity analysis are presented in Appendix 7, *Tables 107* and *108*, and found no differences for all relapses by institution of additional treatment when compared with the base-case analysis. However, in the worst-case sensitivity analysis, for all relapses as stated by authors the difference between lamotrigine and placebo was no longer statistically significant, OR 0.91 (95% CI 0.64 to 1.28).

Manic or depressive relapses

One study provided data on manic and depressive relapses (*Table 38*), and found no significant difference between lamotrigine and placebo for the prevention of manic relapses defined as institution of additional treatment. However, the results suggested that lamotrigine is significantly more effective than placebo for the prevention of depressive relapses defined as institution of additional treatment.

Drop-outs, suicide and adverse events leading to discontinuation

The results of the two studies were inconsistent and the pooled OR revealed no significant difference in the number of drop-outs between the lamotrigine and placebo treatment groups (*Table 39*). However, this was subject to significant heterogeneity and therefore the pooled result cannot be taken as reliable. For adverse events leading to discontinuation, the two studies reported similar findings with no significant difference between treatment groups. No trial reported data on suicide.

Adverse events with lamotrigine identified in placebo-controlled trials

From the trial data available, only rash and accidental injuries appear to be more common with lamotrigine than with placebo (*Table 40*). However, the increase in odds of both of these adverse effects with lamotrigine is not statistically significant; this might be due to the lack of information. The clinical significance of an increase in accidental injuries is unclear.

Summary of results: lamotrigine compared with placebo

The pooled analysis showed efficacy in favour of lamotrigine for the prevention of all relapses defined as institution of additional treatment and when defined as stated by authors. Based on a single study, in which the treatment benefit of lamotrigine over placebo was statistically significant only for prevention of depressive relapses, lamotrigine may be better at preventing depressive rather than manic episodes. Whether lamotrigine has any effect on the rate of drop-outs from treatment is unclear. There appears to be no significant increase in adverse effects leading to discontinuation associated with lamotrigine. However, only participants who had tolerated titration of lamotrigine were randomised into the trials. Rash and accidental injuries appeared to be more common with lamotrigine than with placebo; however, the difference between groups was not statistically significant. Some methodological details of the studies were not adequately reported, making it difficult to judge accurately both the validity of the studies and the consequent reliability of the results.

Lamotrigine compared with lithium

See the section 'Lithium compared with lamotrigine' (p. 24) for the comparison of lithium and lamotrigine.

Conclusions regarding the effectiveness of lamotrigine

The analyses showed a statistically significant efficacy of lamotrigine to prevent all relapses or

TABLE 40 *Adverse events with lamotrigine identified in placebo-controlled trials*

Study	Lamotrigine	Placebo	OR (95% CI), % weight
Adverse events leading to discontinuation			
Bowden, 2003[40]	3/59	3/70	1.19 (0.15 to 9.28), 56.52
Calabrese, 2000[41]	2/93	2/89	0.96 (0.07 to 13.46), 43.48
M–H pooled OR	$\chi^2 = 0.03$ (df = 1), $p = 0.86$		1.09 (0.31 to 3.86)
Test of OR = 1: $z = 0.17$, $p = 0.8529$			
Adverse events: rash			
Calabrese, 2003[42]	12/171	3/121	2.97 (0.82 to 10.75), 100
Adverse events: tremor			
Calabrese, 2003[42]	9/171	6/121	1.06 (0.37 to 3.07), 100
Adverse events: gastrointestinal disturbances			
Bowden, 2003[40]	3/59	6/70	0.57 (0.14 to 2.39), 32.36
Calabrese, 2003[42]	12/171	10/121	0.84 (0.35 to 2.00), 67.64
M–H pooled OR	$\chi^2 = 0.20$ (df = 1), $p = 0.65$		0.75 (0.36 to 1.57)
Test of OR = 1: $z = 0.76$, $p = 0.45$			
Adverse events: headache			
Bowden, 2003[40]	12/59	11/70	1.37 (0.55 to 3.38), 18.20
Calabrese, 2000[41]	21/93	15/89	1.44 (0.69 to 3.01), 26.96
Calabrese, 2003[42]	30/171	25/121	0.82 (0.45 to 1.47), 54.84
M–H pooled OR	$\chi^2 = 1.70$ (df = 2), $p = 0.43$		1.08 (0.72 to 1.63)
Test of OR = 1: $z = 0.39$, $p = 0.70$			
Adverse events: sedation			
Calabrese, 2003[42]	16/171	7/121	1.68 (0.67 to 4.22), 100
Adverse events: accidental injuries			
Calabrese, 2000[42]	10/93	4/89	2.56 (0.81 to 8.02), 100

relapses of depressive episodes compared with placebo, No statistically significant difference was observed for lamotrigine compared with placebo in the prevention of manic relapses, suggesting the possibility that lamotrigine may be better at preventing depressive rather than manic relapse. There were no statistically significant differences between lamotrigine and lithium for any outcome. A lack of detail in the reporting of study methodology made it difficult to assess fully the validity of these studies. Data were not available in any of the included studies comparing lamotrigine with placebo or lithium regarding the numbers of suicides or suicide attempts.

The trials provided only very limited evidence relating to drop-outs or adverse events leading to discontinuation, particularly as only participants who had tolerated titration of lamotrigine were randomised into the trials. In these participants, lamotrigine was not associated with an excess of drop-outs or adverse events leading to discontinuation and was associated with fewer adverse effects leading to discontinuation than was lithium.

Carbamazepine

A total of five randomised trials that investigated the efficacy of carbamazepine were identified for the review.[47,53,57,60,72] Trial details are summarised in *Table 41* and presented in the data extraction tables (Appendix 6).

All studies tested the intervention or comparator in adults. The proportion of females in the study ranged from 54 to 69%. Four studies included participants diagnosed as bipolar I and II or not specified, and one included only participants with bipolar I. None of the studies reported including participants with rapid cycling. The sample size of the included studies varied from 31 to 171 participants.

The quality assessment of the included studies of carbamazepine revealed that in all studies participants were randomly assigned, but only one study had an adequate sequence generation.[53] Two studies used allocation concealment, but only one described an adequate procedure.[53] Assessors and participants were blinded in three studies and care providers in two studies. In more than half of the studies, intervention and comparison groups were described as similar on the baseline measurements; all studies clearly identified eligibility criteria and presented point estimates with variability for the primary outcome and only two studies reported a sample size calculation. Details of the quality of the individual trials are presented in *Table 1*.

TABLE 41 *Characteristics of included studies comparing carbamazepine with lithium*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1
Coxhead, 1992[47]	Mainly adults	31	67.74			Yes	Bipolar – not specified	Mania + depression		Carbamazepine: 200 mg twice daily (38–51mmol/l)	Lithium: 400 mg twice daily (0.6–1.0 mmol/l)
Hartong, 2003[53]	Mainly adults	53	54.30	44.70		Yes	Bipolar I and II	All		Carbamazepine: 400 mg/day (6–10 mg/l)	Lithium: 800 mg/day (0.6–1.0 mmol/l)
Kleindienst, 2000[57]	Mainly adults	171	56.14	50.00		Yes	Bipolar I and II	Mania + depression		Carbamazepine: 4–12 μg/ml	Lithium: 0.6–0.8 mmol/l
Lusznat, 1988[60]	Mainly adults	54	53.70			No	Bipolar I	Mainly mania		Carbamazepine: tablets of 200 mg (0.6–1.2 mg per 100 ml)	Lithium: tablets of 400 mg (0.6–1.4 mmol/l)
Simhandl, 1993[72]	Mainly adults	52	69.05			Unclear	Bipolar – not specified	Not stated		Carbamazepine: 12-h serum level 28–40 μmol/l	Lithium: 12-h serum level 0.6–0.8 mmol/l

Of the five carbamazepine trials, three were sponsored by the pharmaceutical industry.

All the trials of carbamazepine were comparisons with lithium; this analysis is presented in the section 'Lithium compared with carbamazepine' (p. 25).

Conclusions regarding the effectiveness of carbamazepine

No data from placebo-controlled trials were available for carbamazepine. Pooled analyses showed statistically significant efficacy favouring lithium when compared with carbamazepine in the prevention of all relapses defined as admission to hospital or as stated by authors. The quality of studies was mixed, and provides moderate evidence for the relative effects of carbamazepine and lithium. Subgroup analyses suggested a greater level of efficacy with carbamazepine in bipolar II patients. However, this finding was not significant and was based on a very small number of participants, and so may not be reliable. A single study showed no statistically significant difference between carbamazepine and lithium in the prevention of manic or depressive relapses. The variable results regarding drop-outs and adverse effects leading to discontinuation make it difficult to reach conclusions regarding the tolerability of carbamazepine. Also, as with other comparisons, there were insufficient data on suicide.

Olanzapine

Five randomised trials that investigated the efficacy of olanzapine were identified for the review.[38,75–78] One study compared a combination of olanzapine and mood stabilisers with mood stabilisers.[76] Trial details are summarised in *Table 42* and presented in the data extraction tables (Appendix 6). Study quality is summarised in *Table 1*.

All studies tested the intervention or comparator in adults. The proportion of females in the study ranged from 48 to 61%. Two studies included participants diagnosed as bipolar I and II or not specified, and three studies included only participants with bipolar I. The percentage of participants with rapid cycling ranged from 3 to 57% in the included studies. The sample size of the included studies varied from 23 to 431 participants.

All studies randomly assigned participants; however, the sequence generation was adequate in only two studies; two studies used an adequate procedure to guarantee allocation concealment; assessors and care providers were blinded in two studies and participants in four studies. In addition, in almost all studies intervention and comparison groups were described as similar on the baseline measurements; all studies clearly identified eligibility criteria and all but one presented point estimates with variability for the primary outcome, and three studies reported a sample size calculation.

In one study, only responders to olanzapine were randomised,[78] and in another, only responders to a combination of olanzapine and mood stabiliser were randomised.[76] One study randomised patients while they were in the acute phase rather than at the start of the maintenance phase.[75]

Four studies were sponsored by the pharmaceutical industry.

Olanzapine compared with placebo

One study compared olanzapine with placebo.[78]

All relapses

The trial provided data for all relapses, but a best-case/worst-case sensitivity analysis was not performed because all randomised participants were accounted for in the analysis. It should be noted that this trial only included participants who had already responded to the drug being studied, which may have influenced results in favour of olanzapine. The results for all relapses are presented in *Table 43*, and show a statistically significant benefit of olanzapine over placebo for the prevention of relapses by admission to hospital and relapses as stated by authors.

Manic or depressive relapses

The trial provided data for manic and depressive relapses (*Table 43*), and the results suggest that olanzapine is statistically significantly better than placebo for the prevention of manic relapses as stated by authors. The results also favoured olanzapine over placebo for the prevention of depressive relapses as stated by authors, but this treatment difference was not statistically significant.

Drop-outs, suicide and adverse events leading to discontinuation

The results show that there was a significantly greater proportion of drop-outs in the olanzapine group than the placebo group (*Table 44*). In addition, the results for adverse events suggest that a significantly greater number of people discontinued due to adverse events in the olanzapine group than in the placebo group. No suicide data were provided.

TABLE 42 *Characteristics of included studies comparing olanzapine with placebo or other active treatments*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1
Altamura, 2004[38]	Mainly adults	23	50.00			Yes	Bipolar I and II	Mania + depression		Olanzapine: final: 9 ± 3.2 mg	Valproate: final: 415 ± 16.39 mg (62.7 ± 19.5 μg/ml)
Tohen, 2003[75]	Mainly adults	251	57.37		Caucasian	No	Bipolar – not specified	Mania + mixed	57.40	Olanzapine: 5–20 mg/day	Divalproex: 500–2500 mg/day (50–125 μg/ml)
Tohen, 2004[76]	Mainly adults	99	48.48		Caucasian	Yes	Bipolar I	Mania + mixed	41.41	Olanzapine + mood stabilisers: 5, 10, 15 or 20 mg/day (flexible dosage)	Mood stabilisers
Tohen, 2005[77]	Mainly adults	431	52.90		Caucasian	Yes	Bipolar I	Mania + mixed	3.02	Olanzapine: 5–20 mg/day	Lithium: 300–1800 mg/day (0.6–1.2 mEq/l)
Tohen, 2006[78]	Mainly adults	361	61.00		Caucasian	Yes	Bipolar I	Mania + mixed	50.00	Olanzapine: 5–20 mg/day	Placebo

TABLE 43 *Relapses (manic, depressive or mixed episodes)*

Study	Olanzapine	Placebo	OR (95% CI), % weight
All relapses: admission to hospital Tohen, 2006[78]	2/225	7/136	0.17 (0.04 to 0.71), 100
All relapses: as stated by authors Tohen, 2006[78]	105/225	109/136	0.22 (0.13 to 0.36), 100
Manic relapses: as stated by authors Tohen, 2006[78]	37/225	56/136	0.28 (0.17 to 0.46), 100
Depressive relapses: as stated by authors Tohen, 2006[78]	68/225	53/136	0.68 (0.43 to 1.06), 100

TABLE 44 *Drop-outs and adverse events leading to discontinuation*

Study	Olanzapine	Placebo	OR (95% CI), % weight
Drop outs before the end of study Tohen, 2006[78]	72/225	18/136	3.09 (1.75 to 5.42), 100
Adverse events leading to discontinuation Tohen, 2006[78]	17/225	0/136	22.89 (2.31 to 225.39), 100

TABLE 45 *Adverse events with olanzapine identified in placebo controlled trials*

Study	Olanzapine	Placebo	OR (95% CI), % weight
Adverse events leading to discontinuation Tohen, 2006[78]	17/225	0/136	22.89 (2.31 to 225.39), 100
Adverse events: akathisia Tohen, 2006[78]	9/225	1/136	5.63 (0.91 to 33.16), 100
Adverse events: dyskinesia Tohen, 2006[78]	0/225	1/136	0.2 (0.02 to 2.46), 100
Adverse events: parkinsonism Tohen, 2006[78]	5/225	0/136	6.8 (0.65 to 70.27), 100
Adverse events: sedation Tohen, 2006[78]	2/225	0/136	3.05 (0.27 to 34.1), 100
Adverse events: weight gain Tohen, 2006[78]	18/225	2/136	5.83 (1.48 to 22.9), 100

Adverse events of olanzapine identified in placebo-controlled trials

The single available placebo-controlled trial of olanzapine was one in which only patients who had responded to olanzapine were randomised.[78] The adverse effects data available from such a trial may well reflect a more favourable adverse effects profile for olanzapine than would data from a trial in a general bipolar population.

Interpretation of the data from this trial (*Table 45*) is hampered by the low event rates in the placebo group; many treatment differences are not statistically significant, probably as a result of a lack of information. The data indicate that discontinuation due to adverse effects and weight gain occur in a significant proportion of patients despite preselection for a favourable response. Akathisia, parkinsonism and possibly sedation appear to be less common adverse effects associated with olanzapine.

Summary of results: olanzapine compared with placebo

Results are based on a single, large, study where only those patients who previously responded to olanzapine were randomised. Efficacy was demonstrated for prevention of all relapses (all definitions) and for manic episodes. However, the effect on depressive episodes was not statistically significant. It is possible that only randomising individuals who are known to respond to olanzapine may exaggerate the treatment effect, and results may not be generalisable. The data indicate that olanzapine is associated with a significant increase in drop-outs, adverse events leading to discontinuation and weight gain; this was despite limiting the trials to olanzapine responders. Data on suicide and suicide attempts were not available.

Olanzapine compared with lithium

See the section 'Lithium compared with olanzapine' (p. 28) for a comparison of lithium with olanzapine.

Olanzapine compared with valproate

See the section 'Valproate compared with olanzapine' (p. 36) for a comparison of valproate with olanzapine.

Olanzapine plus mood stabilisers compared with mood stabilisers alone

One randomised trial that investigated the efficacy of olanzapine combined with mood stabilisers was identified for the review.[76]

TABLE 46 *All relapses (manic, depressive or mixed episodes)*

Study	Olanzapine + mood stabilisers	Mood stabilisers	OR (95% CI), % weight
All relapses: as stated by authors			
Tohen, 2004[76]	15/51	15/48	0.92 (0.39 to 2.14), 100

TABLE 47 *Drop-outs before end of study*

Study	Olanzapine + mood stabilisers	Mood stabilisers	OR (95% CI), % weight
Drop outs before the end of study			
Tohen, 2004[76]	35/51	43/48	0.25 (0.09 to 0.74), 100

The trial provided data for all relapses, but a best-case/worst-case sensitivity analysis was not performed because all randomised participants were accounted for in the analysis. It should be noted that this trial only included participants who had already responded to a combination of olanzapine and mood stabilisers, which may have influenced the results.

All relapses

The data for all relapses are presented in *Table 46* and show no statistically significant difference between a combination of mood stabilisers and olanzapine and mood stabilisers alone for the prevention of all relapses as stated by authors.

Manic or depressive relapses

The trial did not provide data for manic and depressive relapses.

Drop-outs, suicide and adverse events leading to discontinuation

The results show a significantly greater proportion of drop-outs before the end of the study in the mood stabiliser group than the olanzapine and mood stabiliser combination group (*Table 47*). No data for suicide or adverse events leading to discontinuation were provided.

Summary of results: olanzapine combined with mood stabilisers compared with mood stabilisers alone

Results were only presented for all relapses as stated by authors and showed no statistically significant difference between the group that received the combination of olanzapine and mood stabilisers and the group that received mood stabilisers alone. It should be pointed out that results are based on a single study in which only those who previously responded to olanzapine were randomised, and findings may not be generalisable. The data favoured the combination treatment over mood stabilisers alone for the number of participants dropping out before the end of the study. Data for suicide and adverse events leading to discontinuation were not provided.

Conclusions regarding the effectiveness of olanzapine

Olanzapine was statistically significantly more efficacious than placebo for all relapses (admission to hospital or as stated by authors) and relapses of manic episodes, but not for the prevention of episodes of depression. Olanzapine was statistically significantly better than lithium for the prevention of all relapses and manic relapses but not depressive relapses. No benefit of olanzapine over valproate has been demonstrated. Although these studies were recent and of reasonable quality, the small amount of data for each comparison limits the robustness of the results. In addition, with the exception of the lithium trials, all studies evaluating the primary outcome either did not randomise participants while they were in the maintenance phase[75] or only included participants who had already responded to the study drugs, both of which reduce the confidence with which the results can be generalised to others.

The review failed to demonstrate any impact of olanzapine on suicide or suicide attempts, because the included trials did not provide relevant information. There were significantly more drop-outs, adverse events leading to discontinuation and participants with weight gain on olanzapine than placebo, and olanzapine may be less well tolerated than lithium.

Imipramine

Four randomised or quasi-randomised trials that investigated the efficacy of imipramine were identified for the review.[56,64,65,67] One trial[64] was excluded from all statistical analyses because of its poor quality and lack of reliable data. From the studies included in the analysis, one compared two treatment arms (lithium, imipramine) and placebo,[65] another compared three treatment arms (lithium, lithium + imipramine, imipramine) and placebo[56] and the third compared three treatment arms (lithium, lithium + imipramine, imipramine).[67] For the purposes of the analyses in the current review, results were reported for each comparison separately: lithium compared with imipramine is reported in the section 'Lithium compared with imipramine' (p. 29) and lithium compared with a combination of lithium and imipramine is reported in the section 'Lithium alone compared with a combination of lithium and imipramine' (p. 30). Trial details are summarised in *Table 48* and presented in the data extraction tables (Appendix 6).

All studies tested the intervention or comparator in adults. The proportion of females in the study ranged from 23 to 77%. Two studies included participants diagnosed as bipolar not specified, one study only participants with bipolar I and another study only participants with bipolar II. The proportion of participants with rapid cycling was reported in only one study, as 2.5%. The sample size of the included studies varied from 22 to 117 participants.

In all but one study, participants were randomly assigned; however, the sequence generation was not clearly adequate in any of the studies. Only one study reported using allocation concealment, and it was not clear if this was adequate.[67] Assessors were blinded in two studies, participants in three studies and care providers in two studies. Three studies clearly identified eligibility criteria, but none of the studies described similar baseline measurements for intervention and comparison groups, or reported a sample size calculation. Three studies presented point estimates with variability for the primary outcome. Details of the individual studies are given in *Table 48*. None of the studies were sponsored by the pharmaceutical industry.

Imipramine compared with placebo

Two studies compared imipramine with placebo.[56,65]

All relapses

Both trials provided data for all relapses and were included in the main analysis. A best-case/worst-case sensitivity analysis was not performed because it was not possible to distinguish between the number of participants randomised and the number of participants analysed for these studies.

The results for all relapses are presented in *Table 49* and show no significant difference between imipramine and placebo for the prevention of all relapses. No significant statistical heterogeneity was detected.

One study[56] only included participants with bipolar II disorder. Although there appear to be no differences between the results of the bipolar II study and the other study, the data are of too poor quality to be reliable.

Manic or depressive relapses

Both studies provided data for manic and depressive relapses as stated by authors (*Table 49*). The pooled OR revealed no significant difference between imipramine and placebo for the prevention of manic relapses. However, the pooled OR for depressive relapses was statistically significant in favour of imipramine. No significant statistical heterogeneity was detected.

Drop-outs, suicide and adverse events leading to discontinuation

The results show no statistically significant difference in the number of drop-outs before the end of the study in the imipramine group and in the placebo group (*Table 50*). No data for suicide or adverse events leading to discontinuation were provided.

Adverse events with imipramine identified in placebo-controlled trials

Of the two trials comparing imipramine with placebo, neither provided any adverse effects data.[56,65]

Summary of results: imipramine compared with placebo

Pooling of two very small studies revealed statistically significant results in favour of imipramine for the prevention of depressive relapses only. However, the small number of participants in both studies suggests that the results may not be reliable. One study provided data for individuals with bipolar II disorder only; however, the extremely small number of participants and the poor quality of the study mean there are insufficient reliable data to draw any conclusions. No data on adverse events leading to discontinuation, suicide or suicide attempts were provided in the studies. No

TABLE 48 *Characteristics of included studies comparing imipramine with placebo and other active treatments*

Study	Age	N	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Kane, 1982[56]	Mainly adults	22	77.27		Caucasian	Yes	Bipolar II	Hypomania + depression		Imipramine: 100–150 mg/day	Lithium: 0.8–1.2 mEq/l	Lithium + imipramine: 0.8–1.2 mEq/l + 100–150 mg/day	Placebo
Platman, 1970[64]		79	51.90			Unclear	Bipolar – not specified	Mania + depression		Imipramine	Lithium		
Prien, 1973[65]	Mainly adults	44	23.00			Yes	Bipolar – not specified	Mainly depression		Imipramine: 50–200 mg/day	Lithium: 500–2250 mg/day (median 0.8 mEq/l)	Placebo: identical number of capsules	
Prien, 1984[67]	Mainly adults	117	58.00			Yes	Bipolar I	Mania + depression	2.50	Imipramine: mean 132 mg/day (75–150 mg/day)	Lithium: mean 0.75 mEq/l (0.45–1.10 mEq/l)	Lithium + imipramine: mean 0.75 mEq/l + mean 132 mg/day	

TABLE 49 *Relapses (manic, depressive or mixed episodes)*

Study	Imipramine	Placebo	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	3/5	5/7	0.6 (0.03 to 13.19), 47.43
Prien, 1973[65]	11/13	12/13	0.46 (0.00 to 10.28), 52.57
M–H pooled OR	$\chi^2 = 0.02$ (df = 1), $p = 0.8804$		0.53 (0.09 to 3.02)
Test of OR = 1: $z = 0.28$, $p = 0.7779$			
Manic relapses: as stated by authors			
Kane, 1982[56]	1/5	1/7	1.5 (0.02 to 137.1), 34.74
Prien, 1973[65]	9/13	4/13	5.06 (0.75 to 36.99), 65.26
M–H pooled OR	$\chi^2 = 0.47$ (df = 1), $p = 0.4923$		3.81 (0.91 to 16.01)
Test of OR = 1: $z = 1.48$, $p = 0.1378$			
Depressive relapses: as stated by authors			
Kane, 1982[56]	2/5	4/7	0.5 (0.03 to 8.3), 21.69
Prien, 1973[65]	0/13	7/13	0.03 (0.00 to 0.36), 78.31
M–H pooled OR	$\chi^2 = 2.14$ (df = 1), $p = 0.1433$		0.13 (0.03 to 0.67)
Test of OR = 1: $z = 2.33$, $p = 0.0198$			

TABLE 50 *Drop-outs before end of study*

Study	Imipramine	Placebo	OR (95% CI), % weight
Drop outs before the end of study			
Prien, 1973[65]	10/13	9/13	1.45 (0.19 to 12.85), 67.53
Kane, 1982[56]	2/5	2/7	1.67 (0.08 to 34.55), 32.47
M–H pooled OR	$\chi^2 = 0.0006$ (df = 1), $p = 0.9385$		1.54 (0.37 to 6.37)
Test of OR = 1 : $z = 0.22$, $p = 0.8153$			

TABLE 51 *Relapses (manic, depressive or mixed episodes)*

Study	Imipramine	Imipramine + lithium	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	3/5	1/6	7.5 (0.29 to 470.49), 9.33
Prien, 1984[67]	29/36	18/36	4.14 (1.3 to 13.94), 90.67
M–H pooled OR	$\chi^2 = 0.15$ (df = 1), $p = 0.6969$		4.46 (1.67 to 11.92)
Test of OR = 1: $z = 2.81$, $p = 0.0049$			
Manic relapses: as stated by authors			
Kane, 1982[56]	1/5	0/6	4.5 (0.27 to 64.9), 6.72
Prien, 1984[67]	19/36	10/36	2.91 (0.99 to 8.75), 93.28
M–H pooled OR	$\chi^2 = 0.06$ (df = 1), $p = 0.8106$		3.01 (1.18 to 7.72)
Test of OR=1: $z = 2.08$, $p = 0.0373$			
Depressive relapses: as stated by authors			
Kane, 1982[56]	2/5	1/6	3.33 (0.11 to 37.01), 8.54
Prien, 1984[67]	10/36	8/36	1.35 (0.4 to 4.58), 91.46
M–H pooled OR	$\chi^2 = 0.35$ (df = 1), $p = 0.5527$		1.52 (0.56 to 4.1)
Test of OR=1: $z = 0.57$, $p = 0.5708$			

statistically significant difference was observed among those who dropped out while on imipramine or placebo.

Imipramine compared with lithium

See the section 'Lithium compared with imipramine' (p. 29) for a comparison of lithium with imipramine.

Imipramine compared with a combination of imipramine and lithium

Two studies compared imipramine alone with a combination of lithium and imipramine.[56,67]

All relapses

Both trials provided data for all relapses and were included in the base-case analysis and the best-case/worst-case sensitivity analysis. It should be noted that one trial[56] only included participants with bipolar II disorder. The results for all relapses are presented in *Table 51*. The pooled OR was statistically significant in favour of imipramine and lithium combined for the prevention of all relapses as stated by authors. No significant statistical heterogeneity was detected.

The results of the sensitivity analysis are presented in Appendix 7, *Tables 109* and *110* and showed no difference when compared with the main results.

Manic or depressive relapses

Both studies provided data for manic and depressive relapses as stated by authors (*Table 51*). The pooled OR for manic relapses was statistically significant in favour of imipramine and lithium combined. In contrast, the pooled OR for depressive relapses revealed no statistically significant difference between imipramine alone and imipramine combined with lithium.

Drop-outs, suicide and adverse events leading to discontinuation

The data for drop-outs show no significant difference between treatment groups for the number of drop-outs before the end of the study (*Table 52*). No data for suicide or adverse events leading to discontinuation were provided.

Summary of results: imipramine compared with imipramine and lithium

Two small studies were pooled and results significantly favoured the combination of lithium

TABLE 52 *Drop-outs before end of study*

Study	Imipramine	Imipramine + lithium	OR (95% CI), % weight
Drop-outs before the end of study			
Prien, 1984[67]	4/36	6/37	0.65 (0.12 to 3.05), 66.33
Kane, 1982[56]	2/5	4/6	0.33 (0.02 to 6.46), 33.67
M–H pooled OR	$\chi^2 = 0.21$ (df = 1), $p = 0.6452$		0.55 (0.17 to 1.82)
Test of OR = 1 : $z = 0.68$, $p = 0.4985$			

TABLE 53 *Relapses (manic, depressive or mixed episodes)*

Study	Imipramine + lithium	Placebo	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	1/6	5/7	0.08 (0.01 to 0.98), 100
Manic relapses: as stated by authors			
Kane, 1982[56]	0/6	1/7	0.33 (0.02 to 5.31), 100
Depressive relapses: as stated by authors			
Kane, 1982[56]	1/6	4/7	0.15 (0.02 to 1.68), 100

TABLE 54 *Drop-outs before end of study*

Study	Imipramine + lithium	Placebo	OR (95% CI), % weight
Drop-outs before the end of study			
Kane, 1982[56]	4/6	2/7	5 (0.53 to 47.00), 100

and imipramine as opposed to imipramine alone for the prevention of all relapses as stated by authors and relapses of manic episodes as stated by authors. Given the small number of participants in each of these studies, the results may not be reliable. One study provided data for individuals with bipolar II disorder only; however, the very small number of participants and poor quality of the study mean that there are insufficient reliable data to draw any conclusions. Heterogeneity was not observed among the pooled studies.

No data on adverse events leading to discontinuation, suicide or suicide attempts were provided in the studies. No statistically significant difference was observed among those who dropped out while on imipramine or on the combination of imipramine and lithium.

Efficacy of imipramine combined with lithium against placebo

One study compared a combination of imipramine and lithium with placebo.[56]

All relapses

The trial provided data for all relapses, but best-case/worst-case sensitivity analysis was not performed because all randomised participants were accounted for in the analysis. It should be noted that this trial only included participants with bipolar II disorder. The results for all relapses are presented in *Table 53* and suggest that imipramine combined with lithium is significantly more effective than placebo for the prevention of all relapses as stated by authors.

Manic or depressive relapses

The results for manic and depressive relapses as stated by authors are presented in *Table 53* and reveal no significant difference between treatment groups for the rate of manic or depressive relapses. The number of events in both treatment groups was very small.

Drop-outs, suicide and adverse events leading to discontinuation

The results show no significant difference between treatment groups for the rate of drop-outs before the end of the study (*Table 54*). No data for suicide or adverse events leading to discontinuation were provided.

TABLE 55 *Manic and depressive relapses*

Study	Quetiapine	Mood stabilisers	OR (95% CI), % weight
Manic relapses: as stated by authors			
Altamura, 2003[37]	4/14	3/14	1.47 (0.29 to 7.45), 100
Depressive relapses: as stated by authors			
Altamura, 2003[37]	4/14	5/14	0.72 (0.16 to 3.35), 100

TABLE 56 *Adverse events leading to discontinuation*

Study	Quetiapine	Mood stabilisers	OR (95% CI), % weight
Adverse events leading to discontinuation			
Altamura, 2003[37]	0/14	0/14	Not calculated

Adverse events with imipramine plus lithium identified in placebo-controlled trials
One trial compared imipramine + lithium with placebo but did not provide any adverse effects data.[56]

Summary of results: imipramine combined with lithium compared with placebo
Results tended to favour the combination of lithium and imipramine in participants with bipolar II disorder, but sample size was too small to be reliable. No data on adverse events leading to discontinuation, suicide or suicide attempts were provided in the studies. No statistically significant difference was observed among those who dropped out while on imipramine or placebo.

Imipramine + lithium compared with lithium alone
See the section 'Lithium alone compared with a combination of lithium and imipramine' (p. 30) for a comparison of lithium alone with a combination of imipramine and lithium.

Imipramine + lithium compared with imipramine alone
See the section 'Imipramine compared with a combination of imipramine and lithium' (p. 48) for a comparison of imipramine alone compared with a combination of imipramine and lithium.

Conclusions regarding the effectiveness of imipramine
Results of the main outcome were provided by a maximum of three small studies in each comparison. The results favoured lithium or the combination of lithium and imipramine when the comparison was made with a control group using only imipramine. Only when imipramine was compared with placebo did the results favour imipramine to prevent relapses of depressive episodes. Heterogeneity was not demonstrated in the combined studies. The number of studies for each comparison was very small, and data were sparse. There are insufficient reliable data to draw any firm conclusions regarding the efficacy of imipramine in the maintenance treatment of bipolar disorder.

The review failed to demonstrate any impact of imipramine on suicide or suicide attempts, because the included trials did not provide relevant information. It also failed to provide any information regarding possible troublesome adverse events of imipramine.

Quetiapine, perphenazine

Quetiapine compared with mood stabilisers
One study compared quetiapine with mood stabilisers.[37]

All relapses
No data for all relapses were provided.

Manic or depressive relapses
Results for manic and depressive relapses as stated by authors are presented in *Table 55*. The ORs showed no significant difference between quetiapine and mood stabilisers for the prevention of manic or depressive relapses. Numbers of events were very small in both treatment groups.

Drop-outs, suicide and adverse events leading to discontinuation
No data for drop-outs before the end of the study or suicide were provided. No adverse events leading to discontinuation were seen in either treatment group (*Table 56*).

TABLE 57 *Relapses (manic, depressive or mixed episodes)*

Study	Perphenazine + mood stabilisers	Mood stabilisers	OR (95% CI), % weight
All relapses: as stated by authors			
Zarate, 2004[80]	5/19	2/18	2.86 (0.53 to 14.73), 100
Manic relapses: as stated by authors			
Zarate, 2004[80]	1/19	2/18	0.44 (0.05 to 3.81), 100
Depressive relapses: as stated by authors			
Zarate, 2004[80]	4/19	0/18	10.8 (0.91 to 118.48), 100

TABLE 58 *Drop-outs and adverse events leading to discontinuation*

Study	Perphenazine + mood stabilisers	Mood stabilisers	OR (95% CI), % weight
Drop outs before the end of study			
Zarate, 2004[80]	10/19	3/18	5.56 (1.26 to 23.86), 100
Adverse events leading to discontinuation			
Zarate, 2004[80]	4/19	1/18	4.53 (0.59 to 32.88), 100

Summary of results: quetiapine compared with mood stabilisers

Results of a single, poor-quality study showed no statistically significant difference favouring either quetiapine or mood stabilisers in the maintenance treatment of people with bipolar disorders. However, the sample size was very small, and may have been insufficient to detect treatment effects. No reliable data for adverse events leading to discontinuation, drop-outs or suicide were provided.

Perphenazine combined with mood stabilisers compared with mood stabilisers alone

One study compared a combination of perphenazine and mood stabilisers with mood stabilisers alone.[80]

All relapses

The trial provided data for all relapses, but a best-case/worst-case sensitivity analysis was not performed because all randomised participants were accounted for in the analysis. It should be noted that this trial only included participants who had already responded to a combination of perphenazine and one or more mood stabilisers, which may have influenced results. The results for all relapses are presented in *Table 57* and show no significant difference between perphenazine combined with mood stabilisers and mood stabilisers alone for the prevention of all relapses as stated by authors.

Manic or depressive relapses

The results show no statistically significant differences between perphenazine and mood stabilisers combined and mood stabilisers alone for the prevention of manic or depressive relapses as stated by authors (*Table 57*). Numbers of events in both treatment groups were very small.

Drop-outs, suicide and adverse events leading to discontinuation

The results show a significantly greater number of drop-outs in the mood stabilisers and perphenazine combination group than in the mood stabilisers alone group (*Table 58*). There was no statistically significant difference between treatment groups for adverse events leading to discontinuation. Suicide data were not provided.

Summary of results: perphenazine combined with mood stabilisers compared with mood stabilisers

The results of a single, poor-quality study showed no statistically significant difference between perphenazine combined with mood stabilisers and mood stabilisers alone in the maintenance treatment of people with bipolar disorders. The number of participants was very small; treatment effects may have gone undetected. No reliable data were provided for suicide, suicide attempts or adverse events leading to discontinuation. Participants using the combination of perphenazine and mood stabilisers tended to drop out from the study more frequently.

TABLE 59 *Overall summary of efficacy of pharmaceutical interventions*

	Drugs which have statistically significant benefit compared with placebo	Drugs which have statistically significant benefit compared with lithium
To prevent all relapses	Lithium Valproate Lamotrigine Olanzapine[a]	Olanzapine
To prevent depressive relapses	Valproate Lamotrigine Imipramine	
To prevent manic relapses	Lithium Olanzapine[a]	Olanzapine

[a] Based on the results of a trial that only included participants who had already responded to olanzapine.

Overall summary of efficacy of pharmaceutical interventions

Standard meta-analysis produced the results in *Table 59*. It must be borne in mind that not all findings are supported by equally strong evidence, and the results for the comparison of olanzapine versus placebo may be biased in favour of olanzapine.

Of the drugs that have demonstrated some efficacy above that of placebo, only olanzapine has demonstrated greater efficacy than lithium, and that for all relapses and manic episodes but not for depressive relapse. It should be noted that valproate has not been shown to be less efficacious than olanzapine.

Many comparisons between treatments have not been investigated in trials. In order to investigate further the relative efficacy of the treatments, a further analysis of the data was performed using methods for making indirect comparisons. This is described in the section 'Mixed treatment comparison' (p. 63).

Efficacy of psychosocial interventions

Trials of cognitive behaviour therapy, family therapy, psychoeducation, care management and integrated group therapy, administered in addition to usual pharmacological treatment, were available for the review.

Cognitive behaviour therapy

Five randomised or quasi-randomised trials that investigated the efficacy of CBT as an adjunct to pharmacological treatment were identified for the review.[44,58,59,70,71] Trial details are summarised in *Table 60* and presented in the data extraction tables (Appendix 6).

All studies tested the intervention or comparator in adults. The proportion of females in the studies ranged from 52 to 65%. Three studies included participants diagnosed as bipolar I and II, and two studies included only participants with bipolar I disorder. The proportion of patients with rapid cycling was only reported in one study, as 7.14%. The sample size of the included studies varied from 25 to 253 participants.

Quality assessment of the included CBT studies revealed that although five of the studies randomly assigned participants, the sequence generation was adequate in only three of them.[59,70,71] Two studies used adequate allocation concealment.[59,71] Assessors were blinded in two studies; as would be expected, blinding of care providers and patients was not carried out or was unclear in all of the studies. In four of the five studies, intervention and comparison groups were described as similar on the baseline measurements. All studies clearly identified eligibility criteria and presented point estimates with variability for the primary outcome, and one study reported a sample size calculation. Details of the individual studies are given in *Table 1*.

All the trials of CBT were comparisons with TAU or waiting list control. TAU in all studies consisted of pharmacotherapy, and some studies were also reported to include outpatient services or contact with mental health professionals, which were provided to all participants across both treatment

TABLE 60 *Study characteristics of trials of CBT interventions*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1
Cochran, 1984[44]	Mainly adults	28	61.00	79.00	Caucasian	Unclear	Bipolar I and II	All		CBT: 1 hour per week for 6 weeks	TAU
Lam, 2000[58]	Mainly adults	25	52.00	68.00		Yes	Bipolar I	All		CBT: 12–20 sessions over 6 months	TAU
Lam, 2005[59]	Mainly adults	103	55.50			Yes	Bipolar I	Mania + depression		CBT: mean of 14 (SD 5.5) sessions over 6 months	TAU
Scott, 2001[70]	Mainly adults	42	59.52	66.67		No	Bipolar I and II	Not stated	7.14	CBT: maximum of 25 sessions (45 minutes each)	Waiting list control: varied
Scott, 2005[71]	Mainly adults	253	65.00	60.00		No	Bipolar I and II	All		CBT: 20 sessions and 2 booster sessions	TAU

groups. Further details of the TAU conditions, and co-interventions used across treatment groups can be seen in the data extraction tables (Appendix 6).

Cognitive behaviour therapy compared with treatment as usual (or waiting list)

Four studies compared CBT with TAU,[44,58,59,71] and one compared CBT with a waiting list.[70] Unpublished data from one of these studies were made available by the authors; it has since been published in full.[81]

All relapses

Five trials provided data for all relapses and three were included in both the base-case analysis and the best-case/worst-case sensitivity analysis. Two trials were excluded from the main analysis[70,71] because they randomised participants while in an acute phase of bipolar disorder.

Results for all relapses are presented in *Table 61*. The pooled OR was statistically significant in favour of CBT for all relapses as stated by authors. No statistical heterogeneity was detected. The one study that provided data for relapse defined as admission to hospital found no significant difference between treatment groups.

Results of the sensitivity analysis are presented in Appendix 7, *Tables 111* and *112* and show no differences when compared with the main results.

Subgroup analysis

Two trials[70, 71] randomised participants while they were in the acute phase of bipolar disorder. One of the trials, which was much larger than any of the other CBT trials, found no effect of CBT relative to TAU. When these trials were added to the analysis, the beneficial effect of CBT on all relapses as stated by authors was reduced, but remained statistically significant (*Table 62*). However, these studies introduced between-study differences, and significant statistical heterogeneity was detected. Given that the two additional trials introduced into the analysis were of participants randomised to treatment while still in the acute phase, the results are of limited relevance, as they do not truly reflect maintenance treatment.

Manic or depressive relapses

One study[59] provided data on manic and depressive relapses as stated by authors (*Table 63*). The results revealed no significant difference between treatment groups for the prevention of manic relapses. However, there were significantly fewer depressive relapses in the CBT group than in TAU group.

TABLE 61 *All relapses (manic, depressive or mixed episodes)*

Study	CBT	Control	OR (95% CI), % weight
All relapses: admission to hospital			
Cochran, 1984[44]	2/14	5/14	0.30 (0.05 to 1.91), 100
All relapses: as stated by authors			
Cochran, 1984[44]	3/14	8/14	0.2 (0.03 to 1.35), 21.76
Lam, 2000[58]	3/12	10/11	0.03 (0.001 to 0.47), 27.10
Lam, 2005[59]	30/47	43/52	0.37 (0.13 to 1.03), 51.14
M–H pooled OR	$\chi^2 = 3.37$ (df = 2), $p = 0.1853$		0.24 (0.12 to 0.51)
Test of OR = 1: $z = 3.68$, $p = 0.0002$			

TABLE 62 *Subgroup analysis 1: studies in which participants were randomised in the acute episode included in the analysis*

Study	CBT	Control	OR (95% CI), % weight
All relapses: admission to hospital			
Cochran, 1984[44]	2/14	5/14	0.30 (0.05 to 1.91), 100
All relapses: as stated by authors			
Cochran, 1984[44]	3/14	8/14	0.20 (0.04 to 1.07), 9.81
Lam, 2000[58]	3/13	10/12	0.06 (0.01 to 0.44), 12.48
Lam, 2005[59]	30/51	43/52	0.30 (0.12 to 0.74), 27.36
Scott, 2001[70]	1/21	2/21	0.47 (0.04 to 5.68), 2.97
Scott, 2005[71]	67/127	64/126	1.08 (0.66 to 1.77), 47.37
M–H pooled OR	$\chi^2 = 14.34$ (df = 4), $p = 0.006$		0.63 (0.43 to 0.94)
Test of OR = 1: $z = 2.29$, $p = 0.022$			

TABLE 63 *Manic and depressive relapses*

Study	CBT	TAU	OR (95% CI), % weight
Manic relapses: as stated by authors Lam, 2005[59]	23/46	31/46	0.48 (0.21 to 1.13), 100
Depressive relapses: as stated by authors Lam, 2005[59]	17/44	32/48	0.32 (0.13 to 0.74), 100

TABLE 64 *Drop-outs before end of study*

Study	CBT	TAU	OR (95% CI), % weight
Drop-outs before the end of study Lam, 2000[58]	1/13	1/12	0.92 (0.05 to 16.49), 100

Drop-outs, suicide and adverse events leading to discontinuation

The only study[58] that provided data for drop-outs before the end of the study found no significant difference between treatment groups (*Table 64*). No data for suicide or adverse events leading to discontinuation were provided.

Summary of the efficacy of CBT

Overall, there is evidence that, relative to TAU, CBT in addition to usual treatment is effective for the prevention of relapses in bipolar disorder. It is interesting that the largest trial found no benefit of CBT in the prevention of relapse. However, this trial randomised patients while they were still in the acute phase, and as such the results do not truly reflect maintenance treatment. In the single trial that reported it, CBT was not more effective than TAU in reducing admission to hospital. There was a suggestion that CBT may be more effective in the prevention of depressive than manic relapses. However, data were only available in one small, albeit good-quality study, which makes it difficult to draw any firm conclusions.

Results for drop-outs before the end of the study were based on a single, very small, poor-quality study, and as such are unlikely to be reliable. No data for adverse events leading to discontinuation or suicide were provided.

Family therapy

Two randomised or quasi-randomised trials that investigated the efficacy of family therapy as an adjunct to pharmacological treatment were identified for the review.[62,68] Trial details are summarised in *Table 65* and presented in the data extraction tables (Appendix 6).

Both studies tested the intervention and comparator in adults. The proportion of females was 57 and 63%. Both studies included participants diagnosed as bipolar I and II or not specified. The proportion of participants with rapid cycling was not provided in either study. The sample size of the studies was 53 participants in one study and 101 participants in the other.

The quality of the family therapy studies was mixed. Both studies used random assignment of patients, but the sequence was clearly adequate in only one of the studies.[62] One study used allocation concealment with an adequate procedure.[62] One study stated that assessors were blinded; as would be expected, participants and care providers were not blind in either study. In both studies, intervention and comparison groups were described as similar on the baseline measurements. Both studies clearly identified eligibility criteria and presented point estimates with variability for the primary outcome. Neither of the studies reported a sample size calculation. Details of the quality of individual studies are given in *Table 1*.

Family therapy compared with psychosocial therapy or crisis management

One study compared family therapy with individual psychosocial therapy[68] and one compared family therapy with crisis management.[62]

All relapses

Both trials provided data for all relapses. No best-case/worst-case sensitivity analysis was performed because it was not possible to distinguish the number of participants that were analysed from the number that were randomised.

TABLE 65 *Study characteristics of trials of family therapy interventions*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1
Miklowitz, 2003[62]	Mainly adults	101	63.37		Caucasian	Unclear	Bipolar I and II	All		Family-focused therapy: 21 1-hour sessions (12 weekly, 6 biweekly, 3 monthly)	Crisis management: 2 1-hour sessions in first 2 months, then as needed
Rea, 2003[68]	Mainly adults	53	57.00	85.00	Caucasian	Yes	Bipolar – not specified	Mainly mania		Family therapy: weekly, then biweekly, then monthly	Psychosocial therapy: weekly, then biweekly, then monthly

The results for all relapses are presented in *Table 66*. The results showed no statistically significant difference between family therapy and individual psychosocial therapy for neither relapse as admission to hospital nor relapse as stated by authors. Similarly, there was no statistically significant difference between family therapy and crisis management for all relapses as stated by authors.

Manic or depressive relapses
One study provided data for manic and depressive relapses (*Table 66*). The results show no significant difference between family therapy and crisis management for prevention of manic or depressive relapse as stated by authors.

Drop-outs, suicide and adverse events leading to discontinuation
The proportions of drop-outs from the family therapy group and from the crisis management group were not significantly different (*Table 67*). No data for suicide or adverse events leading to discontinuation were provided.

Summary of the efficacy of family therapy
The available trials found no statistically significant benefit of family therapy compared with individual psychosocial therapy or with crisis management for preventing relapse. The failure to detect any treatment difference may be due to the small sample sizes. Furthermore, the control treatments used in both trials of family therapy were, to some extent, active therapies and therefore the results indicate that family therapy may have some beneficial effect and further investigation is warranted.

Psychoeducation

Three randomised trials that investigated the efficacy of psychoeducation as an adjunct to pharmacological treatment were identified for the review.[45,46,63] Trial details are summarised in *Table 68* (p. 58) and presented in the data extraction tables (Appendix 6). Two of the trials investigated group psychoeducation in comparison with unstructured group meetings; the third trial compared individual psychoeducation with TAU (TAU included pharmacotherapy, monitoring of mood and medication adherence, support, education about bipolar disorder and, if necessary, inpatient care, and was provided to all patients across both treatment groups).

All three studies tested the intervention and comparator in adults. The proportion of females in the studies ranged from 62 to 68%. Two studies included participants diagnosed as bipolar I an II and one study included only participants with bipolar I disorder.[46] The proportion of participants with rapid cycling was not clear in any of the studies. The sample size of the included studies varied from 50 to 120 participants.

The quality of the psychoeducation studies was mixed. In all studies participants were randomly

TABLE 66 *Relapses (manic, depressive or mixed episodes)*

Study	Family therapy	Control	OR (95% CI), % weight
All relapses: admission to hospital			
Rea, 2003[68]	8/28	10/25	0.60 (0.19 to 1.89), 100
All relapses: as stated by authors			
Miklowitz, 2003[62]	11/31	38/70	0.46 (0.19 to 1.11), 100
Rea, 2003[68]	13/28	13/25	0.80 (0.27 to 2.36), 100
Manic relapses: as stated by authors			
Miklowitz, 2003[62]	5/31	12/70	0.93 (0.31 to 2.82), 100
Depressive relapses: as stated by authors			
Miklowitz, 2003[62]	6/31	26/70	0.41 (0.15 to 1.12), 100

TABLE 67 *Drop-outs before end of study*

Study	Family therapy	Control	OR (95% CI), % weight
Drop-outs before the end of study			
Miklowitz, 2003[62]	9/31	27/70	0.65 (0.26 to 1.62), 100

TABLE 68 *Study characteristics of trials of psychoeducation*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1
Colom, 2003a[45]	Mainly adults	120	63.00			Yes	Bipolar I and II	All		Group psychoeducation: 21 sessions of 90 minutes each	Non-structured group meeting: 20 weekly group meetings without psychoeducation
Colom, 2003b[46]	Mainly adults	50	62.00			Yes	Bipolar I	All		Group psychoeducation: 21 sessions 90 minutes each	Non-structured group meeting: 21 sessions of 90 minutes each without psychoeducation
Perry, 1999[63]	Mainly adults	69	68.00	37.68	Caucasian	Yes	Bipolar I and II	All		Psychoeducation: 7–12 1-hour sessions (median 9, range 0–12)	TAU

assigned using adequate sequence generation. Two studies used allocation concealment and described an adequate procedure.[45,46] Assessors were blinded in two studies; as would be expected, care providers and participants were not clearly blinded in any of the studies. In all the studies, intervention and comparison groups were described as similar on the baseline measurements. All studies clearly identified eligibility criteria and presented point estimates with variability for the primary outcome. One study reported a sample size calculation; however, the appropriate sample size was not obtained.[63] Details of the studies are given in *Table 1*.

Group psychoeducation compared with non-structured meeting group

Two studies compared group psychoeducation with non-structured group meetings.[45,46]

All relapses

Both trials provided data for all relapses and were included in the main analysis. No best-case/worst-case sensitivity analysis was performed because all randomised participants were accounted for in the analysis. The results for all relapses are presented in *Table 69*. The pooled ORs were statistically significant in favour of group psychoeducation for both all relapses as admission to hospital and all relapses as stated by authors. No significant statistical heterogeneity was detected.

Manic or depressive relapses

Data for manic and depressive relapses as stated by authors are presented in *Table 69*. The results show significantly fewer manic and depressive relapses in participants attending group psychoeducation than in participants attending non-structured group meetings. No significant statistical heterogeneity was detected.

Drop-outs, suicide and adverse events leading to discontinuation

One study[45] provided data for drop-outs before the end of the study, and the results showed a significantly greater proportion of drop outs in the psychoeducation group than the non-structured group meeting (*Table 70*). No data for suicide or adverse events leading to discontinuation were provided.

TABLE 69 *Relapses (manic, depressive or mixed episodes)*

Study	Group psychoeducation	Group meeting	OR (95% CI), % weight
All relapses: admission to hospital			
Colom, 2003a[45]	14/60	21/60	0.56 (0.25 to 1.26), 66.04
Colom, 2003b[46]	2/25	9/25	0.15 (0.03 to 0.81), 33.96
M–H pooled OR	$\chi^2 = 1.91$ (df = 1), $p = 0.17$		0.42 (0.21 to 0.86)
Test of OR = 1: $z = 2.38$, $p = 0.017$			
All relapses: as stated by authors			
Colom, 2003a[45]	40/60	55/60	0.18 (0.06 to 0.52), 66.59
Colom, 2003b[46]	15/25	23/25	0.13 (0.02 to 0.68), 33.41
M–H pooled OR	$\chi^2 = 0.11$ (df = 1), $p = 0.74$		0.16 (0.07 to 0.40)
Test of OR = 1: $z = 3.97$, $p = 0.000$			
Manic relapses: as stated by authors			
Colom, 2003a[45]	28/60	45/60	0.29 (0.13 to 0.63), 69.77
Colom, 2003b[46]	12/25	20/25	0.23 (0.06 to 0.81), 30.23
M–H pooled OR	$\chi^2 = 0.10$ (df = 1), $p = 0.76$		0.27 (0.14 to 0.53)
Test of OR = 1: $z = 3.86$, $p = 0.000$			
Depressive relapses: as stated by authors			
Colom, 2003a[45]	24/60	43/60	0.26 (0.12 to 0.56), 67.97
Colom, 2003b[46]	6/25	16/25	0.18 (0.05 to 0.61), 32.03
M–H pooled OR	$\chi^2 = 0.29$ (df = 1), $p = 0.59$		0.24 (0.12 to 0.45)
Test of OR = 1: $z = 4.37$, $p = 0.000$			

TABLE 70 *Drop-outs before end of study*

Study	Group psychoeducation	Group meeting	OR (95% CI), % weight
Drop outs before the end of study			
Colom, 2003a[45]	16/60	7/60	2.75 (1.04 to 7.29), 100

Individual psychoeducation compared with TAU

One study compared individual psychoeducation with TAU.[63]

All relapses

The results for all relapses are presented in *Table 71*, and show no significant differences between psychoeducation and TAU for the prevention of all relapses as admission to hospital.

Results of the sensitivity analysis are presented in Appendix 7, *Tables 113* and *114* and show no differences when compared with the main results.

Manic or depressive relapses

The results for manic and depressive relapses are presented in *Table 71*. The results showed significantly fewer manic relapses, defined as admission to hospital, in participants receiving psychoeducation than in participants receiving TAU. However, there was no statistically significant difference in the rate of depressive relapses defined as admission to hospital between the treatment groups.

Drop-outs, suicide and adverse events leading to discontinuation

No data were provided for drop-outs before the end of the study, suicide or adverse events leading to discontinuation.

Summary of the efficacy of psychoeducation

The evidence suggests that group psychoeducation is more effective than non-structured group meetings for the prevention of all relapses, defined both as admission to hospital and as stated by authors. Group psychoeducation also appears to be more effective than non-structured group meetings for the prevention of both manic and depressive relapses. Although the result for drop-outs was statistically in favour of non-structured group meetings, the findings are based on one study, which makes it difficult to draw any firm conclusions. No data for adverse events leading to discontinuation or suicide were provided.

The available results show no difference between individual psychoeducation and TAU for the prevention of all relapses, defined as admission to hospital. However, the results showed that although there was no difference between groups for depressive relapses, individual psychoeducation was significantly better than treatment as usual for the prevention of manic relapses. It should be noted, however, that the results come from one small study, and as such, the findings may not be reliable.

Care management

One randomised trial that investigated the efficacy of care management as an adjunct to pharmacological treatment was identified for the review.[73] Trial details are summarised in *Table 72* and presented in the data extraction tables (Appendix 6).

The study tested the intervention and comparator in adults. The study population was 68% female and included participants diagnosed as bipolar I and II. The proportion of rapid cycling participants was not provided. The sample size was 441 participants.

The quality of the study was generally good. Participants were randomly assigned and adequate sequence generation was used. Allocation concealment was used and an adequate procedure reported. Assessors were blinded and, as would be expected, participants and care providers were not. Eligibility criteria were clearly identified and the intervention and comparator groups were described as similar on the baseline measurements. Point estimates with variability were presented for the main outcome and a sample size calculation was reported.

In this study, care management was compared with TAU (normal services, including pharmacotherapy, which were available to all participants across both treatment groups).

TABLE 71 *Relapses (manic, depressive or mixed episodes)*

Study	Psychoeducation	TAU	OR (95% CI), % weight
All relapses: admission to hospital			
Perry, 1999[63]	12/33	15/35	0.76 (0.29 to 2.02), 100
Manic relapses: admission to hospital			
Perry, 1999[63]	9/33	20/35	0.28 (0.10 to 0.78), 100
Depressive relapses: admission to hospital			
Perry, 1999[63]	18/33	13/35	2.03 (0.77 to 5.35), 100

All relapses
The trial provided data for all relapses but a best-case/worst-case sensitivity analysis was not performed because it was not possible to distinguish the number of participants analysed from the number of participants randomised. It should be noted that participants were randomised while still in the acute phase of bipolar disorder.

The results for all relapses are presented in *Table 73* and show no significant difference between care management and TAU for all relapses defined as admission to hospital.

Manic or depressive relapses
The data for manic and depressive relapses are also given in *Table 73* and show no significant differences between care management and TAU for manic or depressive relapses, defined as admission to hospital.

Drop-outs, suicide and adverse events leading to discontinuation
Data for drop-outs show no significant difference between treatment groups in the rate of drop-outs before the end of the study (*Table 74*). No data for suicide or adverse events leading to discontinuation were provided.

Summary of the efficacy of care management
The results of this study found no significant differences between care management and TAU for all relapses, manic relapses, depressive relapses or drop-outs. Although the study was of reasonably good quality, it should be noted that participants entered the study while still in an acute phase of bipolar disorder, which may have influenced relapse rates. Further controlled trials investigating the effects of care management are required.

Integrated group therapy

One quasi-randomised trial that investigated the efficacy of integrated group therapy as an adjunct to pharmacological treatment was identified for the review.[79] Trial details are summarised in *Table 75* and presented in the data extraction tables (Appendix 6).

The study tested the intervention and comparator in adults. The study population was 49% female and included participants diagnosed as bipolar I and II. The proportion of rapid cycling participants was not provided. The sample size was 45 participants.

The quality of the study was generally poor. Participants were not randomly assigned and allocation concealment was not used. It was not clear that assessors were blinded; as would be expected, care was not provided blind, and participants were not blinded. Eligibility criteria were clearly identified but the intervention and comparator groups differed on the baseline measurements. Point estimates with variability were presented for the main outcome, but no sample size calculation was reported.

In this study, integrated group therapy was compared with treatment as usual, which included pharmacotherapy and various individual and group therapies, which were available to all participants across both treatment groups.

All relapses
The trial provided data for all relapses, but a best-case/worst-case sensitivity analysis was not performed because all randomised participants were accounted for in the analysis. The results for all relapses are presented in *Table 76* and show no statistically significant difference between integrated group therapy and treatment as usual for all relapses, defined as admission to hospital.

Manic or depressive relapses
The trial did not provide any data for manic or depressive relapses separately.

Drop-outs, suicide and adverse events leading to discontinuation
No data on drop-outs before the end of the study or adverse events leading to discontinuation were provided. The numbers of suicides in the integrated group therapy and treatment as usual groups were not significantly different (*Table 77*). However, numbers of events were too small to make a meaningful comparison.

Summary of the efficacy of integrated group therapy
This study found no differences between integrated group therapy and treatment as usual for the prevention of all relapses, defined as admission to hospital. However, given that the study was small, and of very poor quality, it is likely that the findings are not reliable. No separate data for manic and depressive relapses were provided. The number of suicides was not significantly different between groups; however, the number of events was too small to make a meaningful comparison. No data for drop-outs or adverse events leading to discontinuation were provided.

TABLE 72 *Study characteristics of trials of care management*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1
Simon, 2005[73]	Mainly adults	441	68.25	48.53	Caucasian	No	Bipolar I and II	All		Care management: Varied. Group: 5 × 1 hour weekly, then 1 hour bimonthly	TAU

TABLE 73 *Relapses (manic, depressive or mixed episodes)*

Study	Care management	TAU	OR (95% CI), % weight
All relapses: admission to hospital Simon, 2005[73]	12/212	17/229	0.75 (0.35 to 1.61), 100
Manic relapses: admission to hospital Simon, 2005[73]	39/169	58/182	0.64 (0.40 to 1.03), 100
Depressive relapses: admission to hospital Simon, 2005[73]	73/134	74/136	1.00 (0.62 to 1.62), 100

TABLE 74 *Drop-outs before end of study*

Study	Care management	TAU	OR (95% CI), % weight
Drop-outs before the end of study Simon, 2005[73]	13/212	14/229	1.00 (0.46 to 2.19), 100

TABLE 75 *Study characteristics of trials of integrated group therapy*

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1
Weiss, 2000[79]	Mainly adults	45	48.90	80.00	Caucasian	Yes	Bipolar I and II	Not stated		Integrated group therapy: Weekly, 12–20 hour-long sessions	TAU

TABLE 76 *All relapses (manic, depressive or mixed episodes)*

Study	Integrated group therapy	TAU	OR (95% CI), % weight
All relapses: admission to hospital			
Weiss, 2000[79]	8/21	10/24	0.86 (0.26 to 2.85), 100

TABLE 77 *Suicide*

Study	Integrated group therapy	TAU	OR (95% CI), % weight
Suicides			
Weiss, 2000[79]	0/21	1/24	0.36 (0.01 to 9.43), 100

Non-pharmacological interventions for the maintenance of bipolar disorder: summary of results

In general, the studies investigating psychosocial interventions were small, and there were few data for each comparison and outcome, making it difficult to draw any firm conclusions. The evidence surrounding the use of CBT in bipolar disorder was greater than that of the other psychosocial interventions, and did suggest that CBT, in combination with TAU, is effective for the prevention of relapse. However, the lack of effect seen in one study in which patients were randomised while still experiencing an acute episode may suggest that CBT is only effective in selected stable patients. Small trials found no statistically significant benefit of family therapy compared with crisis management or individual psychosocial therapy for relapse prevention. Group psychoeducation was more effective than non-structured meetings for preventing relapse. However, weak evidence suggests that individual psychoeducation was no more effective than TAU for the prevention of all relapses. There was no evidence that care management or integrated group therapy is effective in the prevention of relapse. There was insufficient evidence to draw conclusions regarding the relative efficacy of the different psychosocial interventions. Unfortunately, none of these trials reported any adverse effects data and drop-outs were poorly reported.

Mixed treatment comparison

As described in the section 'Mixed treatment comparison' (p. 10), an indirect analysis of multiple treatments based on an MTC analysis was performed. The clinical data, described in the sections 'Efficacy of pharmaceutical interventions' (p. 15) and 'Efficacy of psychosocial interventions' (p. 52) were combined using Bayesian evidence synthesis methods, which allowed for the simultaneous comparison of multiple treatments, combining direct and indirect evidence and three different outcomes (manic, depressive and all relapses) in a single analysis. Trials that were of bipolar II patients only were not included in the main MTC analysis.

Results from this MTC analysis informed the efficacy parameter estimates for the cost-effectiveness model described in Chapter 6.

Network of evidence

The available studies have been detailed and described in the section 'Efficacy of pharmaceutical interventions' (p. 15). There were no head-to-head trials comparing all the treatments. Of all the treatments included in the systematic review, lithium, valproate, lamotrigine, carbamazepine, olanzapine, imipramine and lithium plus imipramine could be linked in a 'network of evidence'. Valproate, lamotrigine, olanzapine, imipramine and lithium plus imipramine were linked into the network of evidence via a lithium and placebo control. Carbamazepine was linked only through lithium. Olanzapine had an extra link into the network of evidence through a comparison with valproate. Pharmacological treatments that could not be linked into the network of evidence were those that had been compared only with mood stabilisers (quetiapine, perphenazine plus mood stabilisers and olanzapine plus mood stabilisers). Unfortunately, none of the psychosocial interventions could be linked into the network of evidence because none were compared with placebo or any of the pharmacological interventions.

TABLE 78 *Treatment comparisons forming the network of evidence*

Trial[a]	Placebo	Lithium	Valproate	Lamotrigine	Olanzapine	Carbamazepine	Imipramine	Imipramine + lithium
Bowden, 2000[39]	■	■	■					
Bowden, 2003[40]	■	■		■				
Calabrese, 2000[41]	■			■				
Fieve, 1976[50]	■	■						
Prien, 1973[65]	■	■					■	
Prien, 1974[66]	■	■						
Calabrese, 2003[42]	■	■		■				
Coxhead, 1992[47]		■				■		
Calabrese, 2005[43]		■	■					
Kane, 1981[55]		■						■
Kleindienst, 2000[57]		■				■		
Prien, 1984[67]		■					■	■
Simhandl, 1993[72]		■				■		
Tohen, 2005[77]		■			■			
Hartong, 2003[53]		■				■		
Altamura, 2004[38]			■		■			
**Tohen, 2006[78]	■				■			
*Dunner, 1976[48]	■	■						
*Frankenburg, 2002[51]	■		■					
*Kane, 1982[56]	■	■					■	■

[a] Trials marked * or ** included only for the sensitivity analysis (*BPII-only studies and **olanzapine responders).

The comparisons available for those trials that comprised the network of evidence are shown in *Table 78*. *Table 79* summarises the relapse data extracted from the clinical trials and used in the evidence synthesis. As in the standard meta-analysis, the lamotrigine 50-mg dose was not included, the lamotrigine 200-mg and 400-mg dosages were treated as a single treatment and the date for the longest length of follow-up was used.

Statistical model

To allow indirect comparisons of all the comparators, a meta-analysis of all the relapse rates (all relapses, manic and depressive) from the randomised trials was performed, jointly modelled using a logistic regression model.[35,82] The logistic model is designed to model binary trial end-points. In each trial different treatments were compared, with a number of them being three-arm trials.

For numerical convenience, we modelled all treatment effects on the log-odds scale, assuming that they are additive to the baseline. To reflect slight differences in recruitment criteria and patient mix, for each type of relapse (manic, depressive or all types) we used trial-specific baselines. The estimation of the mean baseline was separated from the estimation of the treatment effect using an unconstrained baseline, removing their correlation, so the estimates of the treatment effect do not depend on our prior estimate of between-trial baseline variance. For the purposes of the cost-effectiveness analysis, manic and depressive relapses were specifically modelled ($x = 1$ for mania, 2 for depression). The model was implemented as a Bayesian hierarchical model using WinBUGS.[83]

Due to the limited number of trials (only a maximum of three trials were available for the majority of treatments), the treatment effects are modelled as a **fixed treatment-effect model** on the log-odds scale, additive to the baseline probability of relapse. By default, the most common treatment across all trials (lithium) was used as the control treatment, followed by the second most common treatment (placebo) when lithium was not present in any of the trial arms, and so on.

Where the number of manic relapses and depressive relapses were not reported explicitly in individual trials, we borrowed strength[82] from data reported on all relapses using the constraint that the number of all relapses equals the sum of manic and depressive relapses. This assumption was validated using the data provided by those trials which reported the three types of outcomes: manic, depressive and all relapses.

In order to estimate the absolute probabilities for each treatment required for the economic model, the ORs for treatments were estimated against a single comparator (lithium). Data on the absolute probabilities for lithium acted as the baseline event rate for the analysis. Lithium was selected as the baseline treatment as this was considered to be the standard treatment for prevention of relapse and was a comparator in a significant number of the trials. The ORs for each treatment were then applied to the baseline event rate for lithium in order to estimate treatment-specific probabilities of relapse. The baseline risk of relapse used to estimate these probabilities was not taken from all trials assessing lithium; instead of averaging across all different follow-up periods, we selected trials with a common length of follow-up of 1 year. For the purposes of the cost-effectiveness model, two baseline risks were considered: Analysis 1 used a baseline risk for patients having experienced a pretrial depressive episode (Calabrese and colleagues,[42] data reported for 12 months' follow-up), whereas Analysis 2 used a baseline risk for patients having experienced a pretrial manic episode (Tohen and colleagues[77] and Bowden and colleagues[39]). The selection criteria and the final decision on the selection of these three trials were decided in consultation with our clinical experts.

The evidence synthesis was conducted using WinBUGS version 1.4.[83] The WinBUGS code is reproduced in Appendix 8.

Key assumptions

The estimation of relapse rates from the MTC relies on the key assumption of additivity of treatment effects on a selected scale, which also depends on the appropriate choice of scale (log-odds scale for binary outcomes). In a fixed treatment-effect meta-analysis, it is assumed that the relative effect of one treatment compared with another is the same across the entire set of trials. The randomisation process should ensure exchangeability between patients within a randomised trial. However, the possibility of systematic differences between the sets of trials comparing different sets of treatments cannot be excluded and, although bias would not be expected generally to operate in any particular direction, particular caution has been exercised in combining the trials (e.g. exclusion of trials including responders to a particular treatment and use of contemporary trials for the baseline).

TABLE 79 *Summary of the relapse data extracted from the clinical trials and used in the evidence synthesis*[a]

Author[b]	Year	Type of relapse	Intervention	Number of relapses[c]	*N*	*N* analysis	Conservative number of relapses
Altamura	2004	Manic	Valproate	2	10	10	2
Altamura	2004	Manic	Olanzapine	1	13	10	4
Altamura	2004	Depressive	Valproate	2	10	10	2
Altamura	2004	Depressive	Olanzapine	6	13	10	9
Bowden	2000	Manic	Valproate	33	187	187	33
Bowden	2000	Manic	Lithium	19	91	91	19
Bowden	2000	Manic	Placebo	21	94	94	21
Bowden	2000	Depressive	Valproate	12	187	187	12
Bowden	2000	Depressive	Lithium	9	91	91	9
Bowden	2000	Depressive	Placebo	15	94	94	15
Bowden	2003	Manic	Lamotrigine	20	59	58	21
Bowden	2003	Manic	Lithium	8	46	44	10
Bowden	2003	Manic	Placebo	28	70	69	29
Bowden	2003	Depressive	Lamotrigine	8	59	58	9
Bowden	2003	Depressive	Lithium	10	46	44	12
Bowden	2003	Depressive	Placebo	21	70	69	22
Calabrese	2000	All	Lamotrigine	45	93	90	48
Calabrese	2000	All	Placebo	49	89	87	51
Calabrese	2003	All	Lamotrigine	134	171	165	140
Calabrese	2003	All	Lithium	99	121	120	100
Calabrese	2003	All	Placebo	107	121	119	109
Calabrese	2005	Manic	Valproate	6	28	28	6
Calabrese	2005	Manic	Lithium	7	32	32	7
Calabrese	2005	Depressive	Valproate	8	28	28	8
Calabrese	2005	Depressive	Lithium	11	32	32	11
Coxhead	1992	All	Carbamazepine	6	15	13	8
Coxhead	1992	All	Lithium	8	16	15	9
Dunner*	1976	Manic	Lithium	1	16	16	1
Dunner*	1976	Manic	Placebo	6	24	24	6
Dunner*	1976	Depressive	Lithium	9	16	16	9
Dunner*	1976	Depressive	Placebo	12	24	24	12
Fieve	1976	Manic	Lithium	10	17	17	10
Fieve	1976	Manic	Placebo	17	18	18	17
Fieve	1976	Depressive	Lithium	5	17	17	5
Fieve	1976	Depressive	Placebo	8	18	18	8
Frankenburg*	2002	Depressive	Valproate	0	20	20	0
Frankenburg*	2002	Depressive	Placebo	2	10	10	2
Hartong	2003	Manic	Lithium	1	23	22	2
Hartong	2003	Manic	Carbamazepine	5	30	30	5
Hartong	2003	Depressive	Lithium	2	23	22	3
Hartong	2003	Depressive	Carbamazepine	9	30	30	9
Kane	1981	Manic	Lithium	4	38	38	4
Kane	1981	Manic	Lithium + imipramine	9	37	37	9
Kane	1981	Depressive	Lithium + imipramine	3	37	37	3
Kane	1981	Depressive	Lithium	4	38	38	4
Kane*	1982	Manic	Lithium + imipramine	0	6	6	0
Kane*	1982	Manic	Lithium	0	4	4	0
Kane*	1982	Manic	Imipramine	1	5	5	1
Kane*	1982	Manic	Placebo	1	7	7	1
Kane*	1982	Depressive	Imipramine	2	5	5	2
Kane*	1982	Depressive	Placebo	4	7	7	4
Kane*	1982	Depressive	Lithium + imipramine	1	6	6	1
Kane*	1982	Depressive	Lithium	1	4	4	1
Kleindienst	2000	All	Carbamazepine	28	56	42	42
Kleindienst	2000	All	Lithium	24	58	54	28
Prien	1973	Manic	Lithium	2	18	18	2

continued

TABLE 79 *Summary of the relapse data extracted from the clinical trials and used in the evidence synthesis[a] (cont'd)*

Author[b]	Year	Type of relapse	Intervention	Number of relapses[c]	*N*	*N* analysis	Conservative number of relapses
Prien	1973	Manic	Imipramine	9	13	13	9
Prien	1973	Manic	Placebo	4	13	13	4
Prien	1973	Depressive	Lithium	2	18	18	2
Prien	1973	Depressive	Imipramine	0	13	13	0
Prien	1973	Depressive	Placebo	7	13	13	7
Prien	1974	All	Lithium	47	101	101	47
Prien	1974	All	Placebo	90	104	104	90
Prien	1984	Manic	Lithium + imipramine	10	37	36	11
Prien	1984	Manic	Lithium	11	44	42	13
Prien	1984	Manic	Imipramine	19	36	36	19
Prien	1984	Depressive	Lithium + imipramine	8	37	36	9
Prien	1984	Depressive	Lithium	12	44	42	14
Prien	1984	Depressive	Imipramine	10	36	36	10
Simhandl	1993	All	Carbamazepine	5	14	14	5
Simhandl	1993	All	Lithium	3	21	21	3
Tohen	2005	Manic	Lithium	53	214	193	74
Tohen	2005	Manic	Olanzapine	25	217	202	40
Tohen	2005	Depressive	Olanzapine	28	217	202	43
Tohen	2005	Depressive	Lithium	16	214	193	37
Tohen*	2006	Manic	Olanzapine	37	225	225	37
Tohen*	2006	Manic	Placebo	56	136	136	56
Tohen*	2006	Depressive	Olanzapine	68	225	225	68
Tohen*	2006	Depressive	Placebo	53	136	136	53

N, number of patients randomised; *N* analysis, number of patients analysed; conservative number of relapses, assumes that missing patients relapsed.

[a] Data for 'all relapses' deleted as appropriate, in order to avoid duplication, as the estimation of 'all relapses' is subject to the logical constraint $\text{logit}(p_{3k}) = \min(1, p_{1k} + p_{2k})$.

[b] References as in *Table 78*. Trials marked * included only for the sensitivity analysis.

[c] As stated by authors.

Results of MTC

Table 80 summarises the results of the evidence synthesis in terms of posterior mean probability of relapse and the corresponding 95% credible intervals (CrIs). Results are presented for both types of baseline risk: patients whose pretrial acute episode was depressive (Analysis 1) and patients whose pretrial acute episode was manic (Analysis 2).

Independent models for manic and depressive relapses were also run in order to validate the results of our described model construction, which borrow strength from the all relapses trial data. The estimates for the treatment effects of those treatments for which not all trials reported the split between manic and depressive episodes were more precise (i.e. showed narrower CrIs) when data from trials measuring only all relapses were also considered.

For all types of relapses, the results of the MTC analysis indicate that for patients with a pretrial acute depressive episode (Analysis 1), all the pharmacological treatments, with the exception of carbamazepine (0.84, 95% CrI 0.51 to 1), are associated with a lower probability of relapse than placebo (0.80, 95% CrI 0.62 to 1). For this patient group, the lowest probability of relapse is achieved with valproate (0.42, 95% CrI 0.26 to 0.61), followed by lithium plus imipramine (0.43, 95% CrI 0.24 to 0.68), lithium monotherapy (0.46, 95% CrI 0.37 to 0.56), lamotrigine (0.50, 95% CrI 0.27 to 0.78), olanzapine (0.58, 95% CrI 0.40 to 0.75) and last imipramine monotherapy (0.64, 95% CrI 0.37 to 0.95).

Olanzapine shows the lowest probability of relapse (0.23, 95% CrI 0.16 to 0.31) for patients with a preacute manic episode (Analysis 2). Lithium ranks as the second most effective treatment (0.27, 95% CrI 0.22 to 0.32), followed by valproate (0.29, 95% CrI 0.22 to 0.38), lithium plus imipramine (0.37, 95% CrI 0.21 to 0.57) and last lamotrigine (0.42, 95% CrI 0.26 to 0.61).

TABLE 80 *Results of the evidence synthesis: probability of relapse for patients with pretrial acute depressive episode (Analysis 1) and pretrial acute manic episode (Analysis 2)*[a]

	Analysis 1			Analysis 2		
	Posterior mean	**2.5% CrI**	**97.5% CrI**	**Posterior mean**	**2.5% CrI**	**97.5% CrI**
Type of relapse: all						
Lithium	0.46	0.37	0.56	0.27	0.22	0.32
Placebo	0.80	0.62	1.0	0.57	0.46	0.69
Divalproex/valproate	0.42	0.26	0.61	0.29	0.22	0.38
Imipramine	0.64	0.37	0.95	0.64	0.44	0.83
Lamotrigine	0.50	0.27	0.78	0.42	0.26	0.61
Olanzapine	0.58	0.40	0.75	0.23	0.16	0.31
Carbamazepine	0.84	0.51	1.0	0.66	0.30	1.0
Lithium + imipramine	0.43	0.24	0.68	0.37	0.21	0.57
Type of relapse: depression						
Lithium	0.38	0.29	0.47	0.07	0.05	0.10
Placebo	0.62	0.46	0.77	0.18	0.11	0.27
Divalproex/valproate	0.31	0.17	0.49	0.05	0.03	0.09
Imipramine	0.29	0.13	0.50	0.05	0.02	0.12
Lamotrigine	0.33	0.15	0.55	0.06	0.02	0.13
Olanzapine	0.55	0.37	0.72	0.14	0.08	0.21
Carbamazepine	0.64	0.38	0.92	0.23	0.07	0.62
Lithium + imipramine	0.28	0.12	0.49	0.05	0.02	0.11
Type of relapse: mania						
Lithium	0.08	0.04	0.13	0.20	0.15	0.24
Placebo	0.18	0.08	0.32	0.38	0.29	0.48
Divalproex/valproate	0.10	0.04	0.19	0.23	0.16	0.32
Imipramine	0.34	0.15	0.59	0.59	0.39	0.77
Lamotrigine	0.17	0.06	0.32	0.36	0.21	0.52
Olanzapine	0.03	0.01	0.06	0.08	0.05	0.12
Carbamazepine	0.24	0.05	0.57	0.43	0.17	0.76
Lithium + imipramine	0.14	0.05	0.30	0.31	0.16	0.51

[a] Marginal posterior distributions estimated on the log-odds scale, under the assumption that the relative treatment effect is additive to the (lithium) baseline.

The results are supported by the posterior probabilities that each treatment is best (*Table 81*). For all relapses in patients with a pretrial acute depressive episode (Analysis 1), valproate shows the highest probability (0.39), followed closely by lithium plus imipramine (0.37); for all relapses in patients with a pretrial acute manic episode (Analysis 2), olanzapine has by far the highest probability of being the best treatment (0.74).

It is also interesting that although the ranking of the treatments stays the same, for patients who had a pretrial acute depressive episode (Analysis 1) the probability of experiencing a manic relapse is markedly lower than that for patients who had a pretrial acute manic episode (Analysis 2), and vice versa.

When the probabilities of manic and depressive relapse are considered separately, the differences between the treatments are accentuated. The results of the MTC analysis indicate that for patients with a pretrial acute depressive episode (Analysis 1), two treatments have a greater probability of a manic relapse than placebo: imipramine and carbamazepine. Lamotrigine is only slightly better than placebo (0.17, 95% CrI 0.06 to 0.32). The lowest probability of a manic relapse is with olanzapine (0.03, 95% CrI 0.01 to 0.06), followed by lithium (0.08, 95% CrI 0.04 to 0.13) and valproate (0.10, 95% CrI 0.04 to 0.19). The ranking of treatments is the same for patients with a pretrial acute manic episode (Analysis 2); however, the the lowest probability by far of a manic relapse is with olanzapine (0.08, 95% CrI 0.05 to 0.12), compared with the second (lithium 0.20, 95% CrI 0.15 to 0.24) and third best options (valproate 0.23, 95% CrI 0.16 to 0.32).

For depressive relapse, the results of the MTC analysis indicate that for patients with a pretrial acute depressive episode (Analysis 1), all

TABLE 81 *Percentage relapse and posterior probability that each treatment is best (lowest relapse) in multiple treatment comparison analysis*[a]

	Analysis 1		Analysis 2	
	Relapse (%)	**Probability best**	**Relapse (%)**	**Probability best**
Type of relapse: all[b]				
Lithium	46.7	0.06	27.7	0.09
Placebo	80.8	0.0	57.2	0.0
Divalproex/valproate	42.3	0.39	29.8	0.10
Imipramine	64.2	0.01	64.6	0.0
Lamotrigine	50.8	0.14	42.9	0.0
Olanzapine	58.5	0.01	23.2	0.74
Carbamazepine	84.7	0.0	66.5	0.0
Lithium + imipramine	43.7	0.37	37.4	0.04
Type of relapse: depression				
Lithium	38.3	0.0	7.7	0.0
Placebo	62.2	0.0	18.6	0.0
Divalproex/valproate	31.9	0.16	5.9	0.19
Imipramine	29.5	0.29	5.6	0.30
Lamotrigine	33.4	0.19	6.6	0.16
Olanzapine	55.1	0.0	14.5	0.0
Carbamazepine	64.0	0.0	23.1	0.0
Lithium + imipramine	28.9	0.32	5.4	0.33
Type of relapse: mania				
Lithium	8.3	0.0	20.0	0.0
Placebo	18.7	0.0	38.6	0.0
Divalproex/valproate	10.4	0.0	23.9	0.0
Imipramine	34.7	0.0	59.0	0.0
Lamotrigine	17.4	0.0	36.3	0.0
Olanzapine	3.4	0.99	8.6	0.99
Carbamazepine	24.1	0.0	43.9	0.0
Lithium + imipramine	14.8	0.0	31.9	0.0

[a] Compared against lithium, results identical for both Analysis 1 and Analysis 2 as treatment effect estimated independent from baseline risk attending to previous manic or depressive relapse.
[b] Because of the model construction, a unique OR for all relapses cannot be estimated within our model.

pharmacological treatments, with the exception of carbamazepine (0.64, 95% CrI 0.38 to 0.92), are associated with a lower probability of depressive relapse than placebo (0.62, 95% CrI 0.46 to 0.77). For this patient group, the lowest probability of depressive relapse is achieved with lithium plus imipramine (0.28, 95% CrI 0.12 to 0.49), then imipramine monotherapy (0.29, 95% CrI 0.13 to 0.50), valproate, lamotrigine and lithium monotherapy, all of which are associated with very similar probabilities (between 0.31 and 0.38), and last olanzapine (0.55, 95% CrI 0.37 to 0.72). For patients with a pretrial acute manic episode (Analysis 2), the probability of a depressive relapse is low on placebo (0.18, 95% CrI 0.11 to 0.27) and is reduced further by all treatments, with the exception of carbamazepine and possibly olanzapine.

These results are reflected in the probabilities that each treatment is best. For the prevention of manic relapse, independent of the existence of pretrial mania or depression symptoms, olanzapine was by far the best treatment option (0.99). For depressive relapses in patients with a pretrial acute depressive episode and in patients with a pretrial acute manic episode, lithium plus imipramine has the highest probability (0.32 and 0.33, respectively), followed closely by imipramine (0.29 and 0.30) and lamotrigine (0.19 and 0.16).

MTC sensitivity analyses

The main results from the sensitivity analysis are presented in Appendix 8.

Best- and worst-case scenarios

The ranking of treatments according to the probability of relapse for both patients with mainly depressive symptoms (Analysis 1) and mainly manic symptoms (Analysis 2) is slightly different

when compared with the ranking for the base-case analysis described above. The best option for the prevention of all relapses remains unchanged (olanzapine is still the best treatment option for patients with mainly manic symptoms and valproate for patients with mainly depressive symptoms). However, there are slight changes between the ranking of the second and third best options. Olanzapine also remains the best treatment to prevent **manic relapses** in both patients with mainly manic or depressive symptoms, and lithium also remains the second best option.

Some changes are observed in the case of prevention of **depressive relapses**. For patients with mainly manic symptoms, the ranking of treatments remains unchanged compared with the base-case analysis, as it does for the worst-case scenario for patients with mainly depressive symptoms (Analysis 2). However, for the best scenario, imipramine is now the therapy showing the lowest probability of relapse (0.26), followed by valproate (0.27) and lithium plus imipramine (0.28).

Inclusion of bipolar II studies and the olanzapine responders trial[48,51,56,78]

In the sensitivity analysis including bipolar II and olanzapine responder patients, we would expect a lower probability of experiencing a manic relapse and higher probability of experiencing a depressive relapse for all treatments, especially in patients with mainly depressive symptoms (Analysis 1). We would also expect olanzapine to perform slightly better than in our base-case analysis, as the additional study randomised only responders to olanzapine. The results are consistent with these expectations: valproate, lithium plus imipramine, lamotrigine and also olanzapine show a lower probability of relapse for all types of relapses (0.38, 0.41, 0.44 and 0.54, respectively) compared with the base-case results. Lamotrigine had the highest improvement gain in terms of reduction of probability of relapse.

Summary of results from mixed treatment comparison

The results of the MTC indicate that carbamazepine is not an effective maintenance treatment for bipolar I disorder. The efficacy of the rest of the treatments, measured as absolute probability of relapse, is to some extent dependent on the predominant symptoms, depressive or manic, as manifested according to the patient's latest pretrial acute episode. Although the ranking of the treatments remains the same, for patients who had a pretrial acute depressive episode (Analysis 1) the probability of experiencing a manic relapse is markedly lower than for patients who had a pretrial acute manic episode (Analysis 2), and vice versa.

In patients with mainly depressive symptoms, the lowest probability of relapse is achieved with valproate, lithium plus imipramine, lithium and lamotrigine. If the main focus of treatment in these patients is the prevention of depression, then lithium plus imipramine appears the best therapy, followed by imipramine, although only carbamazepine and olanzapine are much less effective in terms of absolute probabilities of relapse than the other drug therapies analysed.

In patients with mainly manic symptoms, olanzapine is by far the best option for the prevention of all relapses, followed by valproate and lithium. If the main focus of treatment in these patients is the prevention of manic relapses, then the results of the analysis indicate that olanzapine is the best therapy with a 0.99 probability.

The results of the sensitivity analysis indicate that lamotrigine has its highest efficacy in bipolar II patients.

Chapter 5
Economic review

The investigation of cost-effectiveness comprised:

- a systematic review of the cost-effectiveness of pharmacological and psychosocial interventions for the prevention of relapse in bipolar disorder
- an economic model to evaluate the cost-effectiveness of pharmacological treatments for the prevention of relapse in bipolar disorder (Chapter 6).

Cost-effectiveness methods

The databases listed below were searched using an economic methodological search filter. The specialist economic evaluation databases NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluation Database (HEED), and the Internet resource IDEAS, Research Papers in Economics (RePEC) database were also searched.

- MEDLINE (Ovid), 1966–2005/September week 1
- PreMEDLINE (Ovid), 15 September 2005
- EMBASE (Ovid), 1980–2005/week 37
- CINAHL (Ovid), 1982–2005/September week 2
- BIOSIS (Edina), 1985–2005/08
- PsycINFO (Ovid), 1872–2005/08
- Science Citation Index (SCI) (Web of Science), 1900–2005/08
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library/Wiley), 2005:3
- LILACS (BVS Virtual Health Library), 1982–2005/08.

Additional searches were undertaken for the economic model. These searches were undertaken to identify QoL data suitable for informing estimates for the model. These were carried out in MEDLINE, EMBASE, CINAHL, CENTRAL and PsycINFO on 10 March 2006. Only studies reporting QoL data based on utility values, and hence appropriate for estimating quality-adjusted life-years (QALYs), were considered.

The search strategies, dates and results of all searches are listed in Appendix 1.

For the assessment of cost-effectiveness, a broad range of studies were considered, including economic evaluations conducted alongside trials, modelling studies and analysis 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 analysis) were included.

The systematic literature search identified three published studies which met the criteria for inclusion in the cost-effectiveness 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 NHS. A quality checklist for each study is reported in Appendix 9. An overall summary of the cost-effectiveness evidence is provided at the end of this chapter.

Review of the NICE guideline economic model

Overview

The objective of this study[29] was to assess the cost-effectiveness of alternative pharmacological agents for the long-term maintenance treatment of bipolar disorder. Three pharmacological strategies were considered: (1) lithium (1000 mg/day); (2) valproate semisodium (1250 mg/day) and (3) olanzapine (10 mg/day). These strategies were also compared against a strategy of no long-term pharmacological treatment (no treatment/placebo). The study population consisted of patients with bipolar I disorder, in a stable (euthymic) state following an acute manic, mixed or depressive episode.

A Markov model was constructed in order to estimate costs and benefits associated with each of the four alternative strategies over a time horizon of 5 years, using yearly cycles. A hypothetical cohort of bipolar I patients, starting from a stable state and receiving one of the three pharmacological agents or placebo, were considered. During the course of a yearly cycle, patients either remained in a non-acute, stable state, or relapsed and experienced an acute episode which could be either a manic or depressive episode. It was assumed that acute episodes occurred in the middle of the year (i.e. at 6 months) if patients were receiving

pharmacological treatment and at 3 months if patients took no long-term medication. After remission of the acute episode, patients returned to the initial, stable state. Patients could also die during the maintenance phase due to suicide. Heterogeneity within patient subpopulations was considered by undertaking separate analyses for the following groups: males and females with and without child-bearing potential.

Model parameters were based on data obtained from the literature, expert opinion and authors' assumptions. For example, whereas clinical effectiveness of the alternative strategies in preventing relapse was mainly taken from randomised clinical trials, resource use was estimated on the basis of expert opinion by the Guideline Development Group (GDG), given the lack of previously published evidence on resource utilisation for this patient group.

Both incremental cost-effectiveness (cost per episode averted and cost per episode free day) and cost–utility (cost per QALY) analyses were performed. Deterministic (univariate) and probabilistic sensitivity analyses were carried out in order to handle the uncertainty around key model parameters and to assess the robustness of the base-case analysis.

Summary of effectiveness data

The model assumed that patients could only experience one acute episode (either manic or depressive) during each yearly cycle of the model and that the probability of experiencing this episode was constant over time. Thus, the key clinical input parameter for the model was the annual relapse rate for manic and depressive episodes associated with the different treatment regimens.

Data on relapse rates were obtained from a meta-analysis of RCTs based on a systematic review undertaken as part of the NICE guideline. Only RCTs that reported relapse rate as a measure of clinical effectiveness separately for manic/mixed and depressive episodes were considered. Five RCTs[39,42,48,77,78] met these inclusion criteria and relapse rates were obtained for three pharmacological treatments (lithium, valproate and olanzapine). However, none of these trials made direct comparisons between all the pharmaceutical interventions considered in the model. Therefore, indirect approaches were applied in order to facilitate a simultaneous assessment of the full range of treatments. Since four out of the five trials included placebo in one of the treatment arms, the relative risks of manic and depressive relapses for lithium, valproate and olanzapine were estimated in relation to the no treatment/placebo arm (one study was excluded due to the lack of a no treatment/placebo arm).[77] Thus, indirect comparisons across agents were carried out using no treatment/placebo as the baseline common comparator.

In order to undertake the comparisons using indirect approaches, it was necessary to assess the overall annual relapse rate (a combined estimate of both manic/mixed and depressive episodes together) associated with placebo/no treatment. This was obtained from a meta-analysis of the placebo arms of two of the clinical trials reporting data for a 1-year time horizon, which was consistent with the cycle length applied in the model. The rate of manic versus depressive episodes occurring during long-term treatment with placebo was then taken from the findings of a naturalistic study[8] supported by GDG consensus. Applying the rate of manic versus depressive episodes (41–59%) to the overall annual relapse rate, the annual rate of manic/mixed episodes and depressive episodes (0.26 and 0.37, respectively) was calculated for the placebo arm. Therefore, a hypothetical patient suffering from bipolar disorder, currently in stable state and receiving no long-term treatment, was assumed to have a 26% probability of experiencing an acute manic episode and a 37% probability of having a depressive episode each year.

Subsequently, the relative risk specific to manic/mixed and depressive episodes for each pharmacological agent compared with placebo was applied to the annual relapse rate estimated for the no treatment arm and the annual probability of acute episodes for lithium, valproate and olanzapine was obtained. Patients receiving olanzapine were characterised with the lowest annual probability of suffering from a manic/mixed episode (10%), followed by patients receiving lithium (17%) and valproate (20%). For the prevention of depressive episodes, valproate was estimated to be the most effective strategy in reducing the annual probability of depressive episodes (15%), followed by olanzapine (29%) and lithium (34%).

The annual probability of relapse (either manic/mixed or depressive) for each pharmacological agent and placebo was assumed to remain constant over the model time horizon, independent of the year and the number of previous episodes experienced by the patients.

Suicide rate and mortality

Based on a Swiss study of patients with mood disorders followed up for 44 years, the risk of suicide was reported to be lower for patients receiving lithium compared with those not treated with lithium during the maintenance phase.[122] Thus, for the economic model it was assumed that the standardised mortality ratios (SMRs) for suicide were lower for lithium compared with the other strategies and that the SMRs obtained for patients not treated with lithium applied to patients treated with olanzapine and valproate. SMRs were then multiplied by age- and gender-specific absolute suicide rates observed in the UK general population (in the age group 25–44 years) in order to estimate the absolute suicide rates of the study population used in the model. Men were characterised by a higher absolute rate of suicide than women (23.4 versus 6.4 per 100,000, respectively).

Safety

Adverse effects associated with each pharmacological agent were based on the results of a systematic review of clinical studies. However, given that the impact of potential adverse events specific to each treatment on patients' QoL was incorporated in the estimated health utilities, the analysis was limited to weight gain (which was specifically excluded from the calculation of utility values for all other adverse effects). As for treatment efficacy, the rates of weight gain for lithium, valproate and olanzapine were estimated by multiplying relative risks for each agent versus placebo by the 1-year rate of weight gain associated with placebo/no treatment (obtained from two RCTs). Patients receiving olanzapine had the highest probability of experiencing weight gain (21%), followed by valproate (11%), lithium (7%) and placebo (4%). In addition, olanzapine was estimated to be associated with a 21% probability of causing extrapyramidal symptoms.

Health utilities

Utility weights for each health state considered in the model (namely stable state, acute manic/mixed and depressive episodes) were necessary for estimating QALYs for the purpose of the cost–utility analysis. The majority of data were taken from a study by Revicki and colleagues.[84] Details of this study are considered in more detail in the section 'Utility estimates' (p. 88) as part of a separate review of QoL studies in this area. Briefly, 92 outpatient bipolar I patients were asked to rate their current (stable) health state using both a visual analogue scale (VAS) and a standard gamble (SG) approach. In addition, patients were asked to evaluate several hypothetical health states (acute mania with mild or moderate adverse effects) using the SG approach. Thus, the study provided patients' valuations for the stable state of the model, mania requiring inpatient hospitalisation and mania managed in an outpatient setting according to alternative pharmacological treatments and the presence of adverse effects.

Utility values applied to the stable state (excluding weight gain) were 0.82 for olanzapine, 0.74 for valproate and placebo and 0.71 for lithium. QoL scores for inpatient mania were 0.26 and 0.23, respectively, in the case of mild or moderate symptoms/adverse effects. For outpatient acute mania, utility scores ranged from 0.53 to 0.64 on the basis of severity of symptoms and the treatment regimen received during the episode.

Data for depressive episodes were obtained from a study by Revicki and Wood,[85] in which 70 patients with major depressive disorder were asked to rate the utility scores for severe (inpatient) and moderate (outpatient) depression (0.28 and 0.63, respectively). Finally, the decrement in utility due to weight gain was also obtained from Revicki and colleagues[84] and was estimated to be 0.066.

Summary of resource utilisation and cost data

Resource use was required in order to estimate the costs associated with the different health states of the model. Given the lack of published evidence or patient-level data, resource use was based mainly on expert opinion (GDG consensus).

For the stable state of the model, three categories of costs were considered: medications, contacts with professionals and laboratory tests (monitoring costs). For the medications considered, namely lithium, valproate and olanzapine, the daily dosage was determined according to the optimal average dose used in routine clinical practice and was assumed to remain stable over time. Contacts with health professionals included visits to consultant psychiatrists, senior house officers (SHOs), GPs and community psychiatric nurses (CPNs). The number of visits to each of these professionals, and the duration of these visits, were based on expert opinion.

Laboratory tests included full blood count for all medications, plus some drug-specific tests such as liver panel (for all drugs except lithium), glucose (olanzapine only) and serum lithium concentration (lithium only). The number and frequency of tests were based on recommended clinical practice derived using expert opinion. The

costs of treating potential adverse events for each maintenance medication were excluded from the analysis due to a lack of data, and this was acknowledged by the authors as a potential limitation of the study.

Different resource utilisation assumptions were made to reflect the different intensity and type of services provided for the management of manic/mixed and depressive episodes. For example, it was assumed that 80% of patients with an acute manic/mixed episode would be treated as inpatients, and the remaining 20% would be managed in an outpatient setting [by a Crisis Resolution Team (CRT)]. In the case of acute depressive episodes, however, only 10% of patients were assumed to be hospitalised, whereas 70% of patients received outpatient enhanced treatment and 20% were treated as outpatients by a CRT. Thus, the management of an acute manic episode was assumed to be more resource intensive than treatment of depressive episodes, given the higher percentage of hospitalised patients. This was only partially compensated for by the longer length of stay for depressive episodes (35 days) compared with manic episodes (28 days).

Unit costs were obtained from standard UK sources, such as the BNF for drugs, the Unit Costs for Health and Social Care for health professionals' visits and NHS reference costs for inpatient care. The length of stay was taken from the Hospital Episode Statistics for England. The price year was 2004/2005.

Summary of cost-effectiveness

Base-case analysis

Three outcome measures were considered: the number of averted acute episodes compared with no treatment, the number of days free from acute episodes and the number of QALYs gained for each of the pharmacological treatments and for no treatment/placebo. Health benefits were estimated for a hypothetical cohort of 1000 patients who entered in the decision model in the stable state and could experience acute episodes on the basis of the estimated probabilities of relapse for each treatment.

The first outcome measure (number of episodes averted with respect to the no treatment strategy) does not distinguish between the type of episode (manic and depressive), such that all episodes effectively receive the same weight. The second outcome (number of days free of acute episodes) makes a distinction between the alternative episode types, based on the different episode durations assumed (9 weeks for manic and 13 weeks for depressive episodes). However, neither of these two measures gives an adequate consideration of the potential impact of the type of episode on a patient health-related QoL.

The use of QALYs enables both patients' QoL and the annual suicide risk (assumed to be different for lithium compared to the other strategies) to be considered. The distinction between manic and depressive episodes is particularly relevant when QALYs are used as an outcome measure, given that different health utilities were reported for patients who were managed in inpatient or outpatient settings and the different percentage of patients who were assumed to be hospitalised following an acute manic or depressive episode. Hence the QALYs calculated for each medication under study were driven, in part, by the relative risk associated with a reduction in the risk of acute episodes and the differential effect of an agent on prevention of manic versus depressive episodes. In addition, differences in the QALYs of patients in the stable state were reflected using treatment-specific utility data.

Total costs were calculated for lithium, valproate, olanzapine and no treatment through the decision model. The total costs depended on drug acquisition costs and drug monitoring costs, but also on the percentage of patients experiencing acute episodes for each treatment strategy.

Results of the cost-effectiveness analyses where health benefits are expressed as number of averted episodes (compared with no treatment) and number of days free from acute episodes are presented in *Table 82*.

Valproate was reported to be the most effective strategy using both the outcome measures for men and women without child-bearing potential. This result was expected given that valproate was the option associated with the lowest probability of depressive episodes and these were assumed to be more frequent and longer in duration (and hence had a greater impact on QoL) compared with manic episodes. For the remaining strategies considered, the relative ordering based on decreasing effectiveness was olanzapine, lithium and no treatment.

In terms of cost-effectiveness, olanzapine was dominated (i.e. more expensive and less effective) by valproate. No treatment/placebo was dominated by both valproate and lithium. Of the remaining non-dominated strategies, an incremental cost-

TABLE 82 *Cost-effectiveness results (based on a hypothetical cohort of 1000 patients)*

Treatment	No. of adverted episodes	No. of days free from acute episodes	Total costs (£)	ICER (number of episodes averted) (£)	ICER (number of days free from acute episodes) (£)
Men					
Valproate	1,281	1,564,413	12,214,680	260 (versus lithium)	3 (versus lithium)
Olanzapine	1,102	1,535,238	14,101,441	Dominated by valproate	Dominated by valproate
Lithium	569	1,505,296	12,029,711		
No treatment	0	1,454,993	12,699,416	Dominated by lithium and valproate	Dominated by lithium and valproate
Women without child-bearing potential					
Valproate	1,291	1,577,339	12,311,318	341 (versus lithium)	4 (versus lithium)
Olanzapine	1,111	1,547,923	14,213,667	Dominated by valproate	Dominated by valproate
Lithium	561	1,509,579	12,062,406		
No treatment	0	1,467,015	12,804,809	Dominated by lithium and valproate	Dominated by lithium and valproate
Women with child-bearing potential					
Olanzapine	1,111	1,547,923	14,213,667	3,916 (versus lithium)	56 (versus lithium)
Lithium	561	1,509,579	12,062,406		
No treatment	0	1,467,015	12,804,809	Dominated by lithium	Dominated by lithium

effectiveness analysis was performed comparing valproate with lithium [incremental cost-effectiveness ratio (ICER) £260 and £341 per additional averted episode for men and women without child-bearing potential, respectively; £3 and £4 per additional day free from acute episodes for men and women without child-bearing potential, respectively].

Valproate semisodium was considered inappropriate for the long-term management of women of child-bearing potential and was therefore excluded from the analysis. Of the remaining strategies considered, olanzapine was the most effective treatment with an ICER of £3916 per additional averted episode and £56 per additional day free from episodes compared with lithium (no treatment was dominated by lithium).

Different results were obtained in the cost–utility analysis. In this case, olanzapine was the most effective strategy in terms of the number of QALYs for all the subpopulations analysed. This is likely to be due to two main factors. First, the utility associated with olanzapine in the stable state was higher than that for the other strategies. Second, olanzapine led to the lowest probability of manic episodes. Given that 80% of patients suffering from an acute manic episode were assumed to be hospitalised (compared with 10% of patients assumed to be hospitalised for a depressive episode) and that the utility estimate applied to hospitalised patients was markedly worse than other states, this could have had a substantial impact on QALYs. The no treatment/placebo strategy was dominated (i.e. more costly and less effective compared with another strategy) in all analyses. The ICER per QALY gained for valproate over lithium was £1725 for men and £1985 women without child-bearing potential. The ICER per QALY gained for olanzapine over valproate was £5902 for men and women without child-bearing potential. Given that valproate was excluded in the analysis of women with child-bearing potential, only olanzapine and lithium were compared, and the ICER per QALY gained for olanzapine over lithium was £4805. Cost–utility results are presented in detail in *Table 83*.

Sensitivity analysis

A series of univariate sensitivity analyses were performed on a number of model parameters that had been based on assumptions. In particular, the impact on the final ICER of variations in the following inputs was investigated: the rate of manic versus depressive episodes (75:25 and 25:75 versus 41:59 in the base case), health professional contacts during long-term treatment (reduced by 25%), duration of acute episodes (±25%) and time horizon (extended to 20 years). The ranges for parameter variation were based on the authors' assumptions and extreme scenarios were chosen.

A reduction in health professional contacts and changing the rate of manic versus depressive episodes to 25:75 did not have an impact on base-case results, and valproate remained the preferred option in the cost-effectiveness analysis, whereas

TABLE 83 *Cost–utility results (based on a hypothetical cohort of 1000 patients)*

Treatment	Total QALYs	Total costs (£)	ICER (£)
Men			
Olanzapine	3,612	14,101,441	5,902 (versus valproate)
Valproate	3,292	12,214,680	1,725 (versus lithium)
No treatment	3,261	12,699,416	Dominated
Lithium	3,185	12,029,711	
Women without child-bearing potential			
Olanzapine	3,641	14,213,667	5,902 (versus valproate)
Valproate	3,319	12,311,318	1,985 (versus lithium)
No treatment	3,288	12,804,809	Dominated
Lithium	3,194	12,062,406	
Women with child-bearing potential			
Olanzapine	3,641	14,213,667	4,805 (versus lithium)
No treatment	3,288	12,804,809	Dominated
Lithium	3,194	12,062,406	

olanzapine was the best strategy in the cost–utility analysis. However, applying a rate of 25:75 made valproate dominant in the cost-effectiveness analysis and almost doubled the ICER for olanzapine compared with valproate in the cost–utility analysis for both men and women without child-bearing potential (£10,744 per QALY). Increasing or decreasing the duration of the acute episodes did not change the ranking of options in terms of cost and benefits and did not significantly alter the value of the ICERs.

Changing the rate of manic versus depressive episodes to 75:25 had an important impact on the results: in this case, valproate was dominated by olanzapine in the cost-effectiveness analyses for both men and women without child-bearing potential (clearly in this scenario the relative effectiveness of olanzapine in reducing manic episode had a greater influence on the overall cost-effectiveness results). In the cost–utility analysis, the ICER of olanzapine versus lithium fell to £1489 (men) and £1594 (women) per QALY gained.

However, the most striking result was probably found in a threshold analysis, where the utility values used for valproate and olanzapine while patients remained in the stable state were varied. In particular, applying the same utility value for the two drugs resulted in valproate becoming the dominant option with respect to olanzapine. This is a significant departure from the result of the base-case cost–utility analysis where olanzapine dominanted valproate. The utility value used for the stable state is clearly a key element of the decision model and the assumption that the QoL differs between treatments while patients are stable is one of the main drivers of the cost–utility results.

A probabilistic sensitivity analysis was also carried out using Markov-chain Monte Carlo simulations (1000 iterations). The relative risk of relapse for pharmacological agents with respect to no treatment was varied according to a log-normal distribution, while the relapse rate for placebo was varied according to a binomial distribution. Costs associated with health professional contacts and with the management of acute episodes were modelled using a gamma distribution whereas utilities were given a range of values based on a beta distribution. No other details were given.

Results were presented graphically using cost-effectiveness acceptability curves (CEACs), together with the associated probability that interventions were cost-effective based on alternative threshold values for the outcome under consideration. When the number of averted episodes was taken as measure of effectiveness, no treatment had the highest probability of being cost-effective for a willingness to pay (WTP) lower than £500 per averted episode. For a WTP higher than £500, valproate had the highest probability of being cost-effective, followed by olanzapine and lithium. Similar results were found when the number of days free from acute episodes was used as benefit measure. No treatment was the preferred strategy for a WTP lower than approximately £5 per additional day free from acute episodes. For a WTP higher than £50, valproate was again associated with the highest probability of being cost-effective, followed by olanzapine and lithium.

For the cost–utility analysis, the no treatment/placebo option was cost-effective at a WTP lower than £5000 per QALY. However, the probability of olanzapine being cost-effective increased with higher values of WTP for an additional QALY and had the highest probability of being cost-effective starting from £7000 per QALY. At £20,000 per QALY, olanzapine was associated with a probability >90% of being cost-effective.

Comments

This study is based on a systematic and comprehensive approach to identifying relevant evidence relevant to informing a decision model comparing different pharmacological agents for the long-term treatment (maintenance) of patients suffering from bipolar disorder. On this basis, a number of the assumptions and parameters are subsequently utilised in the new decision analytic model presented in Chapter 6.

Clinical evidence was obtained from a meta-analysis of RCTs. The design of the studies included and the statistical techniques used to synthesise the effectiveness data enhance the internal validity of the analysis. However, strict eligibility criteria for clinical studies were subsequently applied in the economic analysis. The consequence of these inclusion criteria was the selection of a very small number of RCTs (i.e. only four studies were considered in the effectiveness calculations used to populate the economic model). Hence the relative risk of relapse for valproate and olanzapine compared with placebo was based on a single study for each drug, and data for lithium were obtained from a meta-analysis of three studies. It is unclear what possible bias (if any) this may introduce into the analysis. In addition, the selective use of RCT evidence may have resulted in the exclusion of potentially relevant alternative pharmacological treatments for the long-term treatment of bipolar patients.

Another issue that arises in the effectiveness analysis is related to the method used to obtain the annual relapse rates with placebo separately for depressive and manic episodes. While the overall relapse rate with placebo was obtained from a meta-analysis of RCTs, the specific relapse rates for manic and depressive episodes were then estimated combining data from a naturalistic study and assumptions of the duration of these events. Since the specific rates for manic and depressive episodes were also reported in the RCTs themselves, it is not clear why the authors did not take the relapse rate specific to each type of episode directly from the clinical trials.

Also, the probability of relapse associated with each pharmacological agent was assumed to remain constant over time. However, the authors acknowledged that the clinical effectiveness of lithium and other agents may instead vary over time. In addition, naturalistic studies[86,87] have shown that the probability of relapse for bipolar patients also depends on the number of previous relapses they had experienced, and there is an increase in the baseline risk of having a depressive or manic relapse conditional to the number of previous episodes. In particular, although the assumption of constant probabilities of relapse might be appropriate for patients who had experienced a high number of acute episodes, it seems less appropriate for bipolar patients with few previous relapses.

A central assumption of the economic model is that patients always receive the same maintenance treatment during the 5-year time horizon, regardless of the number of relapses they may experience. In reality, it seems more realistic to assume that patients who experience repeated relapses may actually switch to other pharmaceutical treatments, due to the lack of efficacy of the initial drugs received.

Another potentially important issue is the approach taken when assigning treatment-specific utility values to the individual strategies evaluated in the economic model. In the study used to inform these parameter inputs, different subgroups of patients provided valuations for these utility estimates. Different results were obtained for each of the pharmacological treatments and olanzapine appeared to be associated with higher utility values (and hence better QoL) than the other interventions. Although this may be due to the less severe adverse effects that patients experience in the long-term treatment of olanzapine, it might also depend on the (unobserved) heterogeneity among patient subgroups providing the valuations. In addition, it should be acknowledged that these scores were assessed in a relatively small sample of patients. This led to a substantial variability around mean scores. If some (or all) of this difference may be explained by heterogeneity as opposed to real differences between the treatments, then the cost–utility results could be biased in favour of olanzapine in the base-case analysis. Clearly, the difference in utility values for the different treatment regimens is a key driver of

the cost-effectiveness results presented here. Sensitivity analyses undertaken by the authors suggest that the results were highly sensitive to this particular assumption, such that in the situation where the same utility values were used for valproate and olanzapine (for patients in the stable state) the opposite conclusion was reached, that is, that valproate was the dominant therapy.

As regards the economic analysis, the costs associated with treating any adverse effects of long-term medications were excluded from the analysis. The authors stated that it was not possible to include this cost category given the lack of data. The inclusion of these costs might have had an impact on the total costs of the different strategies in a long-term analysis where adverse effects can also imply drug discontinuation and switch to alternative medications.

Resource use was mainly based on expert opinion due to lack of published evidence or patient-level data. Some assumptions are likely to have a relatively small impact on final results, such as the number of laboratory tests, contacts with health professionals or average dosage assumed for the pharmacological treatments. The percentage of patients hospitalised in the case of manic or depressive episodes instead seems an important element, because of the high costs of hospitalisation and the low utility scores associated with the management of manic and depressive episodes in an inpatient setting. The higher proportion of patients treated as inpatients for manic episodes, in relation to depressive episodes, might partly explain the contradictory results found in the cost-effectiveness and cost–utility analyses, as previously mentioned. The authors stated that the uncertainty around the costs of management of acute episodes was addressed in the probabilistic sensitivity analysis, but it is not clear what the impact of variations in this parameter was on the final cost-effectiveness ratios.

Finally, the uncertainty around some model parameters was handled using both a deterministic and a probabilistic sensitivity analysis. The univariate sensitivity analysis showed that the rate of manic versus depressive episodes is a crucial element in determining the ranking of options in terms of cost and effects. Some pharmaceutical agents are more effective for depressive than manic episodes (as, for example, valproate), whereas other drugs are more effective in reducing the risk of manic episodes (olanzapine and lithium). In this study, the rate of manic versus depressive episodes was based on a naturalistic study and experts' opinion. The authors did not provide an adequate explanation for the source of these estimates and why these data could not have been estimated directly from the RCTs themselves.

Review of the Chisholm study[88]

Overview

This study[88] evaluated the cost-effectiveness of lithium compared with valproic acid, alone or in combination with psychosocial treatment, in bipolar patients. The aim of the study was to estimate the cost-effectiveness of these interventions for reducing the global burden of bipolar disorder in 14 WHO epidemiological subregions.

Effectiveness and resource use data were based on a review of literature and a multinational Delphi consensus panel. The authors developed a Markov model type with three health states: manic episode, depressive episode and a non-symptomatic state. The primary outcome measure for the cost-effectiveness analysis was cost per disability-adjusted life-years (DALYs) averted annually by first-line treatment of bipolar disorder. Treatment effect was limited to (1) a change of the distribution of time spent in each state and (2) a reduction in the suicidal rate assigned only to lithium. The authors used a lifetime horizon, but only a 10-year implementation period. The evaluation was undertaken from a healthcare system perspective. Two service models were evaluated: a hospital-based inpatient model and a community-based outpatient model.

Average cost-effectiveness ratios were reported for all interventions instead of ICERs. A number of multivariate sensitivity analyses of best- and worst-case scenarios were derived according to lower and upper 95% CIs for the unit costs, the proportion of cases using hospital services and the number of psychosocial treatment sessions. A number of one-way sensitivity analyses were performed on parameters related to discount rates and treatment effect measures (mortality, disability weights and adherence to therapy), among others.

Summary of effectiveness data

Estimates of DALYs were based on a review of external sources. Treatment effect was limited to (1) a change of the distribution of time spent in each state and (2) a reduction in the suicidal rate assigned only to lithium. A composite disability weight for untreated patients was estimated based on data on the time spent with episodes before receiving treatment (50%),[89] adjusted by time

spent in depressive versus manic episodes.[8] Data on prevalence, incidence and case fatality of persons with bipolar disorder for WHO subregions was obtained from the Global Burden of Disease Study.[88] Population-level effects were derived by comparing the number of healthy years lived with and without intervention: the difference represents the DALYs averted resulting from intervention, relative to do nothing. Effects of psychosocial treatment were confined to improved adherence to medication. A reduction of the suicidal rate is applied only to lithium.[90]

Differences in the base-case analysis are modest, but strategies using lithium generate marginally greater population-level health gain than those with valproic acid. This is not surprising bearing in mind the assumptions used in the analysis. Further details are reported in the section 'Comments' (below).

Summary of resource utilisation and cost data

Resource use for an average patient with bipolar disorder was based on earlier empirical or modelling studies[91,92] and on a multinational Delphi consensus panel.[93] Annual expected resource use did not vary between global regions because the same level of effective coverage (50%) was modelled. The main categories of resource use considered included medication, psychosocial support (eight annual sessions), drug-specific laboratory tests for patient monitoring, inpatient hospitalisation, outpatient and primary care attendances and residential care. Subregional unit costs were obtained from the WHO-CHOICE website (www.who.int/choice/costs/en).

Baseline analysis costs for the 10-year implementation period were discounted at an annual rate of 3%, and expressed in international dollars (I$), price year 2000. Hospital-based service models incurred notably higher costs than community-based service models (30–50% in low-income to 70% in high-income regions). Baseline results per treated case were I$538–998 in high-mortality, developing subregions, I$925–1524 in low-mortality, developing subregions and I$1168–4187 in developed subregions.

Summary of cost-effectiveness

The base-case results showed that community-based treatment with lithium and psychosocial care was the most cost-effective option (cost per DALY averted: I$2165–6475 in developing subregions, I$5487–21,123 in developed subregions). However, the results were presented in terms of average cost-effectiveness ratios instead of estimating ICERs as appropriate. The use of average cost-effectiveness ratios can be potentially misleading.

A number of one-way sensitivity analyses were undertaken, such as changes in the discount rate (0 and 6%), the removal of age weighting, reducing the impact of lithium on suicide rates by half and assigning a small anti-suicide treatment effect for valproic acid. Results for a best- and worst-case scenario were also calculated based on the lower and upper 95% CI for some resource use items. The main finding was that lithium-based treatments remain the most cost-effective choice in high-mortality developing countries. Results for the different sensitivity analyses are also reported in terms of average cost-effectiveness ratios, so it is not possible to ascertain their impact.

Comments

There are a number of weaknesses with the analysis and several important issues relating to the model are unclear. First, results were presented in terms of average cost-effectiveness ratios instead of ICERs, which are inappropriate decision rules of cost-effectiveness analysis. Second, it is not clear how the authors estimated the treatment effect in terms of DALYs, or whether DALYs can adequately account for the disability impact of manic and depressive episodes in the analysis. Third, the authors assume maintenance of treatment benefit beyond 10 years for a lifetime horizon. Finally, even if the treatment effect could be generalisable to all 14 global regions, it is unlikely that the baseline estimates on time spent in the manic episode, depressive episode and non-symptomatic state and their corresponding disability weight can be generalised.

In addition, there are a number of assumptions that would need further justification, such as that annual expected resource use is assumed not to vary between global regions because, according to the authors, the same level of effective coverage (50%) was modelled. Differences in reduction of suicidal rate associated with lithium and regional unit costs are the key drivers of the analysis, so the results may potentially overstate the cost-effectiveness of lithium.

Review of the Lam study[94]

Overview

The aim of this study[94] was to assess the cost-effectiveness of adding cognitive therapy to standard care in the prevention of relapse in bipolar disorder. Lam and colleagues[94] have previously published details of their 30-month study of the effect of cognitive therapy in relapse

prevention, and here they presented an economic evaluation of the study results.

The study population consisted of 103 individuals with bipolar I disorder randomly allocated to standard NHS treatment and cognitive therapy (CT) plus standard NHS treatment. Both the control and CT groups received mood stabilisers and regular psychiatric follow-up. In addition, the CT group received an average of 14 sessions of CT during the first 6 months and two booster sessions in the second 6 months. Participants were not currently fulfilling criteria for a bipolar episode, but had to have had at least two episodes in the previous 2 years or three episodes in the previous 5 years.

The primary clinical outcome measured was number of days with bipolar episodes. Service use was measured via 3-monthly interviews with participants and the checking of case notes. Service costs were then obtained from recognised national sources, with the cost of a cognitive therapy session being assumed to be equal to 1 hour of a psychologist's time. Cost-effectiveness was assessed using the net-benefit approach, and probabilities of CT being cost-effective for different values which society may place on a bipolar-free day were used to generate a CEAC.

The evaluation found the probability of CT being cost-effective to be high. The group receiving CT had significantly better clinical outcomes, with the extra costs of the CT being offset by reduced service use elsewhere.

Summary of effectiveness data

The primary measure of effectiveness was the number of bipolar-free days in the period following randomisation to 12- and 30-month follow-ups. The Structured Clinical Instrument for DSM-IV[95] was used to determine any episode that fulfilled DSM-IV criteria for major depression, mania or hypomania. Hospital computerised records were used to confirm the exact length of hospital stays. The rationale given for the use of bipolar-free days is that bipolar episodes are not a sensitive measure of relapse prevention, as they can vary tremendously in length.

The study found a significant difference between the two groups, with those receiving CT spending 62.3 fewer days with bipolar episodes than the comparison group in the first 12 months. Over the whole 30 months, they also spent 110 fewer days with bipolar episodes out of about 900 days in total. The actuarial cumulative relapse rates for bipolar episodes in the CT and comparison groups were 64 and 84%, respectively. In total, 38% of individuals receiving CT were admitted to hospital for bipolar episodes compared with 47% in the comparison group, although this difference was not significant.

Summary of resource utilisation and cost data

Service utilisation data were captured every 3 months through participant interviews. Services measured included contacts with mental healthcare services, GPs, social workers, hospital services, support groups and residential care. In addition, case notes were checked for inpatient stays and medication.

Unit and hospital costs data for most services were taken from Curtis and Netten[96] and medication costs were taken from the BNF.[97] The cost of a CT session was assumed to be equal to 1 hour of a psychologist's time (£61). Unit costs were then multiplied by service utilisation to generate service costs per person.

Whereas hospital use and medication data were available for most participants, information on the use of community services was less complete, and missing data were imputed by taking the mean of the costs for the other periods.

Total cost differences between the groups were tested for statistical significance using a regression model. Non-parametric bootstrapping was used to address the skewness in the cost data, and CIs were constructed at the 90% level.

In the 3 months preceding the 6- and 9-month follow-up assessments, around twice as many from the comparison group were admitted compared with those receiving CT. However, this was reversed in the period before the 18-month follow-up. Community services and medication continued to be used by many throughout the study, although medication numbers declined slightly.

Significance tests were carried out on the difference between the groups in total costs for each 3-month period. For most periods, there were no statistically significant differences; the exceptions were for the period up to the 9-month assessment, when the CT group was significantly less costly, and at the 18-month assessment, when the CT group used significantly more resources. For the first 12 months of the study and the whole of the 30 months, the group receiving CT had lower service costs, although the differences were not statistically significant.

Summary of cost-effectiveness

Base-case analysis

The ICER of CT compared with standard care was determined using the net-benefit approach. The net-benefit for each individual was calculated for different values that society might place on a bipolar-free day ranging from £0 to £50. A regression model was then used to determine the mean difference in net benefit between the CT and standard care groups for each value of a bipolar-free day. For each model, 1000 regression coefficients for the CT/standard care variable were generated using bootstrapping, and the proportion of these greater than zero indicated the probability that CT was cost-effective for that value of a bipolar-free day.

The CEACs generated from these results showed that even with zero value given to a bipolar-free day, the probability of CT being cost-effective was in excess of 0.85 for the first 12 months and 0.80 for 30 months. As the value of a bipolar-free day increased, so did the probability of CT being cost-effective.

Sensitivity analysis

The authors identified that the only addition to the standard package of care was sessions of CT, and that the cost of this might differ from the assumption of 1 hour of a psychologist's time, for example, if other professionals deliver the service. A univariate sensitivity analysis was therefore performed, with the unit cost of CT being increased and decreased by 50%.

The results from this analysis showed that if the cost of therapy falls by 50%, the probability of CT being cost-effective increases. For example, measuring over the first 12 months gives a 93% chance that CT is more cost-effective than standard NHS care even if a zero value is placed on a bipolar-free day. If the cost of therapy is raised by 50%, then even under the worst scenario of measuring costs over 30 months there is a 75% chance of CT being the most cost-effective option with a zero value placed on a bipolar-free day.

Comments

This paper provides an important economic evaluation alongside a single trial. It makes a significant contribution to the bipolar literature since it is the only published study to have evaluated the cost-effectiveness of CT as an addition to standard NHS care for stable bipolar I patients not currently experiencing an acute episode.

However, there are a number of limitations to the study, several of which are recognised by the authors. The limitations noted by the authors are:

1. There was no protocol for standard NHS treatment. Decisions on drugs and frequency of psychiatric follow-up were left to the clinicians responsible for day-to-day care.
2. Service use was based on self-report and hospital records, both of which have problems.
3. There is no general agreement on the value of a bipolar-free day.

As indicated by the first limitation above, patients in the trial may have been receiving any one of a range of pharmaceutical treatment options. The implication of this is that although the addition of CT appears cost-effective for the patients in the study, it is not possible to draw a wider conclusion of whether it would be a cost-effective addition to specific pharmaceutical treatment regimes.

As noted by the authors, the use of bipolar-free days as the primary outcome constrains the extent to which the outcomes from this analysis can be compared with other economic analyses. The use of a recognised generic measure such as the QALY would have permitted such comparisons. However, the fact that CT appeared to be both less costly and more effective than standard care alone in terms of preventing relapse makes it unlikely that the results of a QALY-based analysis would alter the conclusions based on the disease-specific scale considered here.

A further potential limitation of the analysis is that it may lack wider generalisability. In this trial all the participants were outpatients of a single NHS Trust, and four experienced therapists provided all the CT sessions. As a result, there may have been little heterogeneity between patients or variability between treatments. In the wider NHS setting, considerable differences are likely to exist, which means that the benefits seen from the addition of CT to standard care in this setting will not necessarily be repeatable in other settings.

Discussion of existing cost-effectiveness studies

The review of economic evidence from the literature identified three existing published studies looking at the long-term cost-effectiveness of maintenance treatment for bipolar disorder. Of these studies, only two were considered directly relevant from an NHS perspective. The study by Lam and colleagues[94] demonstrated that the addition of CT to usual care for the long-term

prevention of relapse in patients with bipolar disorder appears cost-effective. This study has high internal validity being based on long-term follow-up (18 months), involving prospective follow-up of resource use and clinical outcome data, of patients from a UK RCT. The external validity and generalisability of these findings to a wider context will need further investigation since the design of the study minimised a number of potential sources of heterogeneity and/or variability in practice which may be apparent in a broader range of settings. Despite these concerns, the findings from the study clearly demonstrated that the addition of CT may potentially result in cost savings and improved outcomes in the maintenance treatment of patients with bipolar disorder who are currently stable.

The second study of relevance to the NHS is the recent economic model of long-term maintenance treatment of alternative pharmacological interventions, undertaken as part of the NICE guidelines for the management of bipolar disorder.[29] In general, the model makes an important contribution to the evidence base related to the cost-effectiveness of pharmacological treatments for this patient group. However, the review identified a number of potential limitations, which means that further consideration of a number of issues may be required if these results are to inform NHS practice reliably on the appropriate use of long-term pharmacological treatments on cost-effectiveness grounds. In particular, the selective use of the available RCT evidence appears to be a potential limitation of the current model. By selecting only those RCTs which provided a comparison of one of more pharmacological treatments against placebo/no treatment meant that a significant number of studies were not considered as part of the evidence base used to populate the decision model. One particular concern is that this may have resulted in the exclusion of relevant data and also potentially relevant additional comparators which it may be important to consider in a cost-effectiveness analysis.

In summary, the existing evidence relating to the cost-effectiveness of pharmacological and non-pharmacological interventions has a number of potential limitations which make the current evidence base insufficient to inform decision-making reliably regarding the most appropriate treatment in the NHS. The following chapter therefore presents a new decision analytic model that has been developed to address a number of these issues more formally. Central to this new model is the need to facilitate a direct comparison between the different comparators and to use all relevant RCT evidence in this process.

Chapter 6
Economic model

Introduction

The review of cost-effectiveness studies in Chapter 5 outlined a number of potential limitations of existing studies assessing the cost-effectiveness of alternative treatments for preventing relapse in bipolar disorder. In order to overcome these limitations and to assist the decision-making process in the context of the NHS, a new model was developed. The model focuses on the cost-effectiveness of long-term maintenance treatments of bipolar I patients with a range of alternative pharmacological treatments. Although a comparison involving non-pharmacological interventions was considered important, we have previously highlighted the problems of linking the evidence base for these interventions to the pharmacological interventions due to the lack of an appropriate 'network' of evidence. Consequently, it was concluded that any attempt to include these additional interventions in the economic analysis presented here could not be undertaken using robust approaches and would potentially introduce possible bias into the final results. Furthermore, the study by Lam and colleagues[94] suggests that CT as an adjunct to usual care (including pharmacological interventions) appears potentially cost-effective.

Although there has been a recent cost-effectiveness analysis of maintenance treatments using pharmacological interventions as part of the recent NICE guidelines for the management of bipolar disorder, a number of issues were identified with regard to the selection of trials and the restricted range of potential interventions included in the model. We concluded that these limitations manifested themselves in additional decision uncertainty surrounding the cost-effectiveness of long-term maintenance treatments with pharmacological interventions and hence warranted further consideration in order to further inform NHS practice. In order to address these limitations and to facilitate a direct comparison of the relative cost-effectiveness of a more complete range of relevant comparators, a new decision analytic model was developed. This model provides a framework for the synthesis of data from the clinical effectiveness and economic reviews in order to develop a single, coherent analysis of the main comparators identified. The following sections describe the model, including an overview of the key assumptions and data sources used to populate the model. The results from the model are then reported together with a discussion of these findings.

Model overview

The model was developed to evaluate the relative cost-effectiveness of alternative treatments for patients during the maintenance phase of bipolar I disorder. The model estimates costs from the perspective of the NHS (2004–5 prices) and health outcomes in terms of QALYs. The model uses a lifetime time horizon with costs and outcomes discounted at 3% per annum.

The model is probabilistic in that uncertainties in parameter estimates are characterised by assigning probability distributions. This allows the model to reflect second-order uncertainty, that is, uncertainty in the mean relapse rates for each of the interventions and other key input parameters. Monte Carlo simulation is then 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 (i.e. in order to reflect the combined impact of parameter uncertainty on the uncertainty surrounding the decision to adopt a particular technology).

Model structure

The model takes the form of a Markov state-transition model, with a cycle length of 1 year. The time horizon of the model is 60 years. Given that the average age of patients in the trials is around 40 years, this means that the model approximates the lifetime costs and benefits for each of the strategies.

Figure 2 gives a snapshot of part of the main health states and transitions considered in the Markov model. The circles represent the main health states considered and the arrows represent the potential transitions that a patient may follow over each cycle of the model. Patients enter the model in the stable state. From this state, they can then remain in the stable state, or experience an

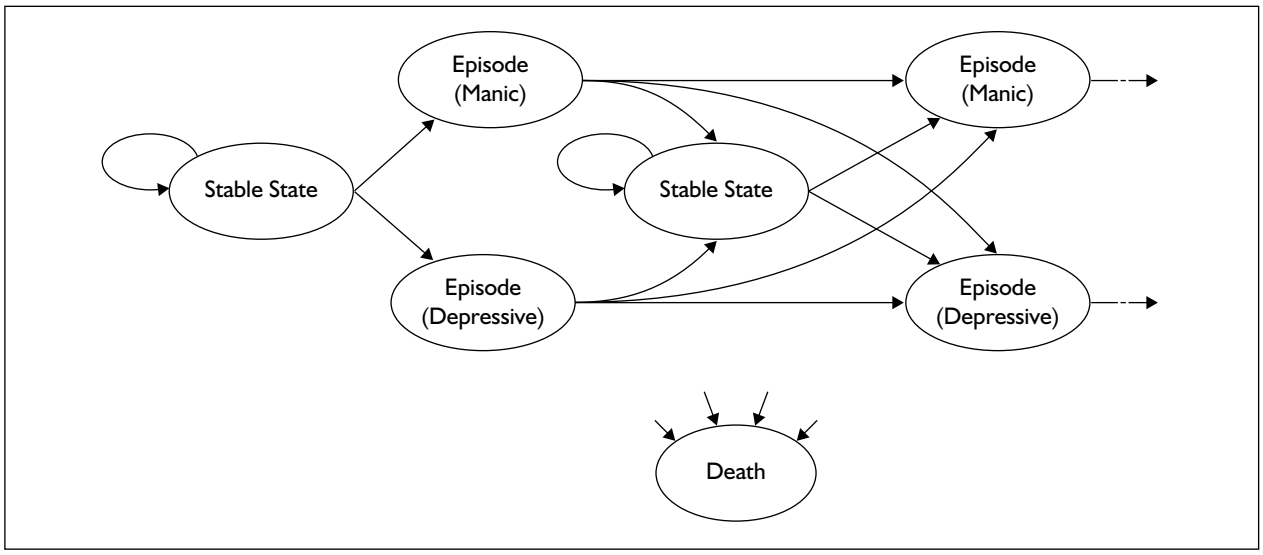

FIGURE 2 *Snapshot of the main health states and transitions applied in the Markov model*

acute episode during the first cycle of the model. This acute episode can be either manic or depressive. The manic and depressive episodes are additionally classified by severity level (not shown in the figure). The severity level is modelled using separate states for episodes requiring hospitalisation treatment or not. This allows for separate cost and utilities to be applied depending on the severity of the episode and also enables the history of the patient to be taken into account in the decision to continue (or not) with the initial treatment. Further details of the link between episode history and the decision to stop initial treatment and to switch to an alternative treatment are detailed in the following sections. In the cycle following an acute episode, the patient can either return to stable state or experience another episode. Patients can also die from any state within the model.

It is assumed that a manic episode lasts 9.9 weeks and a depressive episode lasts 21.3 weeks.[98] For calculation purposes, it is assumed that in a cycle where an episode occurs, a patient spends an equal amount of time in a stable state pre- and post-episode.

In contrast to the approach used in the NICE guideline model, the model outlined here allows for the initial medication to be altered during the course of the model based on whether the initial treatment has been considered to fail. The decision to alter treatment and to switch (or add additional medications) to alternative pharmacological treatments was related to the type and number of relapses experienced by a patient over the time horizon of model. Discussions with our clinical advisors highlighted the issue that patients are unlikely to be continued on the same treatment if they experience either a severe relapse, requiring hospitalisation, or multiple relapses (assumed to be three in total) which do not require hospitalisation. In an attempt to reflect actual clinical practice, the model allows for a change in medication after either of these events. In consultation with our clinical advisors, it was assumed that if initial treatment is considered to have failed then it is more common to add in additional treatments rather than continue on that treatment or switch to another monotherapy. In the absence of clinical evidence on the relative effectiveness of the full range of potential combinations and the problems outlined previously in linking the trials of combination therapy to the monotherapies, the model makes a simplifying assumption that all patients will receive the same second- and third-line treatments. This approach ensured that patients followed the same prognosis (and costs) after the initiation of second- and third-line treatments regardless of the initial therapy received. Second-line maintenance treatment was modelled as a combination treatment of lithium plus valproate and third-line maintenance treatment added in olanzapine.

Although it is recognised that not all patients will in practice be moved on to these specific combinations, they are combinations in common use and allow the model to represent the additional costs incurred when a patient is moved on to combination therapy. In the absence of the required clinical evidence on treatment sequences, the effectiveness of the combination treatment is assumed to be equal to the best of the treatments

within the specific combination. No additive effect is assumed through using multiple treatments since studies[86,87,99,100] have shown that there is an increase in risk of relapse with additional episodes. We therefore assume that any effectiveness benefit from multiple treatments would potentially be cancelled out by this increasing risk.

Figure 3 summarises the full model. Once a patient has experienced one episode requiring hospitalisation or three acute episodes on their initial treatment, they are switched to a combination treatment of lithium and valproate. If the patient then experiences a further hospitalisation (or three acute episodes), they are switched to the combination treatment of lithium plus valproate plus olanzapine.

Comparators

The full range of comparators included in the mixed treatment comparison model reported in the section 'Mixed treatment comparison' (p. 63) was included in the economic model. The specific interventions considered were thus:

- lithium
- valproate
- lamotrigine
- carbamazepine
- imipramine
- olanzapine
- lithium plus imipramine.

Although other potentially relevant monotherapies and combination treatments were identified in Chapter 4, it was not possible to include these in the model as they were not linked into the chain of evidence for the MTC model and hence are not included in the economic model (see *Table 78*, p. 64).

Evidence synthesis for outcome measures

Full details of the Bayesian evidence synthesis approaches used have been reported in detail in the section 'Mixed treatment comparison' (p. 63). The MTC model was used to populate the baseline transition probabilities for relapse (manic and depressive episodes) for lithium and for the relative effectiveness of each of the other interventions. The absolute probability of an event for each treatment was subsequently applied in the economic model.

As previously outlined in the section 'Mixed treatment comparison' (p. 63), there was significant heterogeneity across the three trials used to inform the baseline transition probabilities for lithium. This heterogeneity reflected whether the patient's previous episode had been either a manic or a depressive episode. A patient's likelihood of having either a subsequent manic or depressive episode in the follow-up period of these trials appeared to be largely governed by the nature of their previous episode (such that patients with a previous depressive episode were more likely to experience another depressive episode and vice versa for patients with a recent manic episode). This source of heterogeneity makes a direct comparison between the baseline event rates from the various trials problematic and, to address this issue, two separate analyses were undertaken (Analysis 1 and Analysis 2). Analysis 1 was restricted to a comparison of baseline event rates in the single trial which recruited patients with a previous depressive episode[101]), and Analysis 2 presented the combined event rates reported in the two trials assessing patients with a recent manic episode.[39,77] The relative effectiveness of each intervention was assumed to be independent of the baseline risk, although the absolute event rate (estimated by applying the relative treatment effect to the lithium-specific baseline event rate) will clearly differ between the two analyses. This analysis provides a comparison of the cost-effectiveness in patients who are more likely to be at risk of a further manic or a depressive episode.

In addition to estimating the absolute event rates for each strategy, the MTC model estimated the probability of being hospitalised conditional on having a relapse. The probability of hospitalisation was estimated specifically for the two types of relapse considered in our model (manic or depressive). Due to limited data on hospitalisation events across the full range of trials included in the MTC model, we assumed that the proportion of patients hospitalised following the onset of an acute episode was independent of the treatment received. That is, although the probability of an acute episode was allowed to vary across the different interventions, the conditional probability of a patient requiring hospitalisation following an episode was assumed to be the same for all interventions.

To maintain correlation between the posterior event rate estimates, the simulated output (10,000 iterations) were exported directly into Excel. Sensitivity analyses were also undertaken using 'best-case' and 'worst-case' scenarios to account for missing data in some of the trials considered.

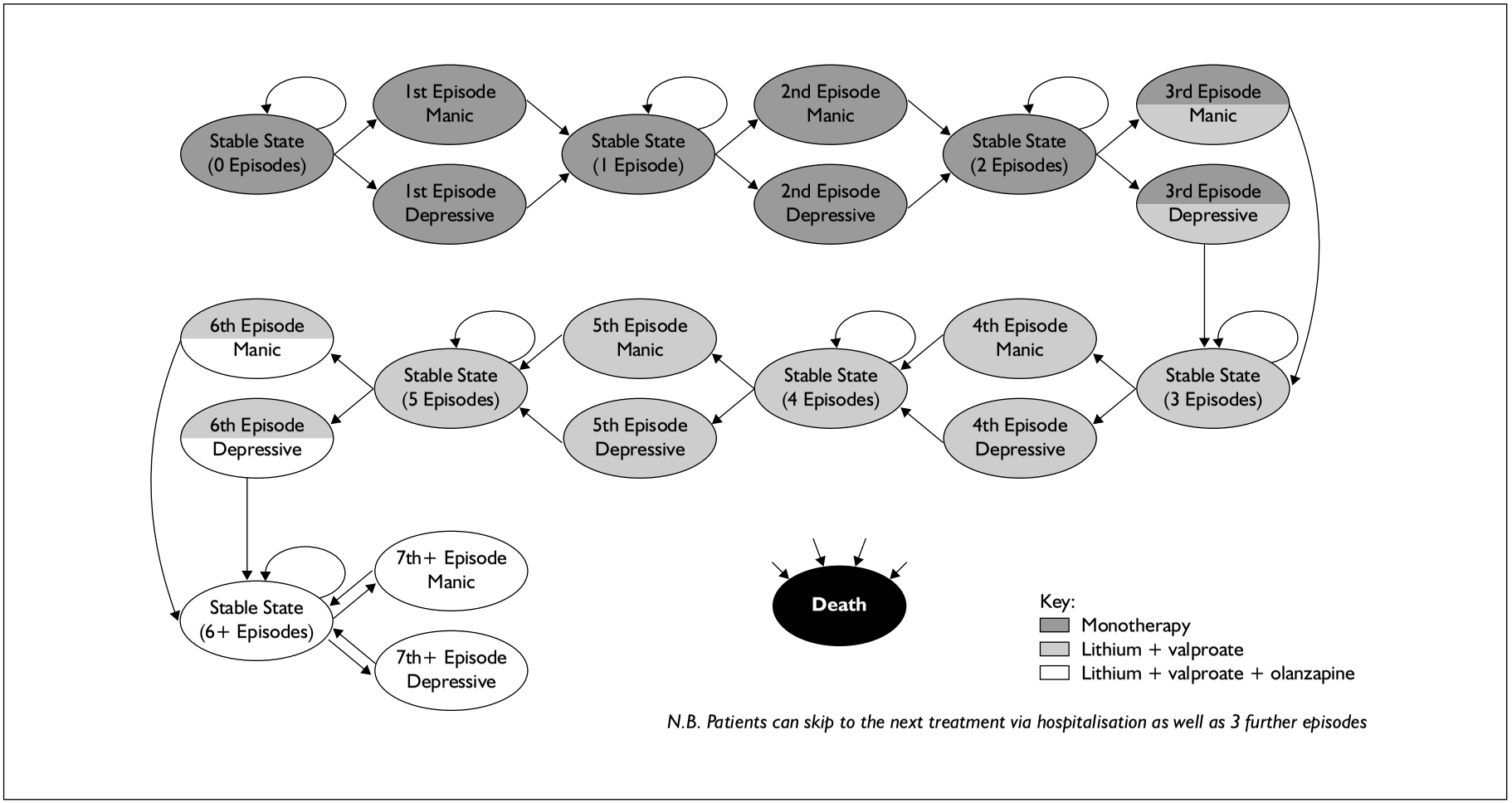

FIGURE 3 *Simplified overview of the full Markov model*

TABLE 84 *Drug acquisition costs*

Treatment	Dosage (mg)	Cost per dose (£)
Stable state		
Carbamazepine	600	0.16
Valproate	1250	0.31
Imipramine	150	0.26
Lamotrigine	200	1.54
Lithium	800	0.08
Olanzapine	10	2.84
Acute state – manic/mixed		
Olanzapine	15	4.26
Acute stage – depression		
Fluoxetine	20	0.05

Sources: expert opinion; BNF.[97]

Resource use and cost estimates

Costs were incorporated into the Markov model by attaching a mean annual cost to the stable, manic episode and depressive episode states. These mean costs comprised the following elements: the acquisition costs of drugs and routine monitoring costs associated with maintenance treatment for each pharmacological therapy, the cost of contacts with health professionals, and the costs of inpatient hospitalisations. Total costs for the cohort were calculated by summing costs for all the patients in a cycle, discounting these costs using a discount rate of 3.5% and then aggregating the discounted costs across the entire time horizon of the model. An average cost per patient was finally calculated by dividing by the size of the cohort.

The drug costs were taken from the BNF[97] and the drug dosages were determined in consultation with our clinical advisors (*Table 84*).

The costs of contacts with health professionals were based on a set of assumptions on the numbers of contacts (including days in hospital), and assumptions on the cost of each contact (see *Tables 85* and *86*). These assumptions were mostly taken from the recent NICE guidelines,[29] with several minor adjustments following discussions with our clinical advisors. The mean numbers of days hospitalised (42 days for manic episodes and 56 days for depressive episodes) were taken from the 2004–5 Hospital Episode Statistics for England.[102]

TABLE 86 *Unit costs of staff time*

	Cost per hour (£)
Psychiatric consultant	279
SHO	38
GP	139
CPN	82
Practice nurse	29
CRT (per contact)	54
Inpatient stay (per day)	205

Source: NICE guidelines.[29]

TABLE 85 *Resource use assumptions for the main health states*

	No. of contacts per year					
	Stable all year	Manic episode with hospitalisation	Manic episode with CRT	Depressive episode with hospitalisation	Depressive episode with CRT	Depressive episode with enhanced outpatient care
Psychiatric consultant	1	5	5	5	5	5
45 minutes	0	1	1	1	1	1
30 minutes	0	1	1	1	1	1
20 minutes	1	3	3	3	3	3
SHO	4	4	4	4	4	5
GP	9	9	9	9	9	10
20 minutes	0	2	2	2	2	2
10 minutes	9	7	7	7	7	8
CPN	13	13	12	13	12	14
CRT	0	0	15	0	15	0
Hospitalised (days)	0	42	0	56	0	0

Sources: NICE guideline; expert opinion.

TABLE 87 *Initial and ongoing laboratory costs*

	Serum lithium concentration	Blood urea and electrolytes	Thyroid function	Full blood count	Liver panel	Glucose test	Lipid profile	ECG
Initial tests								
Carbamazepine				1	1			
Valproate				2	2			
Imipramine		1						1
Lamotrigine								
Lithium	1	1	1					
Olanzapine						2		
Ongoing tests per year								
Carbamazepine						1		
Valproate						1		
Imipramine						1		
Lamotrigine						1		
Lithium	3	1	1			1		
Olanzapine						1		

Sources: NICE guideline; expert opinion.

For acute episodes, there are a number of management options, including hospitalisation, CRTs and enhanced outpatient care. Assumptions on the proportion of patients hospitalised were estimated directly from the trials (see the section 'Comparators', p. 85). For depressive patients the split between CRT and enhanced outpatient care (20:70) was taken from the recent NICE guidelines.[29] In particular, we used the weighted mean of patients with manic episodes (F30.0–F30.9) and recurrent depressive disorders (F33.0–F33.9) as the primary diagnosis.

Laboratory tests were split into tests required on initiation of a treatment and ongoing tests. The types and frequency of tests (*Table 87*) were based on discussions with our clinical advisors, and the costs of these tests were taken from the recent NICE guidelines,[29] with the exception of the cost of an ECG.[103] The unit costs of these tests are reported in *Table 88*.

TABLE 88 *Unit costs of laboratory tests*

Laboratory test	Cost per test (£)
Serum lithium concentration	2.63
Blood urea and electrolytes	2.04
Thyroid function	15.00
Full blood count	2.20
Liver panel	3.40
Glucose test	0.68
Lipid profile	2.04
ECG	16.25

Sources: NICE guidelines;[29] Hobbs and colleagues.[103]

Utility estimates

Overall health outcomes were measured in terms of QALYs and were discounted at a rate of 3.5%. In order to estimate QALYs, it is necessary to quality-adjust the period of time the average patient is alive within the model using an appropriate utility or preference score. QALYs were estimated in the model in a similar way to costs, with a utility value being calculated for the stable state and manic and depressive episodes (adjusting for the severity of these episodes). In order to reflect best-available evidence on utility values for bipolar patients, we conducted a separate review of published sources which could be used to inform this part of the economic analysis.

Review of published papers reporting utility values in bipolar patients

Four studies were found potentially to provide useful estimates of utility values for the health states considered in the model.[84,104–106] Details of the studies are given in *Table 89*.

In the Tsevat study[104] 53 patients suffering from bipolar disorder were recruited from the University of Cincinnati alongside a naturalistic follow-up study between July 1996 and October 1997. The main objective of the study was to estimate the relationship between patient-perceived current mental health and current overall health. All patients in this study (median age 43 years; 38% male) were outpatients receiving medications (mood stabilisers, antidepressants, etc.) and, in some cases, psychotherapy.

TABLE 89 *Overview of QoL studies*

Revicki, 2005[84]	Tsevat, 2000[104]	Vojta, 2001[105]	Hayhurst, 2006[106]
Patient population			
Inclusion criteria Clinically stable, outpatients aged 18 years or older, with DSM-IV bipolar I disorder. Clinical stability was based on DSM-IV criteria for current manic, mixed or depressive episode. Patients had to have more than 2 manic or mixed episodes in the last 5 years *Exclusion criteria* Alcohol or substance dependence in the last 3 months, diagnosis of schizoaffective disorder, impulse control disorder, rapid cycling	*Inclusion criteria* Patients with bipolar disorder. No other details were given *Exclusion criteria* No exclusion criteria were reported	*Inclusion criteria* Patients with bipolar disorder based on the DSM-IV criteria *Exclusion criteria* Comorbid moderate or severe dementia	*Inclusion criteria* Lifetime diagnosis of bipolar disorder according to DSM-IV criteria, with two or more episodes of illness, one of which must have been within 12 months prior to recruitment *Exclusion criteria* Bipolar disorder secondary to an organic cause, evidence of severe borderline personality disorder with suicidal ideation or intent in the past 3 months, continuous illicit substance misuse, other
Setting			
USA. Patients recruited from a community hospital (n = 33), university bipolar disorder research centre (n = 37) and managed care organisation health centre (n = 26)	USA. Patients were recruited from the University of Cincinnati site of the multicentre Stanley Foundation bipolar network naturalistic follow-up study. Patients were outpatients receiving medications (e.g. mood stabilisers, antidepressants) and, in some cases, psychotherapy	USA. Patients were recruited from four Department of Veterans Affairs Medical Centers (outpatient)	UK. Patients were recruited from five centres across three different NHS regions alongside an RCT
Demographics			
Total patients: 92 Mean age: 42.4 ± 12.7 years Men: 44.5% 54% with college or higher education	Total patients: 53 Median age: 43 years (25th, 75th: 37, 50 years) Men: 38% 100% graduated from high school and 45% had college or graduate degrees, or both Many previously hospitalised	Total patients: 86 Mean age: 47.3 ± 6.9 years Men: 81.4% No other details given	Total patients: 221 Mean age: 41.5 ± 11 years Men. 36% In episode at start: 33% (23% depression, 10% mania) Other details were given

continued

TABLE 89 *Overview of QoL studies (cont'd)*

Revicki, 2005[84]

Methods to elicit preferences

Current health state was estimated both with VAS and SG
Hypothetical health states were estimated with SG
Patients were given a choice between living in the hypothetical state for 1 year and a gamble between complete health and the worst state for 1 year

Results

Health state	*n*	Mean (SD)	95% CI
Current health state (VAS)	92	69.5 (23.8)	–
Current health state (SG)	92	0.80 (0.22)	–
Stable			
Lithium	11	0.71 (0.22)	0.56 to 0.86
Valproate	13	0.74 (0.26)	0.58 to 0.89
Risperidone	22	0.83 (0.19)	0.74 to 0.91
Olanzapine	18	0.82 (0.20)	0.72 to 0.92
Haloperidol	12	0.61 (0.26)	0.45 to 0.78
Valproate plus haloperidol	8	0.62 (0.20)	0.46 to 0.78
Mood stabiliser + risperidone	23	0.70 (0.19)	0.62 to 0.79
Mood stabiliser + olanzapine	25	0.58 (0.23)	0.48 to 0.68
Mood stabiliser + haloperidol	20	0.62 (0.23)	0.51 to 0.72

Tsevat, 2000[104]

Current health state (probably stable state) was estimated using VAS, TTO and SG
Current mental health was also estimated separately from current overall health using the same instruments

Health state	Mean (SD)	Median (25th, 75th percentile)
Current (VAS)	68.0 (20.3)	70 (50, 84)
Current (TTO)	0.71 (0.37)	0.85 (0.55, 0.995)
Current (SG)	0.77 (0.32)	0.925 (0.65, 1.0)

Current mental health was also estimated and resulted lower than overall health with VAS, TTO and SG: mean (SD, median [25th, 75th percentiles]):

VAS: 61.0 (25.7; 60 [40, 85])
TTO: 0.61 (0.39; 0.75 [0.25,0.995])
SG: 0.70 (0.35; 0.85 [0.5, 0.995])

Vojta, 2001[105]

EuroQol: VAS
Health states were defined both by physicians and using the ISS

Health state	Mean (SD) (physicians)	Mean (SD) (ISS)
Euthymic	78.1 (16.2)	75.9 (15.4)
Manic/hypomanic	70.8 (15.5)	68.4 (17.1)
Mixed	54.1 (19.9)	46.9 (16.3)
Depressed	54.3 (22.5)	57.0 (25.2)

Mixed category included both those with DSM-IV-defined mixed episode (mania plus major depressive episode) and those with hypomania plus major depressive episode

No. of patients using physicians' definition:
Manic/hypomanic: 16
Major depressive: 26
Euthymic: 30
Mixed: 14

No. of patients using ISS definition:
Manic/hypomanic: 15
Major depressive: 24
Euthymic: 36
Mixed: 11

Hayhurst, 2006[106]

EQ-5D: TTO
VAS

Health state	*n*	Median (Q1, Q3) TTO	Mean (SD) TTO
LIFE Depression Score			
1	87	1.0 (0.80, 1.0)	0.90 (0.16)
2	52	0.85 (0.76, 0.88)	0.82 (0.16)
3	27	0.81 (0.69, 0.88)	0.77 (0.19)
4	20	0.81 (0.63, 0.84)	0.72 (0.25)
5	30	0.57 (0.21, 0.73)	0.49 (0.30)
6	5	0.29 (0.13, 0.59)	0.35 (0.29)
LIFE Mania Score			
1	19	0.85 (0.71, 1.0)	0.78 (0.25)
2	17	0.76 (0.69, 0.92)	0.74 (0.23)
3	6	0.72 (0.67, 1.0)	0.79 (0.17)
4	3	0.69 (0.69, 0.80)	0.72 (0.06)
5 + 6	3	1.0 (0.76, 1.0)	0.92 (0.14)

LIFE Depression or Mania Scores: 1 = no symptoms; 6 = DSM-IV major depressive episode, or mania with psychotic symptoms or severe impairment of function

continued

TABLE 89 *Overview of QoL studies (cont'd)*

Revicki, 2005[84]

Results

Health state	*n*	Mean (SD)	95% CI
No medications	18	0.74 (0.23)	0.63 to 0.85
Severe depression			
Hypothetical state of severe depression	92	0.29 (0.28)	0.16 to 0.42
Mania (mild symptoms/adverse effects)			
Inpatient	61	0.26 (0.29)	0.19 to 0.34
Outpatient:			
Lithium	12	0.56 (0.26)	0.39 to 0.73
Valproate	12	0.47 (0.26)	0.30 to 0.63
Risperidone	14	0.54 (0.24)	0.40 to 0.67
Olanzapine	21	0.64 (0.27)	0.52 to 0.76
Lithium + haloperidol	13	0.37 (0.19)	0.25 to 0.48
Valproate plus haloperidol	13	0.63 (0.25)	0.48 to 0.78
Mood stabiliser + risperidone	27	0.54 (0.25)	0.45 to 0.65
Mood stabiliser + olanzapine	39	0.56 (0.27)	0.48 to 0.66
Mood stabiliser + haloperidol	26	0.49 (0.25)	0.39 to 0.60

Tsevat, 2000[104]

Vojta, 2001[105]

Differences between health states were statistically significant at the following *p*-values:
Euthymic vs mixed ($p = 0.001$, physicians; $p = 0.0001$, ISS)
Euthymic vs depressed ($p = 0.001$, physicians; $p = 0.01$, ISS)
Manic vs mixed ($p = 0.01$, ISS)
Manic vs depressed ($p = 0.02$, physicians)

Hayhurst, 2006[106]

Health state	*n*	Median (Q1, Q3) TTO	Mean (SD) TTO
All cases	221	0.81 (0.69, 1.0)	0.78 (0.25)
Euthymic	76	1.00 (0.82, 1.0)	0.90 (0.16)
Residual symptoms	55	0.85 (0.76, 1.0)	0.83 (0.16)
Subsyndromal depressed	40	0.81 (0.70, 0.85)	0.76 (0.21)
Depressed subgroup	33	0.41 (0.20, 0.76)	0.47 (0.30)

continued

TABLE 89 *Overview of QoL studies (cont'd)*

Revicki, 2005[84]			Tsevat, 2000[104]	Vojta, 2001[105]	Hayhurst, 2006[106]
Results					
Health state	***n***	**Mean (SD)**	**95% CI**		
Mania (moderate symptoms/AE)					
Inpatient	62	0.23 (0.29)	0.16 to 0.31		
Outpatient:					
Lithium	22	0.54 (0.26)	0.42 to 0.65		
Valproate	16	0.44 (0.32)	0.27 to 0.62		
Risperidone	23	0.52 (0.26)	0.40 to 0.63		
Olanzapine	21	0.53 (0.26)	0.40 to 0.66		
Lithium + haloperidol	20	0.44 (0.25)	0.32 to 0.56		
Valproate plus haloperidol	17	0.29 (0.30)	0.13 to 0.44		
Mood stabiliser + risperidone	24	0.41 (0.23)	0.31 to 0.51		
Mood stabiliser + olanzapine	33	0.53 (0.27)	0.44 to 0.63		
Mood stabiliser + haloperidol	37	0.37 (0.28)	0.28 to 0.46		

continued

TABLE 89 *Overview of QoL studies (cont'd)*

Revicki, 2005[84]	Tsevat, 2000[104]	Vojta, 2001[105]	Hayhurst, 2006[106]
Adverse effects			
Utility values associated with stable state include adverse events associated to each treatment, but exclude weight gain For lithium, adverse effects included nausea, thirst, trembling, difficulty remembering and fuzzy mind For haloperidol, adverse effects included stiffness, shaking in the extremities, restlessness and difficulty thinking clearly or remembering things For risperidone, adverse effects included feeling stiff, restlessness, tiredness and hands shaking For valproate, adverse effects were feeling slowed down and sleepy, nausea, diarrhoea, shaking hands and hair loss For olanzapine, adverse effects included dry mouth, sleepiness and constipation Utility loss associated with weight gain was estimated separately by a regression analysis: 0.066 ($p = 0.013$)	Patients were receiving medications such as mood stabilisers or antidepressants, but no information of possible adverse effects was provided	Health states were not associated with specific treatments, hence no details on adverse effects were given	Health states were not associated with specific treatments, hence no details on adverse effects were given

Patients were asked to rate their current overall health state using three instruments: the VAS (0–100), time trade-off (TTO) and SG. The same instruments were also used to evaluate patients' mental health.

The VAS scores appeared marginally lower than values obtained with TTO and SG. Mean utility values were 68.0 ± 20.3 with VAS (median: 70), 0.71 ± 0.37 with TTO (median: 0.85) and 0.77 ± 0.32 with SG (median: 0.925). Current mental health was valued lower than current overall health by most patients with all instruments.

This study has the advantage of using different instruments to evaluate utility values, providing a comparison among the results obtained. However, for the purpose of the model, it only provides values for the stable state and does not give enough information on the medications taken by the patients and their potential adverse effects.

The Vojta study[105] included 86 patients (mean age 47.3 ± 6.9 years; 81.4% male) with bipolar disorder recruited from four Department of Veterans Affairs Medical Centers between November 1996 and June 1997. Based on the DSM-IV criteria, patients were categorised as euthymic, manic/hypomanic or with major depression. Patients who simultaneously met criteria for mania/hypomania and major depressive episode were categorised as mixed. Thus, the definition of mixed health state appears different from that used in our model, where patients suffering from mixed episodes were considered more similar to patients with mania. However, the utility values for the other health states were considered to provide useful information for the 'stable', 'depressive' and 'manic' health states.

Health state distributions were defined both by physicians and using the Internal State Scale (ISS) (a self-report instrument that has been validated for discriminating mood states in patients with bipolar disorder), which gave a slightly different number of patients for each category. In particular, the ISS definition included more patients in the euthymic state (36 versus 30 for physicians) and fewer patients in the major depression state (24 versus 26), manic (15 versus 16) and mixed state (11 versus 14).

Patients were asked to rate their current health state using the EuroQol (EQ-5D) VAS. Mean scores (SD) were 78.1 (16.2) or 75.9 (15.4) for the euthymic state using physicians' or ISS definitions, respectively, 70.8 (15.5) or 68.4 (17.1) for the manic/hypomanic health state, 54.3 (22.5) or 57.0 (25.2) for the depressive state and 54.1 (19.9) or 46.9 (16.3) for the mixed health state.

In the Revicki study,[84] a total of 92 patients (mean age 42.4 ± 12.7 years; 41.5% male) with bipolar disorder were recruited from a community hospital, a university bipolar disorder research centre and a managed care organisation health centre in the USA. Clinically stable outpatients with DSM-IV bipolar I disorder were included in this study. Patients were asked to rate their current (stable) health state using both VAS and SG instruments, but also to evaluate some hypothetical health states (namely, not current but potential future and past health states) using the SG approach. These hypothetical states were severe depression and inpatient and outpatient mania with mild or moderate symptoms/adverse effects. Health states were evaluated for subgroups of patients on the basis of treatments received that included lithium, valproate, risperidone, olanzapine, haloperidol, valproate plus haloperidol, a mood stabiliser plus risperidone, a mood stabiliser plus olanzapine and a mood stabiliser plus haloperidol. Thus, utilities associated with the health states depended also on the adverse effects associated with each medication (excluding weight gain, which was assessed separately).

Mean utility scores (SD) for the current health state estimated from the whole sample of patients were 69.49 (23.83) using the VAS and 0.80 (0.22) using the SG. However, when utility values for the stable state were estimated based on patients' treatments, high variability was found. Mean utility scores (estimated only using the SG) ranged from 0.58 for patients receiving a mood stabiliser plus olanzapine to 0.83 for patients receiving risperidone. This might reflect a difference in the severity of the adverse effects associated with the different medications, but could be due also to patient heterogeneity in the various subgroups.

The mean SG utility score for the hypothetical state of the severe depression state was 0.29 (95% CI 0.16 to 0.42). When patients were asked to rate acute manic health states (using the SG), a substantial difference was found between inpatient and outpatient cases. Mean (SD) utility scores for inpatient mania were 0.26 (0.29) when associated with mild symptoms and 0.23 (0.29) when associated with moderate symptoms. Outpatient mania was instead characterised by higher utilities, although again they depended on the treatment

received and on the severity of symptoms associated with each medication, ranging from 0.29 for valproate plus haloperidol and moderate symptoms to 0.64 for olanzapine and mild symptoms.

This study has the advantage of including several health states and distinguishing between inpatient and outpatient mania, which appears an important issue for our model. Also, the subgroup analysis based on treatment received could provide data to assess the impact of potential adverse effects associated with each medication. However, it is not clear whether the different scores obtained for the same health state for these medications are due to real differences in the severity of adverse events or whether they are determined by a difference in health perception among the subgroups analysed. Also, the number of patients included in each subgroup appears relatively small, ranging from a minimum of eight in the valproate plus haloperidol group to a maximum of 25 for a mood stabiliser plus olanzapine. In addition, the definition of mild versus moderate symptoms/adverse effects was not clearly reported in the paper. In general, the most useful information for the purposes of informing the economic model appears that provided for the inpatient mania state (assessed from 61 patients and using the SG) and that for the stable state (when assessed from the entire sample and using the SG)

Finally, the Hayhurst study[106] was based on 221 patients (mean age 41.5 ± 11 years; 36% male) with bipolar disorder recruited from five UK centres across three different NHS regions alongside an RCT. Patients had a lifetime diagnosis of bipolar disorder according to DSM-IV criteria and could be euthymic or in an episode, but those who met criteria for mania were not included in the study until they became hypomanic. Health utilities were assessed immediately prior to randomisation to TAU or TAU with CT, and then every 2 months up to 18 months of follow-up. Subgroup analyses were performed based on different levels of disease severity using the LIFE-II ratings of Depression and Mania (a six-point scale: 1 = no symptoms to 6 = DSM-IV major depressive episode, or mania with psychotic symptoms or severe impairment of function).

Utility values were elicited both using a VAS and using the EQ-5D (with the TTO method). The mean (median) utility score for the 76 patients in the euthymic state was 0.90 (1) using the EQ-5D and the mean (median) score for the 33 patients in the depressed group was 0.47 (0.41). As expected, scores decreased as the severity of depression increased, ranging from a mean (median) of 0.90 (1) for LIFE Depression Score 1 to 0.35 (0.29) for LIFE Depression Score 6. Less consistency was found for manic patients where mean (median) scores varied from 0.79 (0.85) for LIFE Mania Score 1, to 0.72 (0.69) for LIFE Mania Score 4 but increased again to 0.92 (1) for LIFE Mania Score 5 and 6. This was probably due to the very limited number of patients (three) included in this subgroup.

In general, this work presents some advantages with respect to the previous studies: first it is based on an RCT, which ensures higher internal validity; second, utility scores are obtained from UK patients; third, it includes a relatively high number of patients for the depression and euthymic health states. On the other hand, the manic group is fairly small and presents some inconsistent results that cannot be applied to our model.

In addition to these four potentially relevant articles, another study assessing the QoL of patients with bipolar disorder was found.[107] However, after detailed consideration it was decided that it did not provide sufficient information in order to provide a suitable basis for populating our model.

Briefly, in the Revicki study,[107] 120 patients with a DSM-IV diagnosis of bipolar disorder were randomly assigned to receive divalproex or olanzapine for the treatment of acute mania. This was a 12-week, double-blind RCT, performed in 21 US sites. Subjects (aged from 18 to 65 years) needed to be hospitalised for an acute manic episode in order to be included in the study.

QoL data were collected at hospital discharge and at 6- and 12-week follow-ups using a VAS. However, only 63 patients completed a global QoL questionnaire based on a VAS at hospital discharge and only 52 (27 in the divalproex group and 25 in the olanzapine group) provided at least one follow-up assessment. At hospital discharge, the global QoL score was 62.8 (18.4) for patients in the divalproex group and 71.1 (18.8) for patients in the olanzapine group. Global QoL decreased at the 6-week (–0.8 and –10.5 for the two groups, respectively) and 12-week (–2.4 and –9.0) follow-ups. However, it is not clear whether patients were in a stable state at hospital discharge and whether they suffered from another acute episode during the follow-up. Also, the differences in scores

between the two groups could be due both to real differences in the efficacy and safety between the two drugs or to patients' heterogeneity.

Finally, as previously stated, the instrument used to elicit patient preferences (VAS) presents some weaknesses compared with other approaches. Given all these limitations, we decided that this article was not suitable for estimating utility values for our model.

Utility values applied in the model

The central utility estimate for stable state of 0.8 was taken from Revicki and colleagues,[84] based on a sample of 92 patients (*Table 90*). This estimate was used for all treatments. Although this paper also gave separate stable state estimates for a number of treatments, the small sample sizes on which these estimates were based, together with the potential heterogeneity across the sample, made it difficult to determine whether the observed differences were due to differences in the side-effect profiles or whether they reflected heterogeneity between the samples or indeed pure chance. In this situation, we concluded that assigning treatment specific utilities to the stable state would potentially bias the results. Uncertainty surrounding the utility estimates were characterised by assigning a beta distribution to the input parameters.

The utility estimate for a year with a manic acute estimate was calculated by combining estimates of utilities during both inpatient and outpatient management of episodes from Revicki and colleagues,[84] with estimates of the proportions of patients hospitalised, the duration of hospitalisation and the duration of episodes. The utility estimates for a year with a depressive acute estimate were calculated in the same way as for manic episodes. Data from the paper by Revicki and colleagues[84] were used to estimate the utility of an episode managed as an inpatient. In the absence of a corresponding value for depressive episodes managed in an outpatient setting, these estimates were based on combining Life Scores (4 and 5) reported in the paper by Hayhurst and colleagues.[106]

TABLE 90 *Utility estimates applied in the model*

Health state	Utility score
Stable state	0.8
Manic episode	
Inpatient mild	0.26
Inpatient moderate	0.23
Outpatient mild	0.64
Outpatient moderate	0.53
Depressive episode	
Inpatient	0.29
Outpatient – Life Score 4	0.72
Outpatient – Life Score 5	0.49

Sources: Revicki and colleagues;[84] Hayhurst and colleagues.[106]

Mortality estimates

There is significant evidence that mortality is higher for patients with bipolar disorder than for the general population. This is primarily due to an increased risk of suicide, but also due to some increase in other cause mortality.

Lithium specifically has been demonstrated to have a strong antisuicidal effect in mood disorders.[108] It is the only treatment demonstrated to have a specific anti-suicidal effect on patients with bipolar disorder. A Swiss study of patients with mood disorder followed up for a period of over 40 years reported separate SMRs for patients with bipolar disorder treated with lithium (SMR of 1.2) and patients with bipolar disorder not treated with lithium (SMR of 1.7).[122]

These SMRs have been applied to mortality statistics for the general population,[109] with the lithium SMR being applied to an initial treatment of lithium monotherapy or lithium plus imipramine.

Analyses

The model was developed in Excel, and is run for 10,000 iterations, incorporating all the estimates and assumptions described above. The results are presented in two ways. First, mean costs and QALYs for the various comparators are presented and their cost-effectiveness compared using standard decision rules and estimating ICERs as appropriate. The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. When more than two interventions are being compared, the ICERs are calculated using the following process:

1. The strategies are ranked in terms of cost (from the least expensive to the most costly).
2. If a strategy is more expensive and less effective than any 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 any more effective strategy, then this strategy is ruled out on the basis of extended dominance.

Finally, the ICERs are recalculated excluding any strategies that are ruled out by principles of dominance or extended dominance.

The advantage of entering input parameters as uncertain variables 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, CEACs are used. These show the probability that each strategy is more cost-effective than the others using alternative values for the maximum value that the health service is willing to pay for an additional QALY in these patients. A cost-effectiveness frontier is presented alongside the CEACs. This shows which option the decision-maker would choose when using the decision rule of choosing the treatment with the highest expected value.

As previously stated in the section 'Evidence synthesis for outcome measures' (p. 85), for the purposes of the cost-effectiveness model two separate baseline risks were considered due to the heterogeneity observed across trials selected as sources for baseline event rates in the model. Analysis 1 uses baseline event rates for patients who had experienced a previous depressive episode (from Calabrese and colleagues,[101] data reported for 12 months' follow-up) and Analysis 2 uses event rates specific to patients who have experienced a previous manic episode (using data from both Tohen and colleagues[77] and Bowden and colleagues[39]).

The results are presented for the base-case analysis. A series of sensitivity analyses are then undertaken to assess the robustness of the results from the base-case models.

Results

Base-case results

Results for analysis 1

Table 91 presents the lifetime analysis of the mean costs, QALYs and the ICER for the comparison of the alternative pharmacological treatments for patients with a recent depressive episode. Seven strategies were considered: lithium, valproate, carbamazepine, lamotrigine, olanzapine, imiprimine and a combination treatment of lithium plus imipramine. In this analysis, valproate was the cheapest, non-dominated alternative. Carbamazepine, imipramine, lamotrigine and olanzapine were all dominated by valproate (i.e. they were more costly and less effective). Lithium and the combination treatment of lithium plus imipramine were both more costly and more effective than valproate. Since neither of these treatments was ruled out on dominance grounds, two separate ICERs are reported. The first is for the next most effective strategy (lithium) relative to valproate. The ICER of lithium compared with valproate was estimated to be £10,409 per additional QALY. The second ICER is then based on a comparison between lithium and the combination of lithium and imipramine. The ICER of the combination treatment compared with lithium monotherapy was £21,370 per additional QALY. Hence the results of Analysis 1 indicate that if the NHS is prepared to pay over £10,409 for an additional QALY (but less than £21,370) then lithium appears cost-effective. Clearly, if the NHS is prepared to pay more than £21,370 for an additional QALY, then lithium plus imipramine would be considered cost-effective.

At a threshold WTP for an additional QALY of £30,000 there is considerable decision uncertainty surrounding the optimal strategy on cost-effectiveness grounds. Based on a comparison of the ICERs, at a threshold level, lithium plus imipramine would be considered cost-effective. The probability that this particular strategy is cost-effective is 53%; however, there remains a significant probability that the lithium monotherapy is cost-effective (41%). *Figure 4* presents the decision uncertainty in the form of multiple CEACs, across a range of potential threshold amounts that a decision-maker might be prepared to pay for a QALY. The CEACs demonstrate that the probability that lithium plus imipramine is cost-effective increases as the maximum WTP increases: if society is prepared to pay £20,000 for an additional QALY, the probability that lithium plus imipramine is cost-effective is around 47%, increasing to 56% if the maximum WTP is £40,000.

Although the CEAC provides a useful graphical representation of the uncertainty associated with the probability that individual strategies are cost-effective over a range of threshold values, the results of the CEAC can only be used to identify the optimal implementation decision under a restrictive set of assumptions. This is because the strategy with the highest probability of being cost-effective does not necessarily have the highest

TABLE 91 *Base-case analysis 1: patients with a recent depressive episode*

Treatment	Mean costs (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	96,951	13.95	D	0.04	0.03	0.02
Valproate	56,233	14.73	–	11.96	3.98	1.40
Imipramine	83,314	14.47	D	0.04	0.01	0.00
Lamotrigine	64,117	14.66	D	4.72	1.92	0.99
Lithium	62,649	15.34	10,409	35.74	41.27	41.80
Olanzapine	65,659	14.39	D	0.09	0.00	0.00
Lithium + imipramine	64,602	15.43	21,370	47.41	52.79	55.79

D, dominated.

TABLE 92 *Base-case analysis 2: patients with a recent manic episode*

Treatment	Mean costs (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	103,503	14.24	D	0.29	0.05	0.02
Valproate	57,320	14.98	D	2.40	0.29	0.01
Imipramine	98,961	14.57	D	0.00	0.00	0.00
Lamotrigine	70,964	14.86	D	0.21	0.00	0.00
Lithium	58,657	15.72	11,359	77.04	88.69	89.47
Olanzapine	50,347	14.99	–	11.12	1.13	0.10
Lithium + imipramine	72,954	15.62	D	8.94	9.84	10.40

D, dominated.

expected pay-off (i.e. net benefit), and will only do so when the distribution of these pay-offs is symmetrical. This limitation can be overcome by using a cost-effectiveness frontier to indicate which strategy is optimal (and the associated probability that this strategy is the most cost-effective) across the range of values representing the maximum amount the NHS is prepared to pay for an additional QALY.[110] The frontier for this analysis is also provided in *Figure 4*, demonstrating which intervention is cost-effective (and the probability that this intervention is the most cost-effective) across the range of cost-per-QALY thresholds considered.

Results for analysis 2

Table 92 presents the lifetime analysis of the ICER for the comparison of the same range of comparators considered in Analysis 1. In this analysis, however, a baseline specific to patients who have recently experienced a manic episode is used and the cost-effectiveness of the alternative treatments is re-evaluated. In this analysis, olanzapine dominates all of the strategies with the exception of lithium monotherapy. Lithium monotherapy is more costly and more effective than olanzapine, with an associated ICER of £11,359 per additional QALY. Hence, although Analysis 2 includes the same range of comparators, the final ICER calculations are based on a different set of non-dominated interventions compared with those considered in Analysis 1. Consequently, if the decision-maker is prepared to pay less than £11,359 per additional QALY, then olanzapine would appear the most cost-effective strategy for the long-term maintenance of bipolar patients who have recently experienced a manic episode. Clearly, if the decision-maker is prepared to pay more than £11,359 then lithium monotherapy would be considered the optimal strategy on cost-effectiveness grounds. The results for Analysis 2 suggest that different conclusions can be drawn regarding the optimal intervention according to the most recent episode experienced by a patient.

Figure 5 presents the CEACs and associated frontier for Analysis 2. The CEACs demonstrate that the probability that lithium is cost-effective increases as the maximum WTP increases. If the decision-maker is prepared to pay £20,000 for an additional QALY, the probability that lithium is cost-effective is 77%, increasing to 89% if the maximum WTP is £40,000. The results suggest that there is less decision uncertainty surrounding the choice of optimal intervention for patients who have recently experienced a manic episode, compared with those patients considered in Analysis 1 who had recently experienced a depressive episode.

Results from sensitivity analyses

A series of sensitivity analyses were undertaken in order to assess the robustness of the results of the base-case model to the use of alternative assumptions in the following scenarios:

1. alternative approaches to handling missing data in the estimating relapse data (using best-case and worst-case approaches)
2. variation in the trials included in the base-case analysis

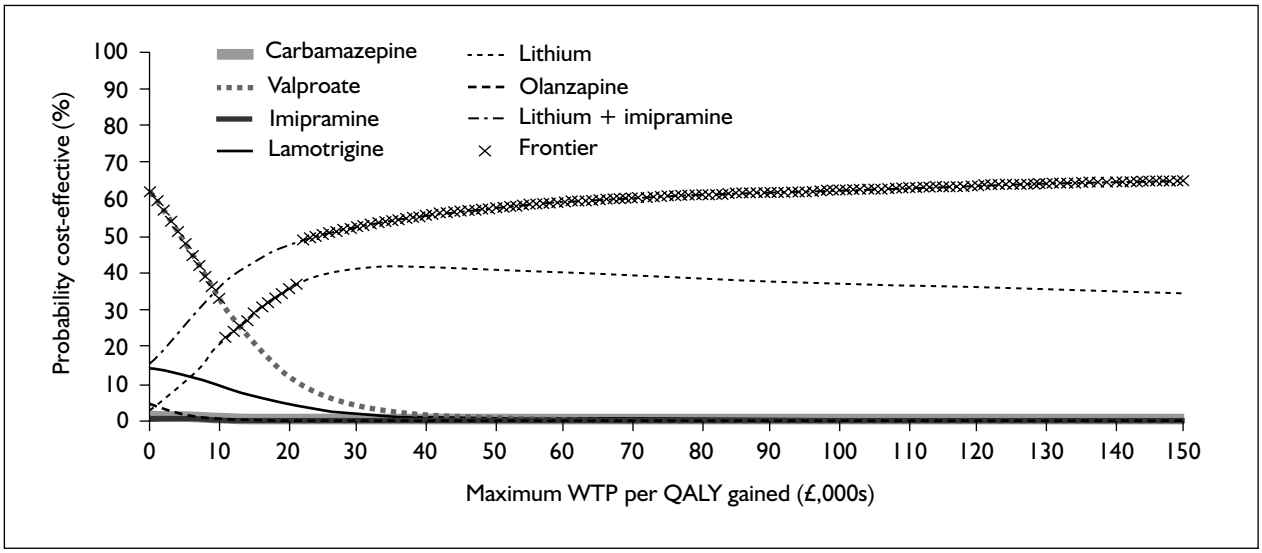

FIGURE 4 *Cost-effectiveness acceptability curves (and frontier) for bipolar patients with a recent depressive episode (Analysis 1)*

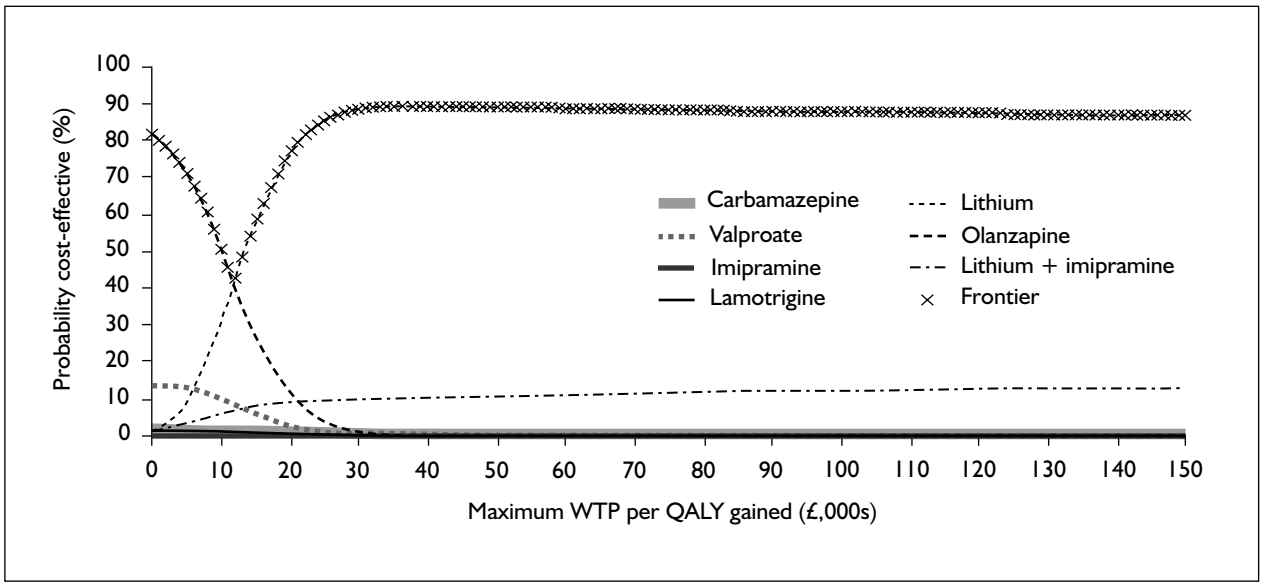

FIGURE 5 *Cost-effectiveness acceptability curves (and frontier) for bipolar patients with a recent manic episode (Analysis 2)*

3. alternative discount rates for costs and outcomes (1.5% for outcomes and 6% for costs)
4. impact of excluding the treatment effect associated with lithium-based strategies on mortality.

Detailed results of the cost-effectiveness results for each of these scenarios are reported in Appendix 10. In general, the results remained broadly consistent across the first three scenarios. In two of the scenarios considered for Analysis 1, lithium monotherapy was ruled out on grounds of extended dominance, hence the ICER was estimated based on a comparison of lithium plus imipramine versus valproate. However, the ordering of strategies based on costs and outcomes was the same across all the analyses. For Analysis 2 the results were largely unaffected by the first three scenarios considered.

The base-case results appeared most sensitive to the impact of excluding a treatment effect on mortality for the lithium-based strategies. This had a marked impact on the results for both Analysis 1 and Analysis 2. In the base-case analyses, the two lithium-based strategies (lithium monotherapy and lithium plus imipramine) were assumed to have an additional impact on mortality compared with the other pharmacological treatments. By assuming that lithium was not associated with any additional mortality effects, the rank ordering of treatments in terms of costs and outcomes was changed, and therefore resulted in a different set of non-dominated treatments. In Analysis 1, all strategies were dominated by valproate. In Analysis 2, all strategies were dominated by olanzapine. Consequently, the assumption that lithium confers additional mortality benefits compared with alternative pharmacological treatments appears central to the cost-effectiveness estimates. If lithium is not associated with any additional mortality benefits, then the most cost-effective treatments for the management of patients with a recent depressive or manic episode appear to be valproate and olanzapine, respectively.

Discussion

The results presented here suggest that the choice between alternative pharmacological treatments based on cost-effectiveness considerations is dependent on a number of factors. First, the previous episode history of a patient appears to be important. The variation reported across baseline event rates for trials recruiting patients with a recent history of either a manic or depressive episode resulted in marked differences in the risk and type of subsequent episodes. Although not a perfect proxy, the patient's most recent episode appears to be related to the type of the next episode. One approach would have been to pool across the three baseline trials and to estimate the 'average' cost-effectiveness of treatments across patients with a recent history of both manic and depressive episodes. However, by averaging across these patients, we are effectively ignoring the fact that the most recent episode is observable and may actually guide more appropriate decisions. Effectively, we are saying that treatments aimed at preventing depression may be more cost-effective

in patients with a recent history of depression compared with patients with a recent manic episode (and vice versa for treatments aimed at preventing manic episodes).

The results from the base-case analysis for patients with a recent history of depression suggest that valproate, lithium and the combination of lithium and imipramine are potentially cost-effective, depending on the amount that a decision-maker is willing to pay for additional health gain (assessed here using QALYs). Using conventional amounts that the NHS is prepared to pay for health gain (£20,000–40,000 per QALY),[111] then the lithium-based strategies appear to be potentially cost-effective for this group.

For patients with a recent history of mania, then the choice of pharmacological intervention appears to be between olanzapine and lithium monotherapy. Again, using the conventional threshold as a reference point, the results suggest that lithium is the most cost-effective therapy.

A number of sensitivity analyses were undertaken to assess the robustness of these findings. Although the results appeared robust to a number of alternative assumptions, they were markedly altered when lithium was assumed to have a similar effect on mortality as the other pharmacological treatments. This suggests that the mortality benefit associated with lithium in the base-case analyses is also central to the cost-effectiveness of the alternative treatments. Excluding the additional mortality benefit associated with lithium-based strategies in the sensitivity analyses resulted in all treatments for patients with a recent history of a depressive episode being dominated by valproate and olanzapine. In the case of patients with a recent history of a manic episode, olanzapine dominated all other treatments. Hence the optimal intervention on cost-effectiveness grounds is highly dependent on the assumption of a mortality benefit associated with lithium.

The model presented here addresses several of the limitations noted in the review of the economic model undertaken as part of the recent NICE guideline for the management of bipolar disorder. In particular, the use of a mixed treatment comparison model for the evidence synthesis facilitated a more inclusive approach to the trials considered and allowed a broader range of comparators. In addition, the assumption that patients would be maintained on a specific treatment for the entire duration of the model, irrespective of the subsequent prognosis (i.e. number and type of episodes arising during the time horizon of the model) was deemed to be unrealistic. Although it was not possible to model the full range of possible treatment sequences that might be considered in patients who have been considered to fail on first-line maintenance treatments, the approach outlined here allows for the additional costs (and benefits) that may arise when patients are considered to fail first-line treatments. While the focus of the model presented here is primarily concerned with the cost-effectiveness of first-line pharmacological treatments, ensuring that patients follow the same treatment pathways and prognosis for second- and third-line treatments means that the differences in cost-effectiveness are primarily driven by the effectiveness of first-line therapies in preventing the onset of further episodes.

It should also be recognised that the current model also has a number of potential limitations which need to be considered when interpreting the findings from the cost-effectiveness analyses. Perhaps the most important limitation was the inability to consider the full range of potential interventions that may be considered relevant in the maintenance treatment of bipolar I patients. In particular, it was not possible to assess directly the relative cost-effectiveness of alternative pharmacological treatments against the psychosocial interventions considered in the effectiveness review. In addition, it was not possible to assess directly the cost-effectiveness of a range of combination pharmacological therapies alongside the range of monotherapies assessed in the main analyses.

Another important limitation associated with the current model was the exclusion of adverse effects from both the costs and outcome assessments. The different side-effect profiles associated with the interventions considered in the model could lead to variations in the cost-effectiveness estimates presented here. However, the poor quality of reporting of adverse effects and the lack of consistency in the effects reported across the trials meant that a formal analysis was not possible. Although it may have been possible to partially reflect the differences by assigning treatment-specific utilities to the stable state using a similar approach to that undertaken in the economic model undertaken as part of the NICE guideline, detailed consideration of the data that underpins these differences meant that it was difficult to establish whether the observed differences could be related to the different side-effect profiles or

not. In this case it was deemed that using treatment-specific utilities was likely to introduce additional bias into the results. As such, the cost-effectiveness estimates presented here need to be considered in relation to the specific adverse event profiles associated with the particular drugs, and these need to be weighed against the possible disutility and costs associated with these adverse effects.

Chapter 7
Discussion

Clinical effectiveness

Limitations of the review

Our review of clinical effectiveness aimed to investigate all treatments available for maintenance therapy in bipolar disorder. In practice, we looked at those used in recent clinical practice for which relevant trial data were available: lithium, valproate, carbamazepine, lamotrigine, olanzapine, imipramine, quetiapine, perphenazine and combinations of lithium with imipramine, valproate, flupenthixol or amitriptyline. It should be noted that the use of the tricyclic antidepressants imipramine and amitriptyline has reduced in recent years. This seems to be a consequence of concerns over adverse effects with the older medications and a concern that tricyclics might more frequently cause mood destabilisation (switch to mania) than newer antidepressant drugs.[24] However, there is an absence of long-term trials evaluating newer antidepressants, particularly SSRIs, in the maintenance treatment of bipolar disorder. In addition, the use of the conventional antipsychotics perphenazine and to some extent flupenthixol has also decreased in favour of newer atypical antipsychotics. Our comprehensive literature searches, use of fairly broad inclusion criteria and our efforts to contact authors should have ensured we are unlikely to have missed any relevant studies.

Although a reasonable number of RCTs (45) were identified for the review, with the exception of perhaps lithium versus placebo, there were not many repetitions of specific comparisons. Hence there were only limited opportunities for pooling data from a number of trials and few of the treatments were thoroughly investigated. Furthermore, the strength of evidence is not equal for all treatments or for all comparisons. Sample sizes and length of treatment and follow-up varied across studies. Several of the older trials and some of the psychosocial trials had very small numbers of participants, providing limited data. In addition, poor reporting of methodological details, particularly in terms of randomisation, allocation concealment and blinding, made full assessment of study quality difficult.

In addition to the number and quality of the trials available, the outcomes that could be summarised were also restricted. The available trials data forced us to use relapse rate rather than time to relapse or duration relapse free as the primary outcome measure in the review. Even then, relapse rates were reported differently in the various trials, with a number of different definitions of relapse across the trials and some trials reporting data separately for manic or depressive relapses, whereas others reported all relapses. This variation further limited the opportunities for pooling data across trials. Analysis of the data on relapse rates was made difficult because the follow-up period varied across the trials. Our compromise in using the data only from the longest available follow-up for each trial is likely to have introduced some degree of heterogeneity and masked or exaggerated some treatment effects or differences.

We had hoped to look at effects of interventions on suicide rates, but unfortunately data on suicide were extremely scarce. Similarly, data on adverse effects resulting in discontinuation or withdrawals from the trials were also poorly reported in the available primary studies and therefore our exploration of treatment effects and differences is very limited.

Given that our review was of all the available treatments for the prevention of relapse in bipolar disorder, we had hoped to explore the effectiveness of the available treatments for bipolar disorder according to specific patient characteristics such as co-morbidity, gender, single status and ethnicity. However, again, data were scarce and not well reported and only the differences in efficacy in those patients with bipolar I and those with bipolar II disorder have been explored at all. We attempted to explore the reasons for heterogeneity based on *a priori* planned subgroup analyses of studies in which patients were randomised to maintenance treatment while in the acute phase of the disease, studies including only patients with bipolar II disorder or studies randomising only responders to treatment. However, we did not observe an important impact of heterogeneity on the pooled

data for most comparisons. Given the limited reporting in published articles, an individual patient data analysis using original data sets would be required to explore the impact of certain patient characteristics fully, and in any case might be compromised by the lack of good-quality trials. However, in our MTC analysis we explored the impact of the predominant symptom – manic or depressive – on the effectiveness of the treatments and in this have been able to go beyond the recently published NICE guideline.[29]

Similarly, the impact of the use of additional drugs (co-interventions) could not be explored due to the lack of information provided for the primary studies.

Key findings from the standard analysis

Different pharmacological interventions used as monotherapy afforded different levels of efficacy for the prevention of relapses of manic and/or depressive episodes in patients with bipolar disorders. Lithium was the most extensively studied treatment. Although some of the older trials were small and of limited quality, there was sufficient reliable evidence to suggest that lithium is a useful treatment for the management of bipolar disorder. Based on the results of standard meta-analysis, lithium is clearly more efficacious than placebo. This finding reflects that of an earlier systematic review published in 2004.[112] Lithium was also demonstrated to be as effective as valproate and lamotrigine (although this was based on a small number of studies for each comparison), and better than carbamazepine and imipramine when used as monotherapy for prevention of all relapses in bipolar disorder. A recent direct comparison trial indicated that lithium may not be as efficacious as olanzapine, particularly in the prevention of manic relapses. However, as this finding is based on only one, albeit good-quality, trial, replication in further trials is needed. There is a possible suggestion that lithium may not be as effective as lamotrigine in the prevention of depressive relapses. However, this result comes from one trial only and was not statistically significant.

When compared with placebo, valproate, lamotrigine, olanzapine and imipramine demonstrated a statistically significant efficacy. However, the results for olanzapine were achieved only in patients who had previously demonstrated a response to olanzapine, and the result for imipramine, which was only more effective than placebo for the prevention of depressive relapse, was based on two very small trials and further trials are required. Of all the treatments compared with lithium, only olanzapine was found to be more efficacious (although not for depressive relapses) and only carbamazepine and imipramine were less effective.

There were few other direct comparisons between monotherapies: the two studies which compared valproate with olanzapine found no significant difference. However, data were sparse and the results may not be reliable.

Although monotherapy with a number of pharmacological agents clearly possesses a clinically significant degree of efficacy, many patients treated with monotherapy will still experience a high rate of relapse. A strategy of combination therapy has been advocated by the BAP 2003 guidelines for treating bipolar disorders,[5] but the evidence base for recommending combination therapy is still weak. The few trials of combination therapy identified for this review were generally small and many were not of good quality. When lithium was compared with a combination of imipramine and lithium,[55,56,67] lithium and flupenthixol,[49] lithium and amitriptyline[54] or lithium and divalproex,[74] no treatment differences were demonstrated, probably due to inadequate study design and sample sizes. Few other combination therapies have been investigated in clinical trials. Two that have been (olanzapine plus mood stabilisers[76] and perphenazine plus mood stabilisers[80]) did not demonstrate increased efficacy over mood stabilisers alone. Hence the benefits of combination lithium therapy and other combination therapies are still to be investigated properly in bipolar disorder.

Currently, a large and simple randomised clinical trial (BALANCE) comparing a combination of lithium and valproate with lithium monotherapy and valproate monotherapy as maintenance treatment for bipolar disorders is under way.[113,114] This trial, conducted in the UK, France, Italy and the USA, will provide answers to the place of valproate and its combination with lithium in the armamentarium of treatments for the prevention of relapse in bipolar I patients.

The data revealed some differences in the efficacy of some drugs according to whether patients were categorised as suffering from bipolar I or bipolar II disorder. There was a suggestion (based on weak evidence) that lithium may be less effective in individuals with bipolar II than bipolar I disorder. Overall, the available data are not sufficient to

permit any reliable conclusions to be drawn regarding the relative efficacy of the different drugs for bipolar I and bipolar II disorder; further controlled trials are required. A new trial, BALANCE 2, comparing lamotrigine with SSRI antidepressants in bipolar II patients,[113] was proposed but has not progressed.

Results reported here are similar to the finding of two published Cochrane reviews evaluating lithium compared with placebo[4] and valproate compared with placebo or other active treatments[115] in the maintenance treatment of bipolar disorders. The synthesis of evidence reported in the recently published NICE guideline[29] did not disagree with our findings.

Mixed treatment comparison

Drawing together the evidence for a number of drugs from various comparisons is difficult. In order to make more explicit comparisons across all the treatments and to help identify which treatments can be recommended for maintenance treatment in bipolar disorder, we conducted an analysis of the trials using the method of MTC to make indirect comparisons between the treatments.

Concerns have been expressed over the use of indirect comparisons of treatments, believing that they are not randomised but are simply observational studies across trials. However, as summarised by Caldwell and colleagues,[34] there are suitable statistical methods for comparing multiple treatments that fully respect randomisation, that have been available for some time. MTC is such a method.[34]

To prevent all relapses, the standard analysis indicates that the following drugs have statistically significant benefit compared with placebo: lithium, valproate, lamotrigine, olanzapine and possibly imipramine plus lithium. Few comparisons have been made and only olanzapine appears better than lithium. The MTC indicates that if the predominant symptom is depressive, then valproate or lithium is the best treatment; if the predominant symptom is manic, then olanzapine is best.

From the standard analysis, to prevent manic relapses the following drugs that have statistically significant benefit compared with placebo are lithium and olanzapine, and olanzapine appears better than lithium. The MTC analysis indicates strongly the superiority of olanzapine.

From the standard analysis, to prevent depressive relapses the drugs that have statistically significant benefit compared with placebo are valproate, lamotrigine and imipramine. In contrast, the MTC tells us that lithium + imipramine appears best, followed by valproate, lamotrigine and imipramine. This difference between the two analyses has arisen because standard meta-analysis uses only direct comparisons whereas the MTC uses all trials to inform the results. Thus, for lithium + imipramine in the standard analysis the evidence for its efficacy compared with placebo is derived from only one very small study (n = 13). However, in the MTC all three trials of this drug are included and the result for lithium + imipramine versus placebo has 'borrowed strength' from the other larger trials.

Another important difference between the analyses is that the MTC main analysis is mostly relevant to bipolar I disorder. The sensitivity analysis that does include the bipolar II trials is not directly comparable with the standard meta-analysis because the sensitivity analysis also includes olanzapine responders, so although improving the presentation of drugs such as lamotrigine that appear to work better on depressive symptoms, it also improves the presentation of olanzapine.

The NICE guideline, however, made use of other types of research in patients with bipolar disorder to clarify issues related to adverse events with different drugs and suicide risks. Their final recommendations were not necessarily restricted to the systematic review findings, as they had tried to match their findings with current practice in the UK. As a result, they recommend as first-line maintenance treatment atypical antipsychotics, particularly olanzapine, and as second-line, valproate. Where monotherapy fails after 6 months, their recommendation was for a combination of at least two of lithium, valproate and olanzapine. Only if second-line combination therapy fails do they recommend the use of lamotrigine, particularly for those with bipolar II disorder. It should be noted that those recommendations differ from the findings of their own review and also from our findings.

Adverse effects

A major weakness of both analyses, but in particular of the MTC, is the failure to incorporate adverse effects of the treatments. Although our review and analyses have been thorough and exploratory in relation to the efficacy of the various treatments available for the maintenance treatment of bipolar disorder, they have not

generated much useful data regarding adverse effects. From the analyses of drop-out rates and adverse effects leading to discontinuation, it appears that lithium is less well tolerated than placebo or lamotrigine in terms of adverse events leading to discontinuation. However, more participants dropped out of placebo groups than lithium groups. Olanzapine does not appear to be well tolerated, with higher numbers of drop-outs than in both placebo and lithium groups, and higher numbers of adverse events leading to discontinuation than in placebo groups, despite all participants being previous responders to olanzapine. However, there were more drop-outs from mood stabilisers alone than mood stabilisers combined with olanzapine. Conversely, there were fewer drop-outs from the mood stabilisers and perphenazine combination group than there were from the mood stabilisers alone group. However, the data for drop-outs and adverse events leading to discontinuation were weak, and may not be reliable. For some comparisons, no adequate data were reported. Indirect comparisons cannot be made due to different follow-up periods, as it is likely that studies with longer lengths of follow-up will record more adverse events. Consequently, the decision to use these treatments, particularly olanzapine, should be made in the light of their problems with tolerability.

Suicide rates

It is of interest that our review failed to find any evidence of lower suicide rates associated with lithium. This association has been reported in the literature,[108] based on data from both patients with unipolar disorder and those with bipolar disorder. However, the lack of evidence in this review is probably due to the poor reporting of suicide data in the included studies. Whereas this review relied on published suicide data, Cipriani and colleagues[108] obtained additional data directly from study authors. Further investigation of the possible effects of lithium on suicide rate in bipolar patients is required. This has important implications for the results of the economic evaluation, where the assumption that lithium confers additional mortality benefits compared with other pharmacological treatments is central to the cost-effectiveness estimates.

Non-pharmacological management of bipolar disorder

We were unable to evaluate the psychosocial interventions for bipolar maintenance together with the pharmacological treatments because there was no overlap between investigations of their efficacy. The available trials investigated psychosocial interventions as adjunctive to standard pharmacological therapy. No trials of psychosocial interventions as monotherapy in comparison with placebo or pharmacological interventions were available.

In general, the studies investigating psychosocial interventions were small, and there were few data for each comparison and outcome, making it difficult to draw any firm conclusions. The evidence surrounding the use of CBT in bipolar disorder was greater than that of the other psychosocial interventions, and did suggest that CBT, in combination with usual treatment, is effective for the prevention of relapse. There was weaker evidence to suggest that group psychoeducation and possibly family therapy may also have roles as adjunctive therapy for preventing relapse. There was insufficient evidence to draw conclusions regarding the relative efficacy of the different psychosocial interventions. The few results for suicide, suicide attempts, adverse events and drop-outs made it impossible to draw firm conclusions about the role of psychosocial therapies in the maintenance treatment of bipolar disorder. An investigation of patient dropouts and the reasons for withdrawal from psychosocial interventions may prove useful, both in terms of guiding the future development of interventions and in identifying potential adverse effects.

Further good-quality studies are required. It appears that the beneficial effects of psychosocial interventions on relapse rates may come about through effects on medication compliance, earlier identification of prodromal symptoms or improvement in understanding of the disorder and the ability to cope. One of the CBT studies primarily targeted compliance,[44] but it was underpowered. Further research and a more detailed analysis of the different components of the psychosocial interventions would be helpful in determining which aspects of the interventions are most effective, and by which indirect routes they may have their effect. Trials to investigate if there is a role for CBT instead of drug treatment as there is in unipolar depression are also warranted.

Economic evaluation

Three published studies met the inclusion criteria for the cost-effectiveness review. The published studies were assessed and a new model was developed to address the limitations identified in these sources and to provide a comparison of a

more complete range of possible pharmacological strategies for long-term maintenance treatment that are relevant to the NHS. The model explored a range of uncertainties and sources of variability that were not fully addressed in existing data sources. A key source of variability that was addressed was the previous history of patients based on their most recent episode. There were marked differences between patients' subsequent risk of relapse (and the type of relapse) depending on whether their most recent acute episode was depressive or manic. Separate analyses were therefore undertaken to reflect this source of heterogeneity. The cost-effectiveness of the alternative treatments was demonstrated to be related to the previous episode history of patients.

An integral component of the model was the use of Bayesian approaches to synthesise effectiveness data for the simultaneous comparison of multiple treatments, combining direct head-to-head and indirect evidence relative to a common comparator in a single analysis. This approach allows consideration of the complete evidence base and facilitates a direct comparison of a broader range of treatment strategies compared with standard approaches.

The results of the economic model suggest that the cost-effectiveness of the alternative pharmacological treatments varies according to whether the patient has mainly depressive symptoms (Analysis 1) or manic symptoms (Analysis 2), according to their most recent acute episode. For patients with a recent depressive episode (and hence who were at higher risk of a subsequent acute depressive than a manic episode), four out of the seven strategies were ruled out on grounds of dominance. Of the remaining three strategies, valproate was the cheapest and least effective option. The cost-effectiveness of the remaining two strategies was then assessed. The ICER of lithium compared with valproate was estimated to be £10,409 per additional QALY. The ICER of the lithium + imipramine combination treatment compared with lithium monotherapy was £21,370 per additional QALY. For patients with a recent manic episode, olanzapine was demonstrated to dominate all of the strategies with the exception of lithium monotherapy. Lithium monotherapy was more costly and more effective than olanzapine with an associated ICER of £11,359 per additional QALY.

The base-case analysis demonstrated that lithium-based strategies for the long-term maintenance treatment of bipolar I disorder appeared cost-effective for patients with either a recent history of manic or depressive episodes. Sensitivity analyses were undertaken to assess the robustness of these conclusions for a range of scenarios. While the conclusions remained robust to a number of these sensitivity analyses, the cost-effectiveness estimates were shown to be sensitive to the assumption concerning the reduction of suicidal risk associated with lithium-based strategies applied in the base-case analyses. An alternative scenario in which it was assumed that lithium conferred the same mortality benefit as other pharmacological interventions led to different conclusions in the cost-effectiveness analysis. In Analysis 1, all strategies were dominated by valproate. In Analysis 2, all strategies were dominated by olanzapine. Consequently, the assumption that lithium confers additional mortality benefits compared with alternative pharmacological treatments appears central to the cost-effectiveness estimates. If lithium is not associated with any additional mortality benefits then the most cost-effective treatments for the management of patients with a recent depressive or manic acute episode appear to be valproate and olanzapine, respectively.

It is worth contrasting the results presented here with the cost-effectiveness estimates reported in the recent NICE guideline model[29] reviewed in detail in Chapter 5. In this model, no account was taken of the previous episode history for patients and hence a single set of results were presented for three subgroups (males, females with child-bearing potential and females without child-bearing potential). The no treatment/placebo strategy was dominated in all analyses. The incremental cost per QALY gained for valproate over lithium was £1725 for men and £1985 for women without child-bearing potential. The incremental cost per QALY gained for olanzapine over valproate was £5902 for men and women without child-bearing potential. Given that valproate was excluded in the analysis of women with child-bearing potential, only olanzapine and lithium were compared, and the incremental cost per QALY gained for olanzapine over lithium was £4805. The results provide strong support for olanzapine being the most cost-effective option in all subgroups.

There are a number of potential reasons for the disparity in the conclusions between the NICE guideline and our model. We have previously outlined some of the potential limitations of the evidence base considered in the NICE guideline

model. The use of Bayesian evidence synthesis methods allowed the consideration of a wider range of studies as our evidence base, permitted the comparison of more relevant therapeutic options (eight different pharmacological therapies for the maintenance of bipolar patients were compared) and enabled us to obtain efficacy estimates specific for both manic and depressive type of relapses. Consequently, the treatment effects considered in the two models are not directly comparable. In addition, by modelling variation based on previous episode history, our model enables separate cost-effectiveness estimates to be presented, as opposed to averaging across patients and presenting a single set of cost-effectiveness estimates. Finally, our results represent lifetime costs and benefits associated with all strategies instead of for a 5-year time horizon as estimated by the NICE model.

A feature of the NICE guideline model which was not considered in the model here is the impact of adverse effects on the QoL of patients. Sensitivity analysis undertaken as part of the NICE guideline highlighted that these differences are key drivers in the cost-effectiveness results. When patients on valproate were assumed to have the same QoL as patients with olanzapine, then valproate was demonstrated to dominate olanzapine in men and women without child-bearing potential. Our review highlighted a number of potential limitations of the data used to populate treatment specific utilities and the assumption that utility differences could be attributed to the adverse effects of the individual treatments. In this situation, the impact of treatment-specific adverse effects was not directly considered in our own analysis. Although this represents a potentially important limitation, it needs to be assessed against the potential bias which may be introduced using existing QoL studies which have considered adverse effects in this area. The lack of suitable data to populate this part of the model represents an important area of research which needs to be addressed in the future. It is clear that the adverse effects of the drugs will have different impacts on patients' QoL and may be important drivers in terms of cost-effectiveness.

We have previously discussed other potential weaknesses of the model and the data used to populate it. However, the analysis presented here represents the most comprehensive comparison of existing pharmacological treatments to date. The approach used allows a wider range of studies and comparators to be assessed compared with previous analyses in this area. The analysis conducted here also helps to reiterate the need for further research into the mortality benefits associated with lithium and other treatments and the impact of adverse effects on QoL.

Recommendations for research

Few data on the adverse effect profiles of the reviewed treatments were available from the clinical trial reports. Adverse effects information is available from a wide range of sources, but the collation of it was beyond the remit of this review. A comprehensive review of the adverse effects profiles of all treatments is required to inform decisions properly about their relative effectiveness and clinical use. The results of such a study should then be incorporated into the economic evaluation of the treatments for bipolar disorder. Where evidence is weak, further research should be conducted into the potential longer term effects of drugs on cognition and mortality and the impact of adverse effects on QoL.

Uncertainty about the best treatments for the long-term prevention of depressive relapse in bipolar patients still remains. The results of the review suggest that a combination of lithium with an antidepressant may be most effective. A trial of a combination of lithium plus an SSRI antidepressant is warranted.

Further investigation of the differential effects in bipolar I and bipolar II disorder and in rapid cycling is warranted. For some drugs this may involve an individual patient data analysis of existing trials, whereas for less studied drugs further primary studies are needed.

Good-quality trials of valproate are required.

Further trials of group therapy and family therapy as adjuncts to pharmacological maintenance treatments are also warranted, as are better and larger trials of CBT. Studies of psychosocial interventions in bipolar disorder should investigate adverse effects in addition to efficacy.

Further investigation of the effects of treatments on suicide rates is required.

Good-quality trials in children are required.

It is very important that future trials should be good-quality RCTs, involving an adequate number of participants, and have sufficient duration of follow-up.

With so much research possible, work of this kind should be conducted via a properly resourced trial network.

Relevance to the NHS

Implications for clinical practice in the NHS

We have conducted an up-to-date review of the available evidence for interventions to improve long-term outcome for people with bipolar disorder. Our synthesis of the evidence deployed the best currently available methods for making optimal use of the research evidence and provides the soundest yet basis for evidence-based clinical decision-making.

One specific finding has emerged from the analysis that is particularly striking: the polarity of the most recent episode is a useful way of guiding therapy for patients, probably because it is a good proxy of the predominant symptomatology in any single patient. The clinical literature has recently highlighted the importance of the nature of index episode in addition to other baseline clinical characteristics such as rapid cycling and gender. However, such conclusions have not usually been based on high-quality evidence. The current analysis has formally quantified some of these clinically important issues in terms of both efficacy and effectiveness. This is a step towards a tailored, evidence-based approach to therapy for people with bipolar disorder.

Implications for NHS policy

Our findings are reasonably consistent with the recommendations in the recent NICE clinical practice guideline for people with bipolar disorder.[29] The NICE guideline has a much broader scope than our review, dealing with acute phase therapy and general issues of service provision in addition to long-term therapy. Nonetheless, our findings on long-term therapies in bipolar disorder go beyond the NICE guideline, relate directly to the evidence rather than relying on clinical impression and provide a sounder basis to underpin decisions about individualising therapy. Our analysis demonstrates the importance of a concentrated synthesis of the evidence in a specific phase of an illness in order to make the most of limited available high-quality evidence.

The publication of the NICE guideline in advance of our report may hinder the implementation of our research recommendations.

Implications for research in the NHS

It is known that many people with bipolar disorder have co-morbid conditions such as anxiety and alcohol and drug misuse. Most of the trials included in this review excluded patients with significant co-morbidities and this limits the confidence with which we can extrapolate the results to real-life clinical practice. In general, co-morbidities reduce the effectiveness of treatments and this must be borne in mind when interpreting the estimates of clinical effectiveness and cost-effectiveness. Future trials need to include more representative samples of patients so that their results can be applied more confidently. This is an example of a general limitation of the research in the area of long-term treatments in bipolar disorder in which most research is targeted at assessment of basic efficacy selected patients who are likely to show optimal outcomes. These trials are largely conducted by the pharmaceutical industry for the purpose of satisfying the needs of regulatory authorities. It is to be hoped that the national research initiatives such as the creation of the UK Clinical Research Network and related policies outlined in *Best research for best health* (Department of Health, 2006)[116] and recommended by the recent Cooksey report[117] will facilitate the efficient conduct of high-quality NHS-based research that addresses the real health priorities of people with bipolar disorder.

This review has also identified that there is a very limited evidence base for the treatment of people with bipolar disorder and this is particularly apparent for patients with bipolar II disorder and for the long-term prevention of bipolar depression. The paucity of high-quality evidence means that there are substantial uncertainties about the most cost-effective and safe therapeutic strategies for preventing depressive relapses in bipolar disorder. The only long-term RCT evidence for continued acute phase treatment is for imipramine, a drug that is no longer considered to have an acceptable balance of risks and benefits for first-line acute phase therapy of bipolar depression and is not recommended in the recent NICE guideline.[29] For many years, the development of pharmaceuticals by industry in the field of mental health has been driven by the markets of unipolar depressive disorder and schizophrenia, and bipolar disorder has been relatively neglected.[118] Although there are signs that this is now changing, that this situation occurred is a clear demonstration of the importance of partnership with the pharmaceutical industry to identify priority areas for development of drug treatments, as identified in the Cooksey report.[117]

Chapter 8
Conclusions

There is evidence from placebo-controlled trials of the efficacy of lithium, valproate, lamotrigine and olanzapine as maintenance therapy for the prevention of relapse in bipolar disorder. For the prevention of manic relapses, olanzapine and lithium are efficacious. For the prevention of depressive relapse, valproate, lamotrigine and imipramine are efficacious.

Despite widespread use in clinical practice, there is no randomised trial evidence for the efficacy of combination therapy.

The results of the MTC indicated that carbamazepine is not an effective maintenance treatment for bipolar I disorder. The MTC also indicated that in patients with mainly depressive symptoms, the lowest probability of relapse is achieved with valproate, lithium plus imipramine, lithium monotherapy and lamotrigine. If the main focus of treatment in these patients is the prevention of depression, then lithium plus imipramine appears to be the best therapy, followed by imipramine. This analysis also found that in patients with mainly manic symptoms the lowest probability of relapse is achieved with olanzapine, followed by valproate and lithium. If the main focus of treatment in these patients is the prevention of manic relapses, then the results of the analysis indicate that olanzapine is the best therapy

The review revealed that psychosocial therapies have not been investigated thoroughly. There is some evidence that CBT, group psychoeducation and family therapy might be beneficial as adjuncts to pharmacological maintenance treatments.

Insufficient information regarding adverse effects and drop-out rates was available to permit any meaningful assessment of the relative tolerability of the treatments reviewed. Similarly, no assessment of the relative effects of the treatment on suicide rate and mortality could be made.

The cost-effectiveness of the alternative treatments was demonstrated to be related to the previous episode history of the patients (i.e. whether their pretrial most recent acute episode was manic or depressive). For patients with a recent depressive episode, four out of the seven strategies were ruled out on grounds of dominance, and the cost-effectiveness of the remaining strategies was then assessed: the ICER of lithium compared with valproate was estimated to be £10,409 per additional QALY and the ICER of the combination treatment compared with lithium monotherapy was £21,370 per additional QALY. For patients with a recent manic episode, olanzapine was demonstrated to dominate all of the strategies with the exception of lithium monotherapy. Lithium monotherapy was more costly and more effective than olanzapine, with an associated ICER of £11,359 per additional QALY.

The cost-effectiveness estimates were also shown to be sensitive to the assumption concerning the reduction of suicidal risk associated with lithium-based strategies. An alternative scenario in which it was assumed that lithium conferred the same mortality benefit of other pharmacological interventions led to different conclusions: for patients with a previous history of depression, all strategies were dominated by valproate; for patients with a previous history of mania, all strategies were dominated by olanzapine.

Summarising across all three analyses included in this review (standard meta-analyses, MTC and economic evaluation), the following conclusions can be drawn. For bipolar patients with predominantly depressive symptoms, the treatments of choice will be lithium, valproate or lamotrigine or a combination of lithium with an antidepressant. For bipolar patients with predominantly symptoms of mania, lithium and olanzapine are to be preferred. These conclusions are limited, however, by the failure of any analysis to incorporate fully data on adverse effects.

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Contribution of authors

Karla Soares-Weiser (Visiting Research Fellow) was the lead reviewer and was responsible for writing the protocol, and contributed to all aspects of the clinical evaluation and report writing. Yolanda Bravo Vergel (Research Fellow) was responsible for the mixed treatment comparison analysis and contributed to the development of the economic model, the protocol and report writing. Suzanne Beynon (Research Fellow) contributed to all aspects of the clinical evaluation and report writing. Gemma Dunn (Research Fellow) was responsible for the development of the economic model and contributed to the mixed treatment comparison analysis and report writing. Marco Barbieri (Research Fellow) contributed to all aspects of the economic evaluation sections of the report and report writing. Steven Duffy (Information Officer) devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. John Geddes (Professor of Epidemiological Psychiatry) provided input at all stages, contributed to the protocol, commented on various drafts of the report and contributed to the discussion section of the report. Simon Gilbody (Senior Lecturer in Mental Health Services Research) provided clinical advice and input at all stages, commented on various drafts of the report and contributed to the development of the economic model. Stephen Palmer (Senior Research Fellow) provided input at all stages, commented on various drafts of the report and had overall responsibility for the economic evaluation sections of the report. Nerys Woolacott (Senior Research Fellow) contributed to all aspects of the clinical and economic evaluation and report writing and had overall responsibility for the clinical evaluation sections of the report and project coordination.

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Appendix 1

Literature search strategy

Randomised controlled trials: search strategies, dates and results

MEDLINE and PreMEDLINE (OVID gateway), 1966–2005/August week 4, 5 September 2005

The MEDLINE and PreMEDLINE databases were searched on 5 September 2005 and identified 5040 records in MEDLINE and 88 in PreMEDLINE.

1. randomized-controlled-trial.pt.
2. controlled-clinical-trial.pt.
3. randomized-controlled-trials/
4. RANDOM ALLOCATION/
5. DOUBLE-BLIND METHOD/
6. SINGLE-BLIND METHOD/
7. clinical trial.pt.
8. CONTROLLED CLINICAL TRIALS/
9. CLINICAL TRIALS/
10. CLINICAL TRIALS, PHASE III/
11. CLINICAL TRIALS, PHASE IV/
12. MULTICENTER STUDIES/
13. Evaluation Studies/
14. Drug Evaluation/
15. exp PRODUCT SURVEILLANCE, POSTMARKETING/
16. (clin$ adj3 trial$).ti,ab.
17. ((singl$ or doubl$ or tripl$ or trebl$) adj3 (mask$ or blind$)).ti,ab.
18. Placebos/
19. placebo$.ti,ab.
20. random$.ti,ab.
21. RESEARCH DESIGN/
22. (control$ adj3 (trial$ or stud$)).ti,ab.
23. crossover.ti,ab.
24. Comparative Study/
25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. Animal/
27. Human/
28. 26 not (26 and 27)
29. 25 not 28
30. exp Bipolar Disorder/
31. (bipolar$ adj3 disorder$).ti,ab.
32. (bipolar$ adj3 depress$).ti,ab.
33. (bipolar$ adj3 illness$).ti,ab.
34. (bipolar$ adj3 disease$).ti,ab.
35. (bipolar$ adj3 episod$).ti,ab.
36. mania.ti,ab.
37. manic.ti,ab.
38. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
39. cyclothym$.ti,ab.
40. or/30-39
41. 29 and 40

EMBASE (OVID gateway), 1980–2005/week 36, 5 September 2005

The EMBASE database was searched on 5 September 2005 and identified 7087 records.

1. Randomized Controlled Trial/
2. RANDOMIZATION/
3. Double Blind Procedure/
4. Single Blind Procedure/
5. random$ control$ trial$.ti,ab.
6. (clin$ adj3 trial$).ti,ab.
7. exp clinical trial/
8. exp controlled study/
9. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
10. placebo$.ti,ab.
11. PLACEBO/
12. EVALUATION/
13. Follow Up/
14. Prospective Study/
15. (control$ or prospective$ or volunteer$).ti,ab.
16. random$.ti,ab.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. editorial.pt.
19. note.pt.
20. 18 or 19
21. (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).ti,ab,sh.
22. exp animal/
23. Nonhuman/
24. exp human/
25. 21 or 22 or 23
26. 25 not (25 and 24)
27. 17 not (20 or 26)
28. exp Bipolar Disorder/
29. (bipolar$ adj3 disorder$).ti,ab.
30. (bipolar$ adj3 depress$).ti,ab.

31. (bipolar$ adj3 illness$).ti,ab.
32. (bipolar$ adj3 disease$).ti,ab.
33. (bipolar$ adj3 episod$).ti,ab.
34. mania.ti,ab.
35. manic.ti,ab.
36. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
37. cyclothym$.ti,ab.
38. or/28-37
39. 27 and 38

CINAHL (OVID gateway), 1982–2005/August week 4, 7 September 2005

The CINAHL database was searched on 7 September 2005 and identified 289 records.

1. exp Clinical Trials/
2. CLINICAL TRIAL.pt.
3. exp Random Sample/
4. (clin$ adj3 trial$).ti,ab.
5. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
6. PLACEBOS/
7. placebo$.ti,ab.
8. random$.ti,ab.
9. exp Study Design/
10. exp Evaluation Research/
11. exp Prospective Studies/
12. (control$ or prospectiv$ or volunteer$).ti,ab.
13. or/1-12
14. Bipolar Disorder/
15. (bipolar$ adj3 disorder$).ti,ab.
16. (bipolar$ adj3 depress$).ti,ab.
17. (bipolar$ adj3 illness$).ti,ab.
18. (bipolar$ adj3 disease$).ti,ab.
19. (bipolar$ adj3 episod$).ti,ab.
20. mania.ti,ab.
21. manic.ti,ab.
22. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
23. cyclothym$.ti,ab.
24. or/14-23
25. 13 and 24

BIOSIS (Edina), 1985–2005/08, 8 September 2005

The BIOSIS database was searched on 8 September 2005 and identified 1061 records.

al:(bipolar* n3 disorder*) or (bipolar* n3 depress*) or (bipolar n3 illness*) or (bipolar* n3 disease*) or (bipolar* n3 episod*)
al:(mania or manic)
al:(hypomanic or hypo-manic or hypomania or hypo-mania)
al: cyclothym*
#1 or #2 or #3 or #4
al:(clinical w2 trial*)
al:(controlled w2 trial*) or (controlled w2 stud*)
al:(random or randomi*ation)
al:(singl* w2 mask*) or (singl* w2 blind*) or (doubl* w2 mask*) or (doubl* w2 blind*) or (tripl* w2 mask*) or (tripl* w2 blind*) or (trebl* w2 mask*) or (trebl* w2 blind*)
al:(placebo* or crossover or evaluation)
al:(prospective w2 stud*) or (comparative w2 stud*)
al:(phase w 4) or (phase w four) or (phase w IV)
al:(post w market* w surveillance)
#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#5 and #14

PsycINFO (Ovid gateway), 1872–2005/08, 8 September 2005

The PsycINFO database was searched on 8 September 2005 and identified 1575 records.

1. exp Clinical Trials/
2. exp PLACEBO/
3. (clin$ adj3 trial$).ti,ab.
4. ((singl$ or doubl$ or tripl$ or trebl$) adj3 (mask$ or blind$)).ti,ab.
5. placebo$.ti,ab.
6. random$.ti,ab.
7. (control$ adj3 (trial$ or stud$)).ti,ab.
8. crossover.ti,ab.
9. or/1-8
10. exp Bipolar Disorder/
11. exp mania/
12. (bipolar$ adj3 disorder$).ti,ab.
13. (bipolar$ adj3 depress$).ti,ab.
14. (bipolar$ adj3 illness$).ti,ab.
15. (bipolar$ adj3 disease$).ti,ab.
16. (bipolar$ adj3 episod$).ti,ab.
17. mania.ti,ab.
18. manic.ti,ab.
19. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
20. cyclothym$.ti,ab.
21. or/10-20
22. 9 and 21

Science Citation Index (SCI) (Web of Science), 1900–2005/August week 4, 8 September 2005

The SCI database was searched on 8 September 2005 and identified 2041 records.

TS=(clinical* SAME trial*)
TS=(controlled SAME trial*) OR TS=(controlled SAME stud*)
TS=(random OR randomisation OR randomization OR randomized or randomised)

TS=(singl* or doubl* or tripl* or trebl*) SAME
TS=(mask* or blind*)
TS=placebo*
TS=crossover
TS=evaluation
TS=(prospective SAME stud*) or
TS=(comparative SAME stud*)
TS=(phase 4) or TS=(phase four) or TS=(phase IV)
TS=(post market* surveillance)
#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
TS=(bipolar*) SAME TS=(disorder*)
TS=(bipolar*) SAME TS=(depress*)
TS=(bipolar*) SAME TS=(illness*)
TS=(bipolar*) SAME TS=(disease*)
TS=(bipolar*) SAME TS=(episode*)
TS=(mania)
TS=(manic)
TS=(hypomanic or hypo-manic or hypomania or hypo-mania)
TS=(cyclothym*)
#20 or #19 or #18 or #17 or #16 OR #15 OR #14 OR #13 OR #12
#11 and #21

CENTRAL (Cochrane Library/Wiley), 2005:3, 8 September 2005

The CENTRAL database was searched on 8 September 2005 and identified 1552 records.

Bipolar Disorder (MeSH)
bipolar* NEAR/3 disorder*
bipolar* NEAR/3 depress*
bipolar* NEAR/3 illness*
bipolar* NEAR/3 disease*
bipolar* NEAR/3 episod*
mania
manic
(hypomanic or hypo-manic or hypomania or hypo-mania)
cyclothym*
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

LILACS (BVS Virtual Health Library), 1982–2005/08, 8 September 2005

The LILACS database was searched on 8 September 2005 and identified 32 records.

(clinical$ trial$) or (controlled trial$) or (controlled stud$) or random OR randomisation OR randomization OR randomized or randomized or (singl$ blind$) or (singl$ mask$) or (doubl$ blind$) or (doubl$ mask$) or (tripl$ blind$) or (tripl$ mask$) or (trebl$ blind$) or (trebl$ mask$) or placebo$ or crossover or evaluation or (prospective stud$) or (comparative stud$) or (phase 4) or (phase four) or (phase IV) or (post market$ surveillance)[words]

AND

bipolar$ or mania or manic or hypomanic or hypo-manic or hypomania or hypo-mania or cyclothym$ [words]

ISI Proceedings: Science and Technology (ISI Proceedings), 1990–2005/September 16, 19 September 2005

The ISI Proceedings: Science and Technology database was searched on 19 September 2005 and identified 402 records.

TS=(clinical* SAME trial*)
TS=(controlled SAME trial*) OR TS=(controlled SAME stud*)
TS=(random OR randomisation OR randomization OR randomized or randomised)
TS=(singl* or doubl* or tripl* or trebl*) SAME
TS=(mask* or blind*)
TS=placebo*
TS=crossover
TS=evaluation
TS=(prospective SAME stud*) or
TS=(comparative SAME stud*)
TS=(phase 4) or TS=(phase four) or TS=(phase IV)
TS=(post market* surveillance)
#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
TS=(bipolar*) SAME TS=(disorder*)
TS=(bipolar*) SAME TS=(depress*)
TS=(bipolar*) SAME TS=(illness*)
TS=(bipolar*) SAME TS=(disease*)
TS=(bipolar*) SAME TS=(episode*)
TS=(mania)
TS=(manic)
TS=(hypomanic or hypo-manic or hypomania or hypo-mania)
TS=(cyclothym*)
#20 or #19 or #18 or #17 or #16 OR #15 OR #14 OR #13 OR #12
#11 and #21

Inside Conferences (DIALOG), 1993–2005/September week 3, 19 September 2005

The Inside Conferences database was searched on 19 September 2005 and identified 78 records.

s bipolar?(3n)disorder?

s bipolar?(3n)depress?
s bipolar?(3n)illness?
s bipolar?(3n)disease?
s bipolar?(3n)episode?
s mania or manic
s hypomanic or hypo(w)manic or hypomania or hypo(w)mania
s cyclothym?
s s1:s8
s clinical(2w)trial?
s controlled(2w)(trial? or stud?)
s random or randomi?ation or randomi?ed
s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
s placebo?
s crossover
s evaluation
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s follow(w)up
s s10:s20
s s9 and s21

National Research Register (NRR) (Update Software Internet), 2005:3, 19 September 2005

The NRR database was searched on 19 September 2005 and identified 335 records.

Bipolar Disorder (MeSH)
bipolar* disorder*
bipolar* depress*
bipolar* illness*
bipolar* disease*
bipolar* episod*
mania
manic
(hypomanic or hypo-manic or hypomania or hypo-mania)
cyclothym*
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

National Technical Information Service (NTIS) (US Department of Commerce website), 1990–2005/September, 19 September 2005

The NTIS database was searched on 19 September 2005 and identified nine records.

"bipolar disorder" or "bipolar depression" or "bipolar illness" or "bipolar disease" or "bipolar episode" or mania or manic or hypomanic or hypo-manic or hypomania or hypo-mania or cyclothymic

Economic evaluations: search strategies, dates and results

NHS Economic Evaluation Database (NHS EED) (CRD internal databases), 1995–2005/08, 15 September 2005

The NHS EED administration database was searched on 15 September 2005 and identified 91 records. The NHS EED public database was also searched on 15 September 2005 and identified 51 records.

s (bipolar$(w3)disorder$)
s (bipolar$(w3)depress$)
s (bipolar$(w3)illness$)
s (bipolar$(w3)disease$)
s (bipolar$(w3)episod$)
s mania
s manic
s (hypomanic or hypo(w)manic or hypomania or hypo(w)mania)
s cyclothym$
s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9

Health Economic Evaluation Database (HEED) (Office of Health Economics CD-ROM), 2005/09, 15 September 2005

The HEED database was searched on 15 September 2005 and identified 74 records.

AX=(bipolar disorder) or (bipolar disorders) or (bipolar depression) or (bipolar depressive) or (bipolar illness) or (bipolar illnesses) or (bipolar disease) or (bipolar diseases) or (bipolar episode) or (bipolar episodes)
AX=mania or manic
AX=hypomanic or hypo-manic or hypomania or hypo-mania
AX=cyclothymic
CS=1 or 2 or 3 or 4

MEDLINE and PreMEDLINE (OVID gateway), 1966–2005/September week 1, 15 September 2005

The MEDLINE and PreMEDLINE databases were searched on 15 September 2005 and identified 370 records in MEDLINE and 11 in PreMEDLINE.

1. economics/
2. exp "costs and cost analysis"/
3. economics, dental/
4. exp "economics, hospital"/
5. economics, medical/
6. economics, nursing/

7. economics, pharmaceutical/
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
9. (expenditure$ not energy).ti,ab.
10. (value adj1 money).ti,ab.
11. budget$.ti,ab.
12. or/1-11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13-15
17. 12 not 16
18. exp Bipolar Disorder/
19. (bipolar$ adj3 disorder$).ti,ab.
20. (bipolar$ adj3 depress$).ti,ab.
21. (bipolar$ adj3 illness$).ti,ab.
22. (bipolar$ adj3 disease$).ti,ab.
23. (bipolar$ adj3 episod$).ti,ab.
24. mania.ti,ab.
25. manic.ti,ab.
26. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
27. cyclothym$.ti,ab.
28. or/18-27
29. 17 and 28

EMBASE (OVID gateway), 1980–2005/week 37, 15 September 2005

The EMBASE database was searched on 15 September 2005 and identified 473 records.

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. exp PHARMACOECONOMICS/
5. or/1-4
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7. (expenditure$ not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget$.ti,ab.
10. or/6-9
11. 5 or 10
12. (metabolic adj cost).ti,ab.
13. ((energy or oxygen) adj cost).ti,ab.
14. ((energy or oxygen) adj expenditure).ti,ab.
15. or/12-14
16. 11 not 15
17. editorial.pt.
18. note.pt.
19. letter.pt.
20. or/17-19
21. 16 not 20
22. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
23. exp animal/
24. Nonhuman/
25. or/22-24
26. exp human/
27. exp human experiment/
28. 26 or 27
29. 25 not (25 and 28)
30. 21 not 29
31. PLACEBO/
32. exp Bipolar Disorder/
33. (bipolar$ adj3 disorder$).ti,ab.
34. (bipolar$ adj3 depress$).ti,ab.
35. (bipolar$ adj3 illness$).ti,ab.
36. (bipolar$ adj3 disease$).ti,ab.
37. (bipolar$ adj3 episod$).ti,ab.
38. mania.ti,ab.
39. manic.ti,ab.
40. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
41. cyclothym$.ti,ab.
42. or/32-41
43. 30 and 42

CINAHL (OVID gateway), 1982–2005/September week 2, 15 September 2005

The CINAHL database was searched on 15 September 2005 and identified 33 records.

1. exp "costs and cost analysis"/ or "economic aspects of illness"/ or "economic value of life"/ or economics, pharmaceutical/
2. ((cost or costs or costed or costly or costing) adj (utilit$ or benefit$ or effective$ or stud$ or minimi$ or analys$)).ti,ab.
3. (economic$ or pharmacoeconomic$ or price$ or pricing).ti,ab.
4. (expenditure$ not energy).ti,ab.
5. (value adj1 money).ti,ab.
6. budget$.ti,ab.
7. or/1-6
8. Bipolar Disorder/
9. (bipolar$ adj3 disorder$).ti,ab.
10. (bipolar$ adj3 depress$).ti,ab.
11. (bipolar$ adj3 illness$).ti,ab.
12. (bipolar$ adj3 disease$).ti,ab.
13. (bipolar$ adj3 episod$).ti,ab.
14. mania.ti,ab.
15. manic.ti,ab.
16. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
17. cyclothym$.ti,ab.
18. or/8-17
19. 7 and 18

BIOSIS (Edina), 1985–2005/08, 15 September 2005

The BIOSIS database was searched on 15 September 2005 and identified 98 records.

al:(bipolar* n3 disorder*) or (bipolar* n3 depress*) or (bipolar n3 illness*) or (bipolar* n3 disease*) or (bipolar* n3 episod*)
al:(mania or manic)
al:(hypomanic or hypo-manic or hypomania or hypo-mania)
al:cyclothym*
#1 or #2 or #3 or #4
al:(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
al:(expenditure* not energy)
al:(value n1 money)
al:budget*
#6 or #7 or #8 or #9
#5 and #10

PsycINFO (Ovid gateway), 1872–2005/08, 15 September 2005

The PsycINFO database was searched on 15 September 2005 and identified 250 records.

1. economics/
2. "costs and cost analysis"/
3. budgets/ or health care costs/
4. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
5. (expenditure$ not energy).ti,ab.
6. (value adj1 money).ti,ab.
7. budget$.ti,ab.
8. or/1-7
9. exp Bipolar Disorder/
10. exp mania/
11. (bipolar$ adj3 disorder$).ti,ab.
12. (bipolar$ adj3 depress$).ti,ab.
13. (bipolar$ adj3 illness$).ti,ab.
14. (bipolar$ adj3 disease$).ti,ab.
15. (bipolar$ adj3 episod$).ti,ab.
16. mania.ti,ab.
17. manic.ti,ab.
18. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
19. cyclothym$.ti,ab.
20. or/9-19
21. 8 and 20

Science Citation Index (SCI) (Web of Science), 1900–2005/September week 1, 15 September 2005

The SCI database was searched on 15 September 2005 and identified 240 records.

TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
TS=(expenditure* not energy)
TS=(value SAME money)
TS=(budget*)
#1 OR #2 OR #3 OR #4
TS=(bipolar*) SAME TS=(disorder*)
TS=(bipolar*) SAME TS=(depress*)
TS=(bipolar*) SAME TS=(illness*)
TS=(bipolar*) SAME TS=(disease*)
TS=(bipolar*) SAME TS=(episode*)
TS=(mania)
TS=(manic)
TS=(hypomanic or hypo-manic or hypomania or hypo-mania)
TS=(cyclothym*)
#6 or #7 or #8 or #9 or #10 OR #11 OR #12 OR #13 OR #14
#5 and #15

CENTRAL (Cochrane Library/Wiley), 2005:3, 15 September 2005

The CENTRAL database was searched on 15 September 2005 and identified 38 records.

Bipolar Disorder (MeSH)
bipolar* NEAR/3 disorder*
bipolar* NEAR/3 depress*
bipolar* NEAR/3 illness*
bipolar* NEAR/3 disease*
bipolar* NEAR/3 episod*
mania
manic
(hypomanic or hypo-manic or hypomania or hypo-mania)
cyclothym*
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
Economics (MeSH)
exp Cost and Cost Analysis (MeSH)
Economics, Dental (MeSH)
exp economics, Hospital (MeSH)
Economics, Medical (MeSH)
Economics, Nursing (MeSH)
Economics, Pharmaceutical (MeSH)
(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
(expenditure* not energy)
(value NEAR/3 money)
budget*
#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#11 and #23

LILACS (BVS Virtual Health Library), 1982–2005/08, 16 September 2005

The LILACS database was searched on 16 September 2005 and identified eight records.

economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or budget$ [words]

AND

bipolar$ or mania or manic or hypomanic or hypo-manic or hypomania or hypo-mania or cyclothym$ [words]

ISI Proceedings: Science and Technology (ISI Proceedings), 1990–2005/September 16, 19 September 2005

The ISI Proceedings: Science and Technology database was searched on 19 September 2005 and identified 51 records.

TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
TS=(expenditure* not energy)
TS=(value SAME money)
TS=(budget*)
#1 OR #2 OR #3 OR #4
TS=(bipolar*) SAME TS=(disorder*)
TS=(bipolar*) SAME TS=(depress*)
TS=(bipolar*) SAME TS=(illness*)
TS=(bipolar*) SAME TS=(disease*)
TS=(bipolar*) SAME TS=(episode*)
TS=(mania)
TS=(manic)
TS=(hypomanic or hypo-manic or hypomania or hypo-mania)
TS=(cyclothym*)
#6 or #7 or #8 or #9 or #10 OR #11 OR #12 OR #13 OR #14
#5 and #15

Inside Conferences (DIALOG), 1993–2005/September week 3, 19 September 2005

The Inside Conferences database was searched on 19 September 2005 and identified 11 records.

s bipolar?(3n)disorder?
s bipolar?(3n)depress?
s bipolar?(3n)illness?
s bipolar?(3n)disease?
s bipolar?(3n)episode?
s mania or manic
s hypomanic or hypo(w)manic or hypomania or hypo(w)mania
s cyclothym?
s s1:s8
s economic or economics or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic or pharmacoeconomics
s expenditure? not energy
s budget?
s value(w)money
s s10:s13
s s9 and s14

National Technical Information Service (NTIS) (US Department of Commerce website), 1990–2005/September, 19 September 2005

The NTIS database was searched on 19 September 2005 and identified four records.

("bipolar disorder" or "bipolar depression" or "bipolar illness" or "bipolar disease" or "bipolar episode" or mania or manic or hypomanic or hypo-manic or hypomania or hypo-mania or cyclothymic) AND (economic or economics or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic or pharmacoeconomics)

IDEAS, Research Papers in Economics (RePEC) database (Internet), 2005/September, 19 September 2005

The IDEAS database was searched on 19 September 2005 and identified no records.

Each line searched separately

bipolar disorder*
bipolar depress*
bipolar illness*
bipolar disease*
bipolar episode*
mania
manic

National Research Register (NRR) (Update Software Internet), 2005:3, 19 September 2005

The NRR database was searched on 19 September 2005 and identified 24 records.

Bipolar Disorder (MeSH)
bipolar* disorder*
bipolar* depress*
bipolar* illness*
bipolar* disease*
bipolar* episod*

mania
manic
(hypomanic or hypo-manic or hypomania or hypo-mania)
cyclothym*
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
Economics (MeSH)
exp Cost and Cost Analysis (MeSH)
Economics, Dental (MeSH)
exp economics, Hospital (MeSH)
Economics, Medical (MeSH)
Economics, Nursing (MeSH)
Economics, Pharmaceutical (MeSH)
(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
(expenditure* not energy)
(value NEAR money)
budget*
#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#11 and #23

Additional searches were carried out for the economic model. Utility searches were carried out in MEDLINE, EMBASE, CINAHL, CENTRAL and PsycINFO from inception to date on 10 March 2006.

MEDLINE search strategy

1. exp Bipolar Disorder/
2. (bipolar$ adj3 disorder$).ti,ab.
3. (bipolar$ adj3 depress$).ti,ab.
4. (bipolar$ adj3 illness$).ti,ab.
5. (bipolar$ adj3 disease$).ti,ab.
6. (bipolar$ adj3 episod$).ti,ab.
7. mania.ti,ab.
8. manic.ti,ab.
9. (hypomanic or hypo-manic or hypomania or hypo-mania).ti,ab.
10. cyclothym$.ti,ab.
11. or/1-10
12. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
13. (multiattribute$ health or multi attribute$ health).ti,ab.
14. (health utilit$ index or health utilit$ indices).ti,ab.
15. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
16. (health utilit$ scale$ or classification of illness state$).ti,ab.
17. health state$ utilit$.ti,ab.
18. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
19. health utilit$ scale$.ti,ab.
20. (euro qual or eruo qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
21. (sf36 or sf 36).ti,ab.
22. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
23. (sf 6d or sf6d or short form 6d or shortform 6d or sf six$ or shortform six$ or short form six$).ti,ab.
24. hrqol.ti,ab.
25. hrql.ti,ab.
26. (health related quality adj2 life$).ti,ab.
27. or/12-26
28. 11 and 27

Appendix 2

Quality assessment tool

Studies of clinical effectiveness were assessed using the following criteria, based on CRD Report No.4.[30]

1. Was the assignment to the treatment groups made randomly?
2. Was sequence generation adequate?
   Adequate = computer-generated random numbers or random number tables. Inadequate = alternation, case record numbers, birthdays, weekdays, etc.
3. Was the treatment allocation concealed?
4. Was concealment of allocation adequate?
   Adequate = e.g. centralised or pharmacy controlled, serially numbered identical containers. Inadequate = e.g. use of alternation, case record numbers, open random numbers lists.
5. Were the groups similar at baseline in terms of prognostic factors?
6. Were the eligibility criteria specified?
7. Were outcome assessors blinded to the treatment allocation?
8. Was the care provider blinded?
9. Was the patient blinded?
10. Were the point estimates and measure of variability presented for the primary outcome measure?
11. Did the analyses include an ITT analysis?
12. Was a sample size calculation reported?

Each criterion was rated as yes, no or unclear, with the exception of questions 2 and 4, which were rated as adequate, inadequate or unclear.

Appendix 3

Studies that could not be obtained

Alimova RA. Peculiarities of the psychopathological clinical picture in treatment of depressions in late age. *Trudy Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta* 1988:81–7.

Baker RW, Kinon B, Liu H, Schuh L, Bergstrom R, Hill A. Rapid initial dose escalation of oral olanzapine for acute agitation. Presented at the XIIth World Congress of Psychiatry, 24–29 August 2002, Yokohama.

Bunney WE. Studies of L-Dopa, L-tryptophan, and alpha-methyl-*para*-tyroslne in affective disorders. Presented at the V World Congress of Psychiatry, 28 November–4 December 1971, Ciudad de Mexico.

Carman JS. Double-blind parallel comparison of citalopram, imipramine and placebo in patients with major depression or bipolar disorder, depressed. Unpublished work, 2002.

Carrillo C. Pharmacological treatment of the emotionally unstable character disorder. Presented at the V World Congress of Psychiatry, 28 November–4 December 1971, Ciudad de Mexico.

Citeline Intelligence Solutions. *Bipolar disorder: expanding acute treatments for use in maintenance therapy*. Petaluma, CA: Citeline Intelligence Solutions; 2004.

Coleman BS, Doogan DP. Medical report on a double-blind comparative study of fluvoxamine and chlorimipramine in institutionalized patients with bipolar and unipolar depression. Unpublished work, 1981.

Crammer JL. The use of lithium in mania. *Compr Ther* 1975;**1**(3):74–8.

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continued

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Appendix 5

Summary of included studies

Study characteristics

Study	Age	N	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Altamura, 2003[37]	Mainly adults	28	57.00			Yes	Bipolar I and II	Mania + depression		Quetiapine: 157.7 (SD 157.6) mg/day	Mood stabilisers		
Altamura, 2004[38]	Mainly adults	23	50.00			Yes	Bipolar I and II	Mania + depression		Valproate: final: 415 ± 16.39 mg (62.7 ± 19.5 μg/ml)	Olanzapine: final: 9 ± 3.2 mg		
Bowden, 2000[39]	Mainly adults	372	51.20		Caucasian	Yes	Bipolar I	Mania + depression		Divalproex: 71–125 μg/ml	Lithium: 0.8–1.2 mmol/l	Placebo	
Bowden, 2003[40]	Mainly adults	175	53.00			Yes	Bipolar I	Mainly mania		Lamotrigine: 100–400 mg/day	Lithium: 0.8–1.1 mEq/l	Placebo	
Calabrese, 2000[41]	Mainly adults	182	57.00			Yes	Bipolar I and II	All	100.00	Lamotrigine: 100–500 mg orally once daily	Placebo: matching to lamotrigine		
Calabrese, 2003[42]	Mainly adults	463	56.00			Yes	Bipolar I	Mainly depression		Lamotrigine: 50, 200, 400 mg/day	Lithium: median 900 mg/day (0.8–1.1 mEq/l)	Placebo	
Calabrese, 2005[43]	Mainly adults	60	51.67			Yes	Bipolar I and II	All	100.00	Divalproex: 900–1200 mg/day (mean 0.92 mEq/l)	Lithium: 750–2750 mg/day (mean 77 μg/ml)		
Cochran, 1984[44]	Mainly adults	28	61.00	79.00	Caucasian	Unclear	Bipolar I and II	All		CBT: 1 hour per week for 6 weeks	No additional treatment		
Colom, 2003a[45]	Mainly adults	120	63.00			Yes	Bipolar I and II	All		Group psychoeducation: 21 sessions of 90 minutes each	Non-structured group meeting: 20 weekly group meetings without psychoeducation		
Colom, 2003b[46]	Mainly adults	50	62.00			Yes	Bipolar I	All		Group psychoeducation: 21 sessions of 90 minutes each	Non-structured group meeting: 21 sessions 90 minutes each without psychoeducation		

continued

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Coxhead, 1992[47]	Mainly adults	31	67.74			Yes	Bipolar – not specified	Mania + depression		Carbamazepine: 200 mg twice daily (38–51 mmol/l)	Lithium: 400 mg twice daily (0.6–1.0 mmol/l)		
Dunner, 1976[48]	Mainly adults	40	57.50			Yes	Bipolar II	Hypomania + depression	15.00	Lithium: 0.8–1.2 mEq/l	Placebo		
Esparon, 1986[49]	Mainly adults	15	73.00			Unclear	Bipolar – not specified	Mania + depression		Lithium + flupenthixol: 0.6–1.2 mmol/l + 20-mg injections every 4 weeks	Lithium: 0.6–1.2 mmol/l		
Fieve, 1976[50]	Mainly adults	53	51.00			Yes	Bipolar I and II	Mania + depression	7.50	Lithium: 0.7–1.3 mEq/l	Placebo		
Findling, 2005[36]	Mainly children	60	35.00			Yes	Bipolar I and II	All	50.00	Lithium: 0.6–1.2 mmol/l	Valproate: 50–100 μg/ml		
Frankenburg, 2002[51]	Mainly adults	30	100.00		Caucasian	Yes	Bipolar II	Hypomania + depression		Valproate: 50–100 mg/l	Placebo		
Gelenberg, 1989[52]	Mainly adults	94	55.30			Yes	Bipolar – not specified	Mania + depression		Lithium: 600–2100 mg/day (0.8–1.0 mmol/l)	Lithium: 450–1350 mg/day (04–0.6 mmol/l)		
Hartong, 2003[53]	Mainly adults	53	54.30	44.70		Yes	Bipolar I and II	All		Lithium: 800 mg/day (0.6–1.0 mmol/l)	Carbamazepine: 400 mg/day (6–10 mg/l)		
Johnstone, 1990[54]	Mainly adults	13	69.23			Unclear	Bipolar I and II	All		Lithium + amitriptyline: 0.5–0.9 mEq/l + 50–225 mg/day	Lithium: 0.5–0.9 mEq/l		
Kane, 1981[55]	Mainly adults	75	52.00			Yes	Bipolar I	Mania + depression		Lithium + imipramine: 300 mg 2–4 times per day (0.8–1.2 mEq/l) + 100–150 mg/day	Lithium: 300 mg 2–4 times per day (0.8–1.2 mEq/l)		

continued

Study	Age	N	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Kane, 1982[56]	Mainly adults	22	77.27		Caucasian	Yes	Bipolar II	Hypomania + depression		Lithium + imipramine: 0.8–1.2 mEq/l + 100–150 mg/day	Lithium: 0.8–1.2 mEq/l	Imipramine: 100–150 mg/day	Placebo
Kleindienst, 2000[57]	Mainly adults	171	56.14	50.00		Yes	Bipolar I and II	Mania + depression		Carbamazepine: 4–12 μg/ml	Lithium: 0.6–0.8 mmol/l		
Lam, 2000[58]	Mainly adults	25	52.00	68.00		Yes	Bipolar I	All		CBT: 12–20 sessions of CBT over 6 months	No additional treatment		
Lam, 2005[59]	Mainly adults	103	55.50			Yes	Bipolar I	Mania + depression		CBT: mean of 14 (SD 5.5) sessions over 6 months	No additional treatment		
Lusznat, 1988[60]	Mainly adults	54	53.70			No	Bipolar I	Mainly mania		Carbamazepine: tablets of 200 mg (0.6–1.2 mg per 100 ml)	Lithium: tablets of 400 mg (0.6–1.4 mmol/l)		
Maj, 1986[61]	Mainly adults	80	56.25			Unclear	Bipolar – not specified	Not stated		Lithium: plasma lithium level 0.30–0.45 mEq/l	Lithium: plasma lithium level 0.46–0.60 mEq/l	Lithium: plasma lithium level 0.61–0.75 mEq/l	Lithium: plasma lithium level 0.76–0.90 mEq/l
Miklowitz, 2003[62]	Mainly adults	101	63.37		Caucasian	Unclear	Bipolar I and II	All		Family-focused therapy: 21 1-hour sessions (12 weekly, 6 biweekly, 3 monthly)	Crisis management: 2 1-hour sessions in first 2 months, then as needed		
Perry, 1999[63]	Mainly adults	69	68.00	37.68	Caucasian	Yes	Bipolar I and II	All		Psychoeducation: 7–12 1-hour sessions (median 9, range 0–12)	No additional treatment		
Platman, 1970[64]		79	51.90			Unclear	Bipolar – not specified	Mania + depression		Imipramine	Lithium		

continued

Study	Age	*N*	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Prien, 1973[65]	Mainly adults	44	23.00			Yes	Bipolar – not specified	Mainly depression		Lithium: 500–2250 mg/day (median 0.8 mEq/l)	Imipramine: 50–200 mg/day	Placebo: identical number of capsules	
Prien, 1974[66]	Mainly adults	205	35.00			Yes	Bipolar – not specified	Mainly mania		Lithium: 0.5–1.4 mEq/l	Placebo: matching capsules		
Prien, 1984[67]	Mainly adults	117	58.00			Yes	Bipolar I	Mania + depression	2.50	Lithium + imipramine: mean 0.75 mEq/l + mean 132 mg/day	Lithium: mean 0.75 mEq/l (0.45–1.10 mEq/l)	Imipramine: mean 132 mg/day (75–150 mg/day)	
Rea, 2003[68]	Mainly adults	53	57.00	85.00	Caucasian	Yes	Bipolar – not specified	Mainly mania		Family therapy: weekly, then biweekly, then monthly	Psychosocial therapy: weekly, then biweekly, then monthly		
Revicki, 2005[69]	Mainly adults	221	51.20		Caucasian	No	Bipolar I	Mania + mixed	12.25	Divalproex: 15–20 mg/kg/day or usual psychiatric practice	Lithium: 900–1200 mg/day		
Scott, 2001[70]	Mainly adults	42	59.52	66.67		No	Bipolar I and II	Not stated	7.14	CBT: maximum of 25 sessions (45 minutes each)	Waiting list control: varied		
Scott, 2005[71]	Mainly adults	253	65.00	60.00		No	Bipolar I and II	All		CBT: 20 sessions and 2 booster sessions	No additional treatment		
Simhandl, 1993[72]	Mainly adults	52	69.05			Unclear	Bipolar – not specified	Not stated		Carbamazepine: 12-h serum level 15–25 μmol/l	Carbamazepine: 12-h serum level 28–40 μmol/l	Lithium: 12-h serum level 0.6–0.8 mmol/l	
Simon, 2005[73]	Mainly adults	441	68.25	48.53	Caucasian	No	Bipolar I and II	All		Care management: varied. Group: 5 × 1-hour weekly, then 1-hour bimonthly	No additional treatment		

continued

Study	Age	N	Female (%)	Single (%)	Ethnicity	Randomised in maintenance?	Diagnostic	Sub-diagnostic	Rapid cycling (%)	Treatment	Comparator 1	Comparator 2	Comparator 3
Solomon, 1997[74]	Mainly adults	12	33.33	50.00		Unclear	Bipolar I	Mania + depression		Lithium + divalproex: 0.8–1.0 mmol/l + twice daily 50–125 μg/ml	Lithium: 0.8–1.0 mmol/l		
Tohen, 2003[75]	Mainly adults	251	57.37		Caucasian	No	Bipolar – not specified	Mania + mixed	57.40	Olanzapine: 5–20 mg/day	Divalproex: 500–2500 mg/day (50–125 μg/ml)		
Tohen, 2004[76]	Mainly adults	99	48.48		Caucasian	Yes	Bipolar I	Mania + mixed	41.41	Olanzapine + mood stabilisers: 5, 10, 15 or 20 mg/day (flexible dosage)	Mood stabilisers		
Tohen, 2005[77]	Mainly adults	431	52.90		Caucasian	Yes	Bipolar I	Mania + mixed	3.02	Olanzapine: 5–20 mg/day	Lithium: 300–1800 mg/day 0.6–1.2 mEq/l		
Tohen, 2006[78]	Mainly adults	361	61.00		Caucasian	Yes	Bipolar I	Mania + mixed	50.00	Olanzapine: 5–20 mg/day	Placebo		
Weiss, 2000[79]	Mainly adults	45	48.90	80.00	Caucasian	Yes	Bipolar I and II	Not stated		Integrated group therapy: weekly, 12–20 1-hour sessions	No additional treatment		
Zarate, 2004[80]	Mainly adults	37	76.00			Yes	Bipolar I and II	Mania + mixed		Perphenazine + mood stabilisers: 4–64 mg/day, mean 28.2, SD 11.7	Mood stabilisers		

Included studies and analyses in which each can be included

Study ID	Author	Year	Comparisons	Standard main analysis	Standard sensitivity analysis	MTC main analysis	MTC sensitivity analysis
12	Altamura[38]	2004	Olanzapine vs valproate	Yes	Yes	Yes	Yes
13	Altamura[37]	2003	Quietapine vs mood stabilisers	Yes	Yes	Yes[a]	Yes[a]
77	Bowden[39]	2000	Valproate vs lithium vs placebo	Yes	Yes	Yes	Yes
79	Bowden[40]	2003	Lamotrigine vs lithium vs placebo	Yes	Yes	Yes	Yes
113	Calabrese[41]	2000	Lamotrigine vs placebo	Yes	Yes	Yes	Yes
154	Cochran[44]	1984	PS	Yes	Yes	No	No
160	Colom[45]	2003a	PS	Yes	Yes	No	No
161	Colom[46]	2003b	PS	Yes	Yes	No	No
177	Coxhead[47]	1992	Carbamazepine versus lithium	Yes	Yes	Yes	Yes
218	Dunner[48]	1976	Lithium vs placebo	Yes	Yes (BP II)	No (BP II)	Yes (BP II)
231	Esparon[49]	1986	Flupenthixol + lithium vs lithium	Only descriptive	No	No	No
238	Fieve[50]	1976	Lithium vs placebo	Yes	Yes	Yes	Yes
243	Findling[36]	2005	Valproate vs lithium	No, paediatric	Yes?	No	No
251	Frankenburg[51]	2002	Valproate vs placebo	Yes	Yes (BP II)	No (BP II)	Yes (BP II)
267	Gelenberg[52]	1989	All lithium	No	No	No	No
307	Kane[56]	1982	Placebo vs lithium vs imipramine vs lithium + imipramine	Yes	Yes (BP II)	No (BP II)	Yes (BP II)
338	Miklowitz[62]	2003	PS	Yes	Yes	No	No
352	Perry[63]	1999	PS	Yes	Yes	No	No
362	Rea[68]	2003	PS	Yes	Yes	No	No
372	Simon[73]	2005	PS	No	Yes	No	No
581	Kane[55]	1981	Lithium vs lithium + imipramine	Yes	Yes	Yes	Yes
592	Kleindienst[57]	2000	Carbamazepine vs lithium	Yes	Yes	Yes	Yes
609	Lam[58]	2000	PS	Yes	Yes	No	No
610	Lam[59]	2005	CBT vs no additional treatment	Yes	Yes	No	No
701	Platman[64]	1970	Imipramine vs lithium	Only descriptive	No	No	No
709	Prien[66]	1974	Lithium vs placebo	Yes	Yes	Yes	Yes
710	Prien[67]	1984	Lithium vs lithium + imipramine vs imipramine	Yes	Yes	Yes	Yes

continued

Study ID	Author	Year	Comparisons	Standard main analysis	Standard sensitivity analysis	MTC main analysis	MTC sensitivity analysis
717	Revicki[69]	2005	Divalproex vs lithium	No, acute randomisation	Yes	No, acute randomisation	No
747	Scott[71]	2005	PS	No, acute randomisation	Yes	No, acute randomisation	No
756	Simhandl[72]	1993	Carbamazepine vs lithium	Yes	Yes	Yes	Yes
795	Tohen[77]	2005	Olanzapine versus lithium	Yes	Yes	Yes	Yes
798	Tohen[75]	2003	Olanzapine versus divalproex sodium	No, possible acute randomisation and limited data	Yes	No, possible acute randomisation and limited data	No, possible acute randomisation and limited data
845	Calabrese[43]	2005	Divalproex vs lithium	Yes	Yes	Yes	Yes
868	Hartong[53]	2003	Lithium versus carbamazepine	Yes	Yes	Yes	Yes
885	Johnstone[54]	1990	Lithium + amitriptyline vs lithium	Only descriptive	No	No	No
909	Lusznat[60]	1988	Carbamazepine vs lithium	No, acute randomisation	Yes	No, acute randomisation	No
910	Maj[61]	1986	All lithium	No	No	No	No
983	Tohen[76]	2004	Olanzapine plus mood stabiliser vs mood stabiliser alone	Yes	Yes	Yes[a]	Yes[a]
993	Zarate[80]	2004	Perphenazine + mood stabilisers vs mood stabilisers	No, responders	Yes	No, responders	Yes[a]
1035	Calabrese[42]	2003	Lamotrigine vs lithium vs placebo	Yes	Yes	Yes	Yes
1102	Scott[70]	2001	PS	No, acute randomisation	Yes	No	No
1111	Solomon[74]	1997	Lithium + divalproex vs lithium	Only descriptive	No	No	No
1147	Weiss[79]	2000	PS	Yes	Yes	No	No
1275	Prien[65]	1973	Imipramine vs lithium vs placebo	Yes	Yes	Yes	Yes
1307	Tohen[78]	2006	Olanzapine vs placebo	No, responders	Yes	No, responders	Yes

PS, psychosocial intervention.
[a] Do not link into chain of evidence in MTC.

Appendix 6

Data extraction tables

Data extraction tables: study details

Study details	Population	Diagnosis	Treatments and outcomes
Altamura, 2003[37] Country: Italy Setting: outpatients Crossover design?: no Length of follow-up: 12 months *N* = 28	Age: mainly adults Ethnicity: not reported Female: 57.00% Single: not reported Co-morbidity: not reported Co-interventions: only benzodiazepinics	Bipolar I and II (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Quetiapine* Dosage: 157.7 (SD 157.6) mg/day Duration: 6 to <12 months Type: monotherapy *Mood stabilisers* Dosage: (see comments) Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Altamura, 2004[38] Country: Italy Setting: outpatients Crossover design?: no Length of follow-up: 6 months *N* = 23	Age: mainly adults Ethnicity: not reported Female: 50.00% Single: not reported Co-morbidity: not reported Co-interventions: benzodiazepines	Bipolar I and II (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Valproate* Dosage: final: 415 ± 16.39 mg (62.7 ± 19.5 μg/ml) Duration: 3 to <6 months Type: monotherapy *Olanzapine* Dosage: final: 9 ± 3.2 mg Duration: 3 to <6 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Bowden, 2000[39] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 52 weeks after randomisation *N* = 372	Age: mainly adults Ethnicity: Caucasian Female: 51.20% Single: not reported Co-morbidity: not reported Co-interventions: lorazepam, haloperidol Patients taking lithium or divalproex at randomisation had the drug reduced and withdrawn over first 2 weeks of maintenance treatment. Patients taking both drugs had one discontinued before randomisation. Two courses of lorazepam permitted (up to 6 mg/day for 14 days maximum during first month and no more than 7 days for rest of study). Up to 10 mg haloperidol permitted during second consecutive week of lorazepam use in first month only. Both used to reduce recurrence of manic symptoms caused by withdrawal from open-label medication. Neither lorazepam nor haloperidol allowed within 8 hours before behavioural assessments. Patients who developed depressive symptoms could take an SSRI and continue in the study.	Bipolar I (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-III-R Mania rating scale: mSRS Depression rating scale: other Stable at randomisation: yes Only responders?: unclear. Patients randomised had not had to respond to one particular treatment Only tolerators?: unclear	**Treatments** *Divalproex* Dosage: 71–125 μg/ml Duration: 6 to <12 months Type: monotherapy *Lithium* Dosage: 0.8–1.2 mol/l Duration: 6 to <12 months Type: monotherapy *Placebo* Dosage: not stated Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Bowden, 2003[40] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 76 weeks *N* = 175	Age: mainly adults Ethnicity: not reported Female: 53.00% Single: not reported Co-morbidity: not reported Co-interventions: short-term use of chloral hydrate, lorazepam, temazepam or oxazepam	Bipolar I (mainly mania) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. Beginning at week 8 of the open-label phase, patients who had reached a stable dose of lamotrigine and met the criterion for response (CGI-S (Clinical Global Impressions – Severity) ≤3 for 4 weeks) could enter the double-blind phase of the study Only tolerators?: yes	**Treatments** *Lamotrigine* Dosage: 100–400 mg/day Duration: 12 to <18 months Type: monotherapy *Lithium* Dosage: 0.8–1.1 mEq/l Duration: 12 to <18 months Type: monotherapy *Placebo* Dosage: not stated Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Calabrese, 2000[41] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 6 months *N* = 182	Age: mainly adults Ethnicity: not reported Female: 57.00% Single: not reported Co-morbidity: 7% hypothyroidism Co-interventions: lorazepam (up to 2 mg/day) allowed to control agitation, irritability, restlessness, insomnia or hostile behaviour	Bipolar I and II (all) Rapid cycling: 100.00% Diagnostic criteria: DSM-IV Mania rating scale: other Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. Patients had to have successfully completed tapering of other psychotropic medications while maintaining 'wellness'. During the final week of the preliminary phase, patients should have not required their dose of lamotrigine to be altered nor to have experienced a mood episode Only tolerators?: yes	**Treatments** *Lamotrigine* Dosage: 100–500 mg orally once daily Duration: 3 to <6 months Type: monotherapy *Placebo* Dosage: matching to lamotrigine Duration: 3 to <6 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Calabrese, 2003[42] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 76 weeks *N* = 463	Age: mainly adults Ethnicity: not reported Female: 56.00% Single: not reported Co-morbidity: not reported Co-interventions: short-term use of chloral hydrate, lorazepam, temazepam, oxazepam or midazolam	Bipolar I (mainly depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. Beginning at week 8 of the open-label phase, patients who had reached a stable dose of lamotrigine and met the criterion for randomisation (CGI ⩽3 for 4 weeks) could enter the double-blind phase of the study Only tolerators?: yes	**Treatments** *Lamotrigine* Dosage: 50 mg/day Duration: 12 to <18 months Type: monotherapy *Lamotrigine* Dosage: 200 mg/day Duration: 12 to <18 months Type: monotherapy *Lamotrigine* Dosage: 400 mg/day Duration: 12 to <18 months Type: monotherapy *Lithium* Dosage: median 900 mg/day (0.8–1.1 mEq/l) Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Calabrese, 2005[43] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 20 months *N* = 60	Age: mainly adults Ethnicity: not reported Female: 51.67% Single: not reported Co-morbidity: not reported Co-interventions: lorazepam up to 4 mg/day or alprazolam up to 2 mg/day (7 patients in each group). Patients were permitted to continue any psychotherapy initiated before randomisation	Bipolar I and II (all) Rapid cycling: 100.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. 6-month stabilisation phase where patients began using both drug interventions concurrently. Patients stable after week 12 were eligible for the randomised phase Only tolerators?: yes. Patients who had experienced intolerable side-effects to lithium (0.8 mEq/l) or divalproex (50 μg/ml) were excluded from entering the acute phase	**Treatments** *Lithium* Dosage: 900–1200 mg/day (mean 0.92 mEq/l) Duration: 18 to <24 months Type: monotherapy *Divalproex* Dosage: 750–2750 mg/day (mean 77 μg/ml) Duration: 18 to <24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Cochran, 1984[44] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 6 months *N* = 28	Age: mainly adults Ethnicity: Caucasian Female: 61.00% Single: 79.00% Co-morbidity: not reported Co-interventions: all patients used lithium (dosage not specified)	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: RDC Mania rating scale: not stated Depression rating scale: not stated Stable at randomisation: unclear Only responders?: no Only tolerators?: no	**Treatments** *CBT* Dosage: 1 hour per week for 6 weeks Duration: < 3 months Type: monotherapy *No additional treatment* Dosage: not stated Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Colom, 2003a[45] Country: Spain Setting: outpatients Crossover design?: no Length of follow-up: 2 years *N* = 120	Age: mainly adults Ethnicity: not reported Female: 63.00% Single: not reported Co-morbidity: none Co-interventions: standard psychiatric care and pharmacological treatment	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Group psychoeducation* Dosage: 21 sessions of 90 minutes each Duration: 3 to <6 months Type: monotherapy *Non-structured group meeting* Dosage: 20 weekly group meetings without psychoeducation Duration: 3 to <6 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Colom, 2003b[46] Country: Spain Setting: outpatients Crossover design?: no Length of follow-up: 2 years *N* = 50	Age: mainly adults Ethnicity: not reported Female: 62.00% Single: not reported Co-morbidity: not reported Co-interventions: all patients received naturalistic pharmacological treatment	Bipolar I (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Group psychoeducation* Dosage: 21 sessions of 90 minutes each Duration: ⩾24 months Type: monotherapy *Non-structured group meeting* Dosage: 21 sessions of 90 minutes each without psychoeducation Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Coxhead, 1992[47] Country: UK Setting: outpatients Crossover design?: no Length of follow-up: 1 year *N* = 31	Age: mainly adults Ethnicity: not reported Female: 67.74% Single: not reported Co-morbidity: not reported Co-interventions: only temazepam up to 20 mg at night permitted (10 mg at night for sleep disturbance administered to one patient)	Bipolar – not specified (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-III Mania rating scale: BRMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. Only patients currently stabilised on lithium included Only tolerators?: yes. Only patients currently stabilised on lithium included	**Treatments** *Carbamazepine* Dosage: 200 mg twice daily (38–51 mmol/l) Duration: 6 to <12 months Type: monotherapy *Lithium* Dosage: 400 mg twice daily (0.6–1.0 mmol/l) Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Dunner, 1976[48] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: mean approximately 16 months *N* = 40	Age: mainly adults Ethnicity: not reported Female: 57.50% Single: not reported Co-morbidity: not reported Co-interventions: none	Bipolar II (hypomania + depression) Rapid cycling: 15.00% Diagnostic criteria: Freightner Mania rating scale: other Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Lithium* Dosage: 0.8–1.2 mEq/l Duration: 12 to <18 months Type: monotherapy *Placebo* Dosage: not stated Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Esparon, 1986[49] Country: Australia Setting: unclear Crossover design?: yes Length of follow-up: first year of crossover trial *N* = 15	Age: mainly adults Ethnicity: not reported Female: 73.00% Single: not reported Co-morbidity: not reported Co-interventions: all patients received benzhexol throughout the trial to avoid extrapyramidal adverse events; benzodiazepine, antidepressant, phenothiazines. No restrictions were placed on other prescribed medication. Three patients were taking thyroxin, one was diabetic receiving chlorpropamide	Bipolar – not specified (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: none Mania rating scale: other Depression rating scale: other Stable at randomisation: unclear Only responders?: unclear Only tolerators?: unclear	**Treatments** *Lithium + flupenthixol* Dosage: 0.6–1.2 mmol/l + 20-mg injections every 4 weeks Duration: 6 to <12 months Type: combination *Lithium* Dosage: 0.6–1.2 mmol/l Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Fieve, 1976[50] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 4 years *N* = 53	Age: mainly adults Ethnicity: not reported Female: 51.00% Single: not reported Co-morbidity: none Co-interventions: patients were treated for an episode with antidepressants or antipsychotic drugs	Bipolar I and II (mania + depression) Rapid cycling: 7.50% Diagnostic criteria: Feightner Mania rating scale: other Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Lithium* Dosage: 0.7–1.3 mEq/l Duration: ⩾24 months Type: monotherapy *Placebo* Dosage: not stated Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Findling, 2005[36] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 76 weeks *N* = 60	Age: mainly children Ethnicity: not reported Female: 35.00% Single: not reported Co-morbidity: not reported Co-interventions: psychostimulants or clonidine for patients with attention deficit hyperactivity disorder	Bipolar I and II (all) Rapid cycling: 50.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: other Stable at randomisation: yes Only responders?: yes. Phase I: 139 patients received lithium + valproate for up to 20 weeks. To enter phase II (maintenance), patients had to meet criteria for syndromal remission Only tolerators?: yes. Patients who could not tolerate the minimum drug serum concentration of lithium (≥0.6 mmol/l) or valproate (≥50 μg/ml) were withdrawn from the trial in the acute phase	**Treatments** *Lithium* Dosage: 0.6–1.2 mmol/l Duration: 12 to <18 months Type: monotherapy *Valproate* Dosage: 50–100 μg/ml Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Frankenburg, 2002[51] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 6 months *N* = 30	Age: mainly adults Ethnicity: Caucasian Female: 100.00% Single: not reported Co-morbidity: personality disorder Co-interventions: none	Bipolar II (hypomania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Valproate* Dosage: 50–100 mg/l Duration: 3 to <6 months Type: monotherapy *Placebo* Dosage: not stated Duration: 3 to <6 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Gelenberg, 1989[52] Country: USA Setting: unclear Crossover design?: no Length of follow-up: 182 weeks *N* = 94	Age: mainly adults Ethnicity: not reported Female: 55.30% Single: not reported Co-morbidity: not reported Co-interventions: none	Bipolar – not specified (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-III, RDC Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: yes. 10 patients were not randomised because they relapsed during the 2 months of open-label treatment with lithium Only tolerators?: yes. At least 2 months of tolerating serum lithium levels of 0.6–1.0 mmol/l	**Treatments** *Lithium* Dosage: 600–2100 mg/day (0.8–1.0 mmol/l) Duration: ⩾24 months Type: monotherapy *Lithium* Dosage: 450–1350 mg/day (04–0.6 mmol/l) Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Hartong, 2003[53] Country: The Netherlands Setting: outpatients Crossover design?: no Length of follow-up: 2 years *N* = 53	Age: mainly adults Ethnicity: not reported Female: 54.30% Single: 44.70% Co-morbidity: none Co-interventions: benzodiazepines, doses equivalent to a maximum of 50 mg/day of oxazepam, or of 100 mg/day of oxazepam for no more than 14 days	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-III-R Mania rating scale: BRMRS Depression rating scale: other Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Lithium* Dosage: 800 mg/day (0.6–1.0 mmol/l) Duration: ⩾24 months Type: monotherapy *Carbamazepine* Dosage: 400 mg/day (6–10 mg/l) Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Johnstone, 1990[54] Country: UK Setting: unclear Crossover design?: no Length of follow-up: 3 years *N* = 13	Age: mainly adults Ethnicity: not reported Female: 69.23% Single: not reported Co-morbidity: not reported Co-interventions: none	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-III Mania rating scale: BRMRS Depression rating scale: HAM-D Stable at randomisation: unclear. It is unclear whether patients had been hospitalised or entered the study in the acute phase Only responders?: no Only tolerators?: no	**Treatments** *Lithium + amitriptyline* Dosage: 0.5–0.9 mEq/l + 50–225 mg/day Duration: ⩾24 months Type: combination *Lithium* Dosage: 0.5–0.9 mEq/l Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Kane, 1981[55] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: >19 months *N* = 75	Age: mainly adults Ethnicity: not reported Female: 52.00% Single: not reported Co-morbidity: not reported Co-interventions: none	Bipolar I (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: RDC Mania rating scale: not stated Depression rating scale: not stated Stable at randomisation: yes Only responders?: unclear. Patients had to remain euthymic on lithium for 6 weeks prior to study entry Only tolerators?: unclear	**Treatments** *Lithium + imipramine* Dosage: 300 mg 2–4 times per day (0.8–1.2 mEq/l) + 100–150 mg/day Duration: 18 to <24 months Type: combination *Lithium* Dosage: 300 mg 2–4 times per day (0.8–1.2 mEq/l) Duration: 18 to <24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Kane, 1982[56] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: up to 2 years *N* = 22	Age: mainly adults Ethnicity: Caucasian Female: 77.27% Single: not reported Co-morbidity: not reported Co-interventions: use of ancillary services and psychotherapy was not controlled	Bipolar II (hypomania + depression) Rapid cycling: 0.00% Diagnostic criteria: RDC Mania rating scale: not stated Depression rating scale: not stated Stable at randomisation: yes Only responders?: unclear. Most patients received tricyclic antidepressants in the 6 months prior to the study, and the most commonly used drug was imipramine. Patients had to be euthymic for 6 months prior to study entry, and had to maintain euthymia for the last 6 weeks on imipramine (maximum 150 mg/day) Only tolerators?: unclear	**Treatments** *Lithium + imipramine* Dosage: 0.8–1.2 mEq/l + 100–150 mg/day Duration: 18 to <24 months Type: combination *Lithium* Dosage: 0.8–1.2 mEq/l Duration: 18 to <24 months Type: monotherapy *Imipramine* Dosage: 100–150 mg/day Duration: 18 to <24 months Type: monotherapy *Placebo* Dosage: not stated Duration: 18 to <24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Kleindienst, 2000[57] Country: Germany Setting: outpatients Crossover design?: no Length of follow-up: 2.5 years *N* = 171	Age: mainly adults Ethnicity: not reported Female: 56.14% Single: 50.00% Co-morbidity: not reported Co-interventions: most common: perazine, clozapine, amitriptyline, doxepine	Bipolar I and II (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-III-R, ICD-9, RDC Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Carbamazepine* Dosage: 4–12 μg/ml Duration: ⩾24 months Type: monotherapy *Lithium* Dosage: 0.6–0.8 mmol/l Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Lam, 2000[58] Country: UK Setting: outpatients Crossover design?: no Length of follow-up: 1 year *N* = 25	Age: mainly adults Ethnicity: not reported Female: 52.00% Single: 68.00% Co-morbidity: not reported Co-interventions: mood stabilisers, usual outpatients and multidisciplinary team input	Bipolar I (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: BRMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *CBT* Dosage: 12–20 sessions of CBT over 6 months Duration: 6 to <12 months Type: monotherapy *No additional treatment* Dosage: not stated Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Lam, 2005[59] Country: UK Setting: outpatients Crossover design?: no Length of follow-up: up to 30 months *N* = 103	Age: mainly adults Ethnicity: not reported Female: 55.50% Single: not reported Co-morbidity: not reported Co-interventions: medication as prescribed. No restrictions. Recorded monthly. Around 85% of all patients taking one mood stabiliser and 10–20% taking 2. Around 30% antidepressants and 45% major tranquillisers	Bipolar I (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: BRMRS Depression rating scale: other Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *CBT* Dosage: mean of 14 (SD 5.5) sessions over 6 months Duration: ⩾24 months Type: monotherapy *No additional treatment* Dosage: not stated Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Lusznat, 1988[60] Country: UK Setting: mixed Crossover design?: no Length of follow-up: 12 months *N* = 54	Age: mainly adults Ethnicity: not reported Female: 53.70% Single: not reported Co-morbidity: not reported Co-interventions: antidepressants or neuroleptic for persistent and distressing mood swings; temazepam	Bipolar I (mainly mania) Rapid cycling: 0.00% Diagnostic criteria: DSM-III, ICD-9 Mania rating scale: BRMRS Depression rating scale: HAM-D Stable at randomisation: no. Patients were randomised in acute phase and were treated for 6 weeks (study medication + antipsychotics) before starting the follow-up Only responders?: no Only tolerators?: unclear. Patients with a known sensitivity to carbamazepine or lithium were excluded	**Treatments** *Carbamazepine* Dosage: tablets of 200 mg (0.6–1.2 mg per 100 ml) Duration: 12 to <18 months Type: monotherapy *Lithium* Dosage: tablets of 400 mg (0.6–1.4 mmol/l) Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Maj, 1986[61] Country: Italy Setting: unclear Crossover design?: no Length of follow-up: 2 years *N* = 80	Age: mainly adults Ethnicity: not reported Female: 56.25% Single: not reported Co-morbidity: not reported Co-interventions: none	Bipolar – not specified (not stated) Rapid cycling: 0.00% Diagnostic criteria: DSM-III Mania rating scale: other Depression rating scale: other Stable at randomisation: unclear. It is believed they were not, because the authors refer all the time to the index episode Only responders?: unclear. Inclusion criteria: history of at least one affective episode during the past 2 years preceding the index episode and the commencement of lithium prophylaxis Only tolerators?: unclear	**Treatments** *Lithium* Dosage: plasma lithium level 0.30–0.45 mEq/l Duration: ⩾24 months Type: monotherapy *Lithium* Dosage: plasma lithium level 0.46–0.60 mEq/l Duration: ⩾24 months Type: monotherapy *Lithium* Dosage: plasma lithium level 0.61–0.75 mEq/l Duration: ⩾24 months Type: monotherapy *Lithium* Dosage: plasma lithium level 0.76–0.90 mEq/l Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Miklowitz, 2003[62] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 2 years *N* = 101	Age: mainly adults Ethnicity: Caucasian Female: 63.37% Single: not reported Co-morbidity: not reported Co-interventions: mood stabilisers (*n* = 93), alone, or in combination with other agents (lithium carbonate, *n* = 69; carbamazepine, *n* = 29; divalproex sodium, *n* = 12; calcium channel blockers, *n* = 9). 17 received adjunctive antidepressants and 38 adjunctive antipsychotic agents	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-III-R Mania rating scale: other Depression rating scale: other Stable at randomisation: unclear. Patients were recruited while in the hospital (82) or as outpatients (19), and they had DSM-III-R criteria for bipolar disorder in the past 3 months Only responders?: no Only tolerators?: no	**Treatments** *Family-focused therapy* Dosage: 21 1-hour sessions (12 weekly, 6 biweekly, 3 monthly) Duration: 6 to <12 months Type: monotherapy *Crisis management* Dosage: 2 1-hour sessions in first 2 months, then as needed Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Perry, 1999[63] Country: UK Setting: outpatients Crossover design?: no Length of follow-up: 18 months *N* = 69	Age: mainly adults Ethnicity: Caucasian Female: 68.00% Single: 37.68% Co-morbidity: personality disorders Co-interventions: lithium (*n* = 50), carbamazepine (*n* = 31), antidepressants (*n* = 31), neuroleptics (*n* = 49). All participants received routine care (drugs, monitoring of mood and treatment adherence, support, education about bipolar disorder and, if necessary, inpatient care)	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-III Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Psychoeducation* Dosage: 7–12 1-hour sessions (median 9, range 0–12) Duration: 12 to <18 months Type: monotherapy *No additional treatment* Dosage: not stated Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Platman, 1970[64] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: lithium, mean 53.8 weeks; imipramine, mean 39.9 weeks *N* = 79	Age: not reported Ethnicity: not reported Female: 51.90% Single: not reported Co-morbidity: not reported Co-interventions: not reported	Bipolar – not specified (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: none Mania rating scale: other Depression rating scale: other Stable at randomisation: unclear. Patients entered the study "in their normal interval". It is assumed that this means after the episode; however, data are presented also counting the current episode Only responders?: unclear. All patients received lithium before randomisation Only tolerators?: unclear. All patients received lithium before randomisation	**Treatments** *Imipramine* Dosage: not stated Duration: 6 to <12 months Type: monotherapy *Lithium* Dosage: not stated Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: no Continuous outcomes reported?: yes
Prien, 1973[65] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 2 years *N* = 44	Age: mainly adults Ethnicity: not reported Female: 23.00% Single: not reported Co-morbidity: not reported Co-interventions: none	Bipolar – not specified (mainly depression) Rapid cycling: 0.00% Diagnostic criteria: none Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: unclear. Following remission of the depressive episode, each patient was stabilised on maintenance doses of imipramine or lithium carbonate Only tolerators?: unclear	**Treatments** *Lithium* Dosage: 500–2250 mg/day (median 0.8 mEq/l) Duration: 18 to <24 months Type: monotherapy *Imipramine* Dosage: 50–200 mg/day Duration: 18 to <24 months Type: monotherapy *Placebo* Dosage: identical number of capsules Duration: 18 to <24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Prien, 1974[66] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 2 years *N* = 205	Age: mainly adults Ethnicity: not reported Female: 35.00% Single: not reported Co-morbidity: not reported Co-interventions: none	Bipolar – not specified (mainly mania) Rapid cycling: 0.00% Diagnostic criteria: none Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: unclear. All patients received lithium which yielded levels of 0.5–1.4 mEq/l. Patients were then randomised to continue lithium or to receive placebo Only tolerators?: unclear. All patients received lithium which yielded levels of 0.5–1.4 mEq/l. Patients were then randomised to continue lithium or to receive placebo	**Treatments** *Lithium* Dosage: 0.5–1.4 mEq/l Duration: ⩾24 months Type: monotherapy *Placebo* Dosage: matching capsules Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Prien, 1984[67] Country: USA Setting: mixed Crossover design?: no Length of follow-up: 2 years *N* = 117	Age: mainly adults Ethnicity: not reported Female: 58.00% Single: not reported Co-morbidity: unipolar major depression Co-interventions: only if patients relapsed – treated according to the clinician decision	Bipolar I (mania + depression) Rapid cycling: 2.50% Diagnostic criteria: RDC Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: unclear Only tolerators?: yes. Only patients who had tolerated the combination of imipramine and lithium were randomised into the study	**Treatments** *Lithium + imipramine* Dosage: mean 0.75 mEq/l + mean 132 mg/day Duration: ⩾24 months Type: combination *Lithium* Dosage: mean 0.75 mEq/l (0.45–1.10 mEq/l) Duration: ⩾24 months Type: monotherapy *Imipramine* Dosage: mean 132 mg/day (75–150 mg/day) Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Rea, 2003[68] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 2 years *N* = 53	Age: mainly adults Ethnicity: Caucasian Female: 57.00% Single: 85.00% Co-morbidity: not reported Co-interventions: medication tailored as required	Bipolar – not specified (mainly mania) Rapid cycling: 0.00% Diagnostic criteria: DSM-III-R Mania rating scale: other Depression rating scale: other Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Family therapy* Dosage: weekly, then biweekly, then monthly Duration: 6 to <12 months Type: monotherapy *Psychosocial therapy* Dosage: weekly, then biweekly, then monthly Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Revicki, 2005[69] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 12 months *N* = 221	Age: mainly adults Ethnicity: Caucasian Female: 51.20% Single: not reported Co-morbidity: alcohol and drug abuse Co-interventions: usual psychiatric care, antipsychotics, antidepressants	Bipolar I (mania + mixed) Rapid cycling: 12.25% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: other Stable at randomisation: no. Divalproex at 15–20 mg/kg/day or based on usual psychiatric practice, or up to 1800 mg/day lithium. Given in addition to usual psychiatric care. Mean length of hospitalisation in acute phase was 11 days. After stabilisation, patients were followed up Only responders?: no Only tolerators?: no	**Treatments** *Divalproex* Dosage: 15–20 mg/kg/day or usual psychiatric practice Duration: 12 to <18 months Type: monotherapy *Lithium* Dosage: 900–1200 mg/day Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Scott, 2001[70] Country: UK Setting: outpatients Crossover design?: no Length of follow-up: 18 months (only 6 months extracted here) *N* = 42	Age: mainly adults Ethnicity: not reported Female: 59.52% Single: 66.67% Co-morbidity: not reported Co-interventions: lithium alone (*n* = 19), lithium + another mood stabiliser (*n* = 13), other mood stabilisers without lithium (*n* = 7), antidepressants (*n* = 10), antipsychotics or benzodiazepines (*n* = 4)	Bipolar I and II (not stated) Rapid cycling: 7.14% Diagnostic criteria: not stated Mania rating scale: other Depression rating scale: other Stable at randomisation: no. At baseline, 16 participants met criteria for an affective episode Only responders?: no Only tolerators?: no	**Treatments** *CBT* Dosage: maximum of 25 sessions (45 minutes each) Duration: 6 to <12 months Type: monotherapy *Waiting list control* Dosage: varied Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Scott, 2005[71] Also published as Scott 2006[81] Country: UK Setting: outpatients Crossover design?: no Length of follow-up: 18 months *N* = 253	Age: mainly adults Ethnicity: not reported Female: 65.00% Single: 60.00% Co-morbidity: not reported Co-interventions: patients standard medication and psychiatric care	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: BRMRS Depression rating scale: HAM-D Stable at randomisation: no. 82 participants were in an acute episode at baseline (depressed *n* = 60, hypomanic *n* = 14, manic/mixed *n* = 8) Only responders?: no Only tolerators?: no	**Treatments** *CBT* Dosage: 20 sessions and 2 booster sessions Duration: 6 to <12 months Type: monotherapy *No additional treatment* Dosage: not stated Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Simhandl, 1993[72] Country: Austria Setting: mixed Crossover design?: no Length of follow-up: 2 years *N* = 52	Age: mainly adults Ethnicity: not reported Female: 69.05% Single: not reported Co-morbidity: none Co-interventions: patients given rescue medication as required for as short a time as possible	Bipolar – not specified (not stated) Rapid cycling: 0.00% Diagnostic criteria: DSM-III-R Mania rating scale: BRMRS Depression rating scale: not stated Stable at randomisation: unclear. At randomisation patients had moderate symptoms at the end of the index episode Only responders?: unclear Only tolerators?: unclear	**Treatments** *Carbamazepine* Dosage: 12-h serum level 15–25 μmol/l Duration: ⩾24 months Type: monotherapy *Carbamazepine* Dosage: 12-h serum level 28–40 mmol/l Duration: ⩾24 months Type: monotherapy *Lithium* Dosage: 12-h serum level 0.6–0.8 mmol/l Duration: ⩾24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no
Simon, 2005[73] Country: USA Setting: unclear Crossover design?: no Length of follow-up: 52 weeks *N* = 441	Age: mainly adults Ethnicity: Caucasian Female: 68.25% Single: 48.53% Co-morbidity: not reported Co-interventions: mood stabilisers (including newer anticonvulsants), all atypical antipsychotics. No services normally available were withheld	Bipolar I and II (all) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: other Depression rating scale: other Stable at randomisation: no. Some patients were not stable at baseline (40% met criteria for current DSM mood episode and 22% were in remission) Only responders?: no Only tolerators?: no	**Treatments** *Care management* Dosage: varied. Group: 5 × 1 hour weekly, then 1 hour bimonthly Duration: 12 to <18 months Type: monotherapy *No additional treatment* Dosage: not stated Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Solomon, 1997[74] Country: USA Setting: unclear Crossover design?: no Length of follow-up: up to 52 weeks (mean 43.25 weeks) *N* = 12	Age: mainly adults Ethnicity: not reported Female: 33.33% Single: 50.00% Co-morbidity: not reported Co-interventions: antidepressant, benzodiazepine, neuroleptic. Participants regularly met with the psychiatrist for clinical management, support, encouragement and advice	Bipolar I (mania + depression) Rapid cycling: 0.00% Diagnostic criteria: DSM-III-R Mania rating scale: other Depression rating scale: other Stable at randomisation: unclear. Patients were in acute phase at recruitment. When patients showed signs of improvement, they were randomised to study treatments. It appears that some participants may not have been stable at this stage Only responders?: no Only tolerators?: no	**Treatments** *Lithium + divalproex* Dosage: 0.8–1.0 mmol/l + twice daily 50–125 μg/ml Duration: 12 to <18 months Type: combination *Lithium* Dosage: 0.8–1.0 mmol/l Duration: 12 to <18 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Tohen, 2003[75] Country: USA Setting: mixed Crossover design?: no Length of follow-up: 47 weeks *N* = 251	Age: mainly adults Ethnicity: Caucasian Female: 57.37% Single: not reported Co-morbidity: not reported Co-interventions: lorazepam; benztropine (for treatment, not prophylaxis, of extrapyramidal syndrome)	Bipolar – not specified (mania + mixed) Rapid cycling: 57.40% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: no. Initial doses were olanzapine 15 mg/day and divalproex 750 mg/day. Dose adjustments were made according to clinical response, serum concentrations and adverse events Only responders?: unclear Only tolerators?: yes. Patients who did not tolerate the minimum dosage treatment (olanzapine 5 mg/day; divalproex 500 mg/day) were removed from the study	**Treatments** *Olanzapine* Dosage: 5–20 mg/day Duration: 6 to <12 months Type: monotherapy *Divalproex* Dosage: 500–2500 mg/day (50–125 μg/ml) Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Tohen, 2004[76] Country: USA Setting: unclear Crossover design?: no Length of follow-up: 18 months *N* = 99	Age: mainly adults Ethnicity: Caucasian Female: 48.48% Single: not reported Co-morbidity: not reported Co-interventions: benzodiazepines (lorazepam); anticholinergic therapy (beztropine mesylate) for treatment, not prophylaxis, of extrapyramidal syndrome	Bipolar I (mania + mixed) Rapid cycling: 41.41% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. Patients received olanzapine + lithium or valproate for an acute treatment of bipolar disorder before randomisation Only tolerators?: yes. Patients with documented history of intolerance to olanzapine were excluded	**Treatments** *Olanzapine + mood stabilisers* Dosage: 5, 10, 15 or 20 mg/day (flexible dosage) Duration: 18 to <24 months Type: combination *Mood stabilisers* Dosage: not stated Duration: 18 to <24 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Tohen, 2005[77] Country: USA Setting: mixed Crossover design?: no Length of follow-up: 12 months *N* = 431	Age: mainly adults Ethnicity: Caucasian Female: 52.90% Single: not reported Co-morbidity: not reported Co-interventions: some benzodiazepines allowed (maximum 2 mg/day lorazepam equivalents for no more than 60 cumulative days). Concomitant medication for treatment-emergent extrapyramidal symptoms allowed Oral or i.m. haloperidol and zuclopenthixol were permitted for extreme agitation in the open label phase	Bipolar I (mania + mixed) Rapid cycling: 3.02% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. Only patients who met remission criteria during open label were randomised Only tolerators?: yes. Those who did not tolerate olanzapine or lithium were not randomised	**Treatments** *Olanzapine* Dosage: 5–20 mg/day Duration: 6 to <12 months Type: monotherapy *Lithium* Dosage: 300–1800 mg/day (0.6–1.2 mEq/l) Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

continued

Study details	Population	Diagnosis	Treatments and outcomes
Tohen, 2006[78] Country: UK Setting: mixed Crossover design?: no Length of follow-up: 48 weeks *N* = 361	Age: mainly adults Ethnicity: Caucasian Female: 61.00% Single: not reported Co-morbidity: not reported Co-interventions: no more than 4 mg/day of lorazepam equivalent in the first week, and less than 2 mg/day for the remainder of the study period. No longer than 60 cumulative days in total. Anticholinergic allowed for extrapyramidal symptoms	Bipolar I (mania + mixed) Rapid cycling: 50.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. Patients treated openly with olazapine (5–20 mg/day) for 6–12 weeks. Patients achieving symptomatic remission for at least two consecutive weeks were randomised Only tolerators?: yes. Patients unable to tolerate the minimum dose of olanzapine were discontinued	**Treatments** *Olanzapine* Dosage: 5–20 mg/day Duration: 6 to <12 months Type: monotherapy *Placebo* Dosage: not stated Duration: 6 to <12 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes
Weiss, 2000[79] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 6 months *N* = 45	Age: mainly adults Ethnicity: Caucasian Female: 48.90% Single: 80.00% Co-morbidity: drug abuse Co-interventions: mood stabiliser and saw a pharmacotherapist. Individual therapist (*n* = 37); family or couple treatment and group therapy (*n* = 4); individual drug counselling (*n* = 2); self-help group (*n* = 28); partial hospital treatment (*n* = 22)	Bipolar I and II (not stated) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: no Only tolerators?: no	**Treatments** *Integrated group therapy* Dosage: weekly, 12–20 1-hour sessions Duration: 3 to <6 months Type: monotherapy *No additional treatment* Dosage: not stated Duration: 3 to <6 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: no

continued

Study details	Population	Diagnosis	Treatments and outcomes
Zarate, 2004[80] Country: USA Setting: outpatients Crossover design?: no Length of follow-up: 6 months *N* = 37	Age: mainly adults Ethnicity: not reported Female: 76.00% Single: not reported Co-morbidity: not reported Co-interventions: lorazepam <2 mg/day for less than 10 days; benztropine mesylate, <2 mg/day for extrapyramidal symptoms	Bipolar I and II (mania + mixed) Rapid cycling: 0.00% Diagnostic criteria: DSM-IV Mania rating scale: YMRS Depression rating scale: HAM-D Stable at randomisation: yes Only responders?: yes. All patients were treated with perphenazine (4–64 mg/day) and one or more mood stabilisers for a manic or mixed episode. Only those that achieved remission by week 10 were randomised Only tolerators?: yes. Only those who had been treated with perphezipine and were prepared to continue it entered the randomised phase	**Treatments** *Perphenazine + mood stabilisers* Dosage: 4–64 mg/day, mean 28.2, SD 11.7 Duration: 3 to <6 months Type: combination *Mood stabilisers* Dosage: not stated Duration: 3 to <6 months Type: monotherapy **Outcomes** Discrete outcomes reported?: yes Continuous outcomes reported?: yes

Data extraction tables: continuous data

Study	Outcome	Treatment	*N*	Results	Units
Bowden, 2003[40]	Time to first episode: institution of additional treatment	Lamotrigine	59	Median 141, 95% CI 71 to 547	days
		Lithium	46	Median 292, 95% CI 123 to 547	days
		Placebo	70	Median 85, 95% CI 37 to 121	days
	Time to first episode: institution of additional treatment (survival in the study)	Lamotrigine	59	Median 85, 95% CI 44 to 142	days
		Lithium	46	Median 101, 95% CI 59 to 202	days
		Placebo	70	Median 58, 95% CI 34 to 108	days
Calabrese, 2000[41]	Time to first episode: institution of additional treatment	Lamotrigine	93	Median 18	weeks
		Placebo	89	Median 12	weeks
Calabrese, 2003[42]	Time relapse free: institution of additional treatment (survival in study)	Lamotrigine	124	Median 105, 95% CI 59 to 163	days
		Lamotrigine	47	Median 68, 95% CI 42 to 144	days
	Time to first episode: institution of additional treatment (survival in study)	Lamotrigine	50	Median 88, 95% CI 56 to 151	days
		Lamotrigine	124	Median 105, 95% CI 59 to 163	days
		Lamotrigine	47	Median 68, 95% CI 42 to 144	days
		Lithium	121	Median 86, 95% CI 63 to 111	days
		Placebo	121	Median 46, 95% CI 30 to 73	days
		Lamotrigine	171	Median 92, 95% CI 59 to 144	days
	Time to first episode: institution of additional treatment (survival in the study)	Lamotrigine	50	Median 88, 95% CI 56 to 151	days
		Lithium	121	Median 86, 95% CI 63 to 111	days
		Placebo	121	Median 46, 95% CI 30 to 73	days
		Lamotrigine	171	Median 92, 95% CI 59 to 144	days
	Time to first episode: institution of additional treatment (time to intervention)	Lamotrigine	50	Median 118, 95% CI 64 to 241	days
		Lamotrigine	124	Median 256, 95% CI 163 to 482	days
		Lamotrigine	47	Median 144, 95% CI 49 to 453	days
		Lithium	121	Median 170	days
		Placebo	121	Median 93, 95% CI 58 to 180	days
		Lamotrigine	171	Median 200, 95% CI 146 to 399	days
	Adverse events: specifically related to intervention (weight gain)	Lithium	121	Mean 4.2	kg
		Placebo	121	Median 1.2	kg
		Lamotrigine	171	Median –2.2	kg
Calabrese, 2005[43]	Time to first episode: institution of additional treatment	Divalproex	28	Median 45, range 5 to 58	weeks
		Lithium	32	Median 18, range 2 to 48	weeks
Colom, 2003a[45]	All relapses: admission to hospital (all randomised)	Group psychoeducation	NR	Mean 0.3	
		Non-structured group meeting	NR	Mean 0.78	

continued

Study	Outcome	Treatment	*N*	Results	Units
Dunner, 1976[48]	Number of relapses per patient year (depressive)	Lithium	16	Mean 0.85	
		Placebo	24	Mean 0.72	
	Number of relapses per patient year (hypomanic)	Lithium	16	Mean 0.09	
		Placebo	24	Mean 0.27	
Fieve, 1976[50]	Number of relapses per patient year (bipolar I/4 years)	Lithium	17	Mean 0.194	
		Placebo	18	Mean 0.853	
	Number of relapses per patient year (bipolar II/4 years)	Lithium	7	Mean 0.212	
		Placebo	11	Mean 0.367	
	Time to first episode: relapse as stated by authors (all patients/28 months)	Lithium	25	Mean 17.88 (SD 10.47)	months
		Placebo	27	Mean 6.33 (SD 7.21)	months
Findling, 2005[36]	Time to first episode: institution of additional treatment	Lithium	30	Median 114 (SE 57.4)	days
		Valproate	30	Median 112 (SE 56)	days
Kane, 1981[55]	Time to first of depressive episodes: relapse as stated by authors	Lithium + imipramine	37	Mean 3 (SD 0.8)	months
		Lithium	38	Mean 10.8 (SD 10.1)	months
	Time to first of manic episodes: relapse as stated by authors	Lithium + imipramine	37	Mean 10.2 (SD 10.6)	months
		Lithium	38	Mean 7.3 (SD 8)	months
Lam, 2000[58]	All relapses: admission to hospital	CBT	13	Mean 0 (SD 0)	
		No additional treatment	12	Mean 0.45 (SD 0.8)	
	Number of relapses	CBT	NR	Mean 0.42 (SD 0.9)	
		No additional treatment	NR	Mean 2 (SD 1.8)	
	Relapse of depressive episodes: relapse as stated by authors	CBT	13	Mean 0.17 (SD 0.6)	
		No additional treatment	12	Mean 0.73 (SD 0.9)	
	Relapse of manic episodes: relapse as stated by authors	CBT	13	Mean 0.08 (SD 0.3)	
		No additional treatment	12	Mean 0.63 (SD 0.8)	
Maj, 1986[61]	Number of relapses	Lithium	20	Mean 0.94 (SD 0.83)	
		Lithium	20	Mean 0.65 (SD 0.79)	
		Lithium	20	Mean 0.47 (SD 0.62)	
		Lithium	20	Mean 0.51 (SD 0.74)	
	Adverse events: any troublesome adverse event	Lithium	20	Mean 0.79 (SD 0.74)	
		Lithium	20	Mean 1.43 (SD 0.99)	
		Lithium	20	Mean 2.03 (SD 1.1)	
		Lithium	20	Mean 2.22 (SD 0.94)	
Miklowitz, 2003[62]	Time to first episode: relapse as stated by authors	Family-focused therapy	31	Mean 73.5 (SD 28.8)	weeks
		Crisis management	70	Mean 53.2 (SD 39.6)	weeks

continued

Study	Outcome	Treatment	*N*	Results	Units
Perry, 1999[63]	Time to first of depressive episodes: relapse as stated by authors (25th centile)	Psychoeducation	34	IQR 21	weeks
		No additional treatment	35	IQR 26	weeks
	Time to first of manic episodes: relapse as stated by authors (25th centile)	Psychoeducation	34	IQR 65	weeks
		No additional treatment	35	IQR 17	weeks
Platman, 1970[64]	Number of relapses	Imipramine	21	Mean 1	
		Lithium	49	Mean 0.6	
Revicki, 2005[69]	All relapses: admission to hospital	Divalproex	112	Mean 11.3 (SD 21.4)	days
		Lithium	109	Mean 14.1 (SD 27.7)	days
	Time relapse free: admission to hospital	Divalproex	112	Mean 5.3 (SD 4.6)	months
		Lithium	109	Mean 5.4 (SD 4.4)	months
Tohen, 2003[75]	Time to first episode: relapse as stated by authors	Olanzapine	125	Median 14	days
		Divalproex	126	Median 42	days
	Adverse events: specifically related to intervention (weight gain)	Olanzapine	125	Mean 2.79 (SE 0.32)	kg
		Divalproex	126	Mean 1.22 (SE 0.32)	kg
Tohen, 2004[76]	Time to first episode: relapse as stated by authors	Olanzapine + mood stabilisers	51	Median 94	days
		Mood stabilisers	48	Median 40.5	days
	Adverse events: specifically related to intervention (weight gain)	Olanzapine + mood stabilisers	51	Mean –1.8, 95% CI –3.2 to –0.4	kg
		Mood stabilisers	48	Mean 2, 95% CI 0.3 to 3.7	kg
Tohen, 2005[77]	Adverse events: specifically related to intervention (weight gain)	Olanzapine	217	Mean 1.8 (SD 5.8)	kg
		Lithium	214	Mean -1.4 (SD 5)	kg
Tohen, 2006[78]	Time to first episode: relapse as stated by authors (12 to <18 months)	Olanzapine	225	Median 174	days
		Placebo	136	Median 22	days
	Time to first of depressive episodes: relapse as stated by authors (12 to <18 months)	Olanzapine	225	IQR 49	days
		Placebo	136	IQR 18	days
	Time to first of manic episodes: relapse as stated by authors (12 to <18 months)	Placebo	136	IQR 26	days
	Adverse events: specifically related to intervention (weight gain)	Olanzapine	225	Mean 1 (SD 5.2)	kg
		Placebo	136	Mean –2 (SD 4.4)	kg
Zarate, 2004[80]	Time to first of depressive episodes: relapse as stated by authors (3 to <6 months)	Perphenazine + mood stabilisers	NR	Mean 157 (SE 10)	days

IQR, interquartile range; NR, not reported; SD, standard deviation; SE, standard error.

Appendix 7

Sensitivity analyses tables

Data are reported in *Tables 93–114*.

TABLE 93 *Lithium compared with placebo: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Lithium	Placebo	OR (95% CI), % weight
All relapses: admission to hospital			
Fieve BPI, 1976[50]	3/17	9/18	0.21 (0.04 to 1.01), 12.78
Fieve BPII, 1976[50]	1/7	2/11	0.75 (0.05 to 10.23), 2.37
Prien, 1974[66]	31/101	70/104	0.21 (0.12 to 0.39), 84.85
M–H pooled OR	$\chi^2 = 0.84$ (df = 2), $p = 0.66$		0.23 (0.13 to 0.39)
Test of OR = 1: $z = 5.38$, $p = 0.000$			
All relapses: institution of additional treatment			
Bowden, 2003[40]	18/46	49/70	0.28 (0.12 to 0.65), 33.19
Calabrese, 2003[42]	56/121	66/121	0.72 (0.42 to 1.23), 49.75
Prien, 1974[66]	12/101	14/104	0.87 (0.35 to 2.15), 17.06
M–H pooled OR	$\chi^2 = 5.05$ (df = 2), $p = 0.08$		0.6 (0.41 to 0.87)
Test of OR = 1: $z = 2.64$, $p = 0.0084$			
All relapses: as stated by authors			
Bowden, 2000[39]	28/91	36/94	0.72 (0.37 to 1.38), 24.26
Calabrese, 2003[42]	99/121	107/121	0.59 (0.26 to 1.28), 19.25
Kane, 1982[56]	1/4	5/7	0.13 (0.00 to 3.50), 2.7
Prien, 1973[65]	9/18	12/13	0.08 (0.00 to 0.85), 6.89
Prien, 1974[66]	47/101	90/104	0.14 (0.06 to 0.28), 46.91
M–H pooled OR	$\chi^2 = 16.61$ (df = 4), $p = 0.0023$		0.36 (0.25 to 0.52)
Test of OR = 1: $z = 5.63$, $p < 0.0001$			

TABLE 94 *Lithium compared with placebo: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Lithium	Placebo	OR (95% CI), % weight
All relapses: admission to hospital			
Fieve BPI, 1976[50]	3/17	9/18	0.21 (0.04 to 1.01), 12.78
Fieve BPII, 1976[50]	1/7	2/11	0.75 (0.05 to 10.23), 2.37
Prien, 1974[66]	31/101	70/104	0.21 (0.12 to 0.39), 84.85
M–H pooled OR	$\chi^2 = 0.84$ (df = 2), $p = 0.66$		0.23 (0.13 to 0.39)
Test of OR = 1: $z = 5.38$, $p = 0.000$			
All relapses: institution of additional treatment			
Bowden, 2003[40]	20/46	50/70	0.31 (0.13 to 0.72), 31.78
Calabrese, 2003[42]	57/121	68/121	0.69 (0.41 to 1.19), 50.99
Prien, 1974[66]	12/101	14/104	0.87 (0.35 to 2.15), 17.23
M–H pooled OR	$\chi^2 = 3.897$ (df = 2), $p = 0.1425$		0.60 (0.41 to 0.87)
Test of OR = 1: $z = 2.58$, $p = 0.0098$			
All relapses: as stated by authors			
Bowden, 2000[39]	28/91	36/94	0.72 (0.39 to 1.32), 24.38
Calabrese, 2003[42]	100/121	109/121	0.52 (0.24 to 1.12), 18.81
Kane, 1982[56]	1/4	5/7	0.13 (0.01 to 2.18), 2.71
Prien, 1973[65]	9/18	12/13	0.08 (0.01 to 0.78), 6.93
Prien, 1974[66]	47/101	90/104	0.13 (0.07 to 0.27), 47.15
M–H pooled OR	$\chi^2 = 15.82$ (df = 4), $p = 0.003$		0.35 (0.24 to 0.50)
Test of OR = 1: $z = 5.67$, $p = 0.000$			

TABLE 95 *Lithium compared with lamotrigine: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Lithium	Lamotrigine	OR (95% CI), % weight
All relapses: institution of additional treatment			
Bowden, 2003[40]	18/46	28/59	0.71 (0.32 to 1.55), 28.78
Calabrese, 2003[42]	56/121	83/171	0.91 (0.57 to 1.45), 71.22
M–H pooled OR	$\chi^2 = 0.29$ (df = 1), $p = 0.59$		0.85 (0.57 to 1.28)
Test of OR = 1: $z = 0.76$, $p = 0.44$			
All relapses: as stated by authors			
Calabrese, 2003[42]	99/121	134/171	1.24 (0.69 to 2.24), 100

TABLE 96 *Lithium compared with lamotrigine: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Lithium	Lamotrigine	OR (95% CI), % weight
All relapses: institution of additional treatment			
Bowden, 2003[40]	20/46	29/59	0.79 (0.37 to 1.73), 26.91
Calabrese, 2003[42]	57/121	89/171	0.82 (0.51 to 1.31), 73.09
M–H pooled OR	$\chi^2 = 0.00$ (df = 1), $p = 0.95$		0.81 (0.54 to 1.21)
Test of OR = 1: $z = 1.01$, $p = 0.31$			
All relapses: as stated by authors			
Calabrese, 2003[42]	100/121	140/171	1.05 (0.57 to 1.94), 100

TABLE 97 *Lithium compared with carbamazepine: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Lithium	Carbamazepine	OR (95% CI), % weight
All relapses: admission to hospital			
Kleindienst BPI, 2000[57]	20/58	21/56	0.88 (0.38 to 2.02), 65.54
Kleindienst BPII, 2000[57]	7/28	3/29	2.89 (0.56 to 19.09), 10.39
Simhandl, 1993[72]	3/21	5/14	0.3 (0.04 to 2.02), 24.06
M–H pooled OR	$\chi^2 = 4.14$ (df = 2), $p = 0.1263$		0.95 (0.52 to 1.74)
Test of OR = 1: $z = 0.02$, $p = 0.9821$			
All relapses: as stated by authors			
Coxhead, 1992[47]	8/16	6/15	1.50 (0.36 to 6.23), 8.44
Hartong, 2003[53]	3/23	14/30	0.17 (0.04 to 0.70), 28.80
Kleindienst BPI, 2000[57]	24/58	28/56	0.70 (0.34 to 1.48), 45.53
Kleindienst BPII, 2000[57]	10/28	10/29	1.05 (0.35 to 3.13), 17.22
M–H pooled OR	$\chi^2 = 5.50$ (df = 3), $p = 0.14$		0.68 (0.41 to 1.12)
Test of OR = 1: $z = 1.50$, $p = 0.13$			

TABLE 98 *Lithium compared with carbamazepine: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Lithium	Carbamazepine	OR (95% CI), % weight
All relapses: admission to hospital			
Kleindienst BPI, 2000[57]	24/58	39/56	0.31 (0.13 to 0.71), 65.93
Kleindienst BPII, 2000[57]	14/28	14/29	1.07 (0.34 to 3.43), 19.5
Simhandl, 1993[72]	3/21	5/14	0.3 (0.04 to 2.02), 14.57
M–H pooled OR	$\chi^2 = 3.84$ (df = 2), $p = 0.1464$		0.46 (0.26 to 0.8)
Test of OR = 1: $z = 2.60$, $p = 0.0093$			
All relapses: as stated by authors			
Coxhead, 1992[47]	9/16	8/15	1.12 (0.22 to 5.78), 8.33
Hartong, 2003[53]	4/23	14/30	0.24 (0.05 to 1), 23.09
Kleindienst BPI, 2000[57]	28/58	42/56	0.31 (0.13 to 0.74), 50.83
Kleindienst BPII, 2000[57]	17/28	20/29	0.7 (0.2 to 2.37), 17.76
M–H pooled OR	$\chi^2 = 3.93$ (df = 3), $p = 0.2696$		0.43 (0.26 to 0.73)
Test of OR = 1: $z = 3.06$, $p = 0.0022$			

TABLE 99 *Lithium compared with olanzapine: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Lithium	Olanzapine	OR (95% CI), % weight
All relapses: admission to hospital			
Tohen, 2005[77]	49/214	31/217	1.78 (1.08 to 2.93), 100
All relapses: as stated by authors			
Tohen, 2005[77]	69/214	53/217	1.47 (0.96 to 2.24), 100

TABLE 100 *Lithium compared with olanzapine: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Lithium	Olanzapine	OR (95% CI), % weight
All relapses: admission to hospital			
Tohen, 2005[77]	49/214	31/217	1.78 (1.08 to 2.93), 100
All relapses: as stated by authors			
Tohen, 2005[77]	90/214	68/217	1.59 (1.07 to 2.36), 100

TABLE 101 *Lithium compared with imipramine: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Lithium	Imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	1/4	3/5	0.22 (0.01 to 3.98), 8.47
Prien, 1973[65]	9/18	11/13	0.18 (0.03 to 1.06), 27.05
Prien, 1984[67]	23/44	29/36	0.26 (0.09 to 0.73), 64.48
M–H pooled OR	$\chi^2 = 0.13$ (df = 2), $p = 0.94$		0.24 (0.10 to 0.55)
Test of OR = 1: $z = 3.34$, $p = 0.001$			

TABLE 102 *Lithium compared with imipramine: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Lithium	Imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	1/4	3/5	0.22 (0.01 to 3.98), 9.02
Prien, 1973[65]	9/18	11/13	0.18 (0.03 to 1.06), 28.82
Prien, 1984[67]	25/44	29/36	0.32 (0.11 to 0.88), 62.15
M–H pooled OR	$\chi^2 = 0.31$ (df = 2), $p = 0.86$		0.27 (0.12 to 0.62)
Test of OR = 1: $z = 3.05$, $p = 0.002$			

TABLE 103 *Lithium compared with lithium + imipramine: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Lithium	Lithium + imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1981[55]	8/38	12/37	0.55 (0.20 to 1.57), 49.15
Kane, 1982[56]	1/4	1/6	1.67 (0.07 to 37.72), 3.07
Prien, 1984[67]	23/44	18/37	1.16 (0.48 to 2.77), 47.78
M–H pooled OR	$\chi^2 = 1.29$ (df = 2), $p = 0.53$		0.88 (0.46 to 1.68)
Test of OR = 1: $z = 0.40$, $p = 0.69$			

TABLE 104 *Lithium compared with lithium + imipramine: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Lithium	Lithium + imipramine	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1981[55]	8/38	12/37	0.55 (0.20 to 1.57), 50.22
Kane, 1982[56]	1/4	1/6	1.67 (0.07 to 37.72), 3.14
Prien, 1984[67]	25/44	19/37	1.25 (0.52 to 3.00), 46.63
M–H pooled OR	$\chi^2 = 1.50$ (df = 2), $p = 0.47$		0.91 (0.48 to 1.75)
Test of OR = 1: $z = 0.28$, $p = 0.78$			

TABLE 105 *Valproate compared with olanzapine: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Valproate	Olanzapine	OR (95% CI), % weight
All relapses: as stated by authors			
Tohen, 2003[75]	13/126	20/125	0.60 (0.29 to 1.27), 100

TABLE 106 *Valproate compared with olanzapine: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Valproate	Olanzapine	OR (95% CI), % weight
All relapses: as stated by authors			
Tohen, 2003[75]	119/126	114/125	1.64 (0.61 to 4.38), 100

TABLE 107 *Lamotrigine compared with placebo: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Lamotrigine	Placebo	OR (95% CI), % weight
All relapses: institution of additional treatment			
Bowden, 2003[40]	28/59	49/70	0.39 (0.19 to 0.80), 26.41
Calabrese, 2000[41]	45/93	49/89	0.76 (0.43 to 1.37), 28.98
Calabrese, 2003[42]	83/171	66/121	0.78 (0.49 to 1.25), 44.61
M–H pooled OR	$\chi^2 = 2.86$ (df = 2), $p = 0.24$		0.67 (0.49 to 0.93)
Test of OR = 1: $z = 2.38$, $p = 0.02$			
All relapses: as stated by authors			
Calabrese, 2003[42]	134/171	107/121	0.47 (0.24 to 0.92), 100

TABLE 108 *Lamotrigine compared with placebo: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Lamotrigine	Placebo	OR (95% CI), % weight
All relapses: institution of additional treatment			
Bowden, 2003[40]	29/59	50/70	0.39 (0.19 to 0.80), 26.83
Calabrese, 2000[41]	48/93	51/89	0.79 (0.44 to 1.43), 29.10
Calabrese, 2003[42]	89/171	68/121	0.84 (0.53 to 1.35), 44.08
M–H pooled OR	$\chi^2 = 3.36$ (df = 2), $p = 0.19$		0.71 (0.51 to 0.98)
Test of OR = 1: $z = 2.09$, $p = 0.037$			
All relapses: as stated by authors			
Calabrese, 2003[42]	140/171	109/121	0.91 (0.64 to 1.28), 100

TABLE 109 *Imipramine compared with imipramine + lithium: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Imipramine	Imipramine + lithium	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	3/5	1/6	7.5 (0.29 to 470.49), 9.42
Prien, 1984[67]	29/36	18/37	4.37 (1.38 to 14.63), 90.58
M–H pooled OR	$\chi^2 = 0.13$ (df = 1), $p = 0.7231$		4.67 (1.75 to 12.44)
Test of OR = 1: $z = 2.93$, $p = 0.0034$			

TABLE 110 *Imipramine compared with imipramine + lithium: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Imipramine	Imipramine + lithium	OR (95% CI), % weight
All relapses: as stated by authors			
Kane, 1982[56]	3/5	1/6	7.5 (0.29 to 470.49), 9
Prien, 1984[67]	29/36	19/37	3.92 (1.24 to 13.14), 91
M–H pooled OR	$\chi^2 = 0.18$ (df = 1), $p = 0.6706$		4.25 (1.6 to 11.31)
Test of OR = 1: $z = 2.73$, $p = 0.0064$			

TABLE 111 *CBT compared with TAU: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	CBT	TAU	OR (95% CI), % weight
All relapses: admission to hospital			
Cochran, 1984[44]	2/14	5/14	0.30 (0.05 to 1.91), 100
All relapses: as stated by authors			
Cochran, 1984[44]	3/14	8/14	0.20 (0.04 to 1.07), 19.14
Lam, 2000[58]	3/13	10/12	0.06 (0.01 to 0.44), 25.14
Lam, 2005[59]	30/51	43/52	0.30 (0.12 to 0.74), 55.10
M–H pooled OR	$\chi^2 = 2.08$ (df = 2), $p = 0.35$		0.22 (0.11 to 0.46)
Test of OR = 1: $z = 4.07$, $p = 0.000$			

TABLE 112 *CBT compared with TAU: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	CBT	TAU	OR (95% CI), % weight
All relapses: admission to hospital			
Cochran, 1984[44]	2/14	5/14	0.30 (0.05 to 1.91), 100
All relapses: as stated by authors			
Cochran, 1984[44]	3/14	8/14	0.20 (0.04 to 1.07), 22.13
Lam, 2000[58]	4/13	11/12	0.04 (0.00 to 0.43), 27.89
Lam, 2005[59]	34/51	43/52	0.42 (0.17 to 1.05), 49.98
M–H pooled OR	$\chi^2 = 3.47$ (df = 2), $p = 0.18$		0.26 (0.13 to 0.55)
Test of OR = 1: $z = 3.53$, $p = 0.000$			

TABLE 113 *Psychoeducation compared with TAU: pooled OR for all randomised participants added to the denominator (best outcome)*

Study	Psychoeducation	TAU	OR (95% CI), % weight
All relapses: admission to hospital			
Perry, 1999[63]	12/34	15/35	0.73 (0.27 to 1.92), 100

TABLE 114 *Psychoeducation compared with TAU: pooled OR for all randomised participants added to the denominator (worst outcome)*

Study	Psychoeducation	TAU	OR (95% CI), % weight
All relapses: admission to hospital			
Perry, 1999[63]	13/34	15/35	0.82 (0.31 to 2.16), 100

Appendix 8

Mixed treatment comparison

Method details

The logistic model is designed to model binary trial end-points. Trials reported number of manic, depressive and/or all relapses. In each trial, different treatments were compared, with a number of them being three-arm trials. Eight different treatments for bipolar disorder relapse prevention were analysed. The comparisons available for those trials that comprised the network of evidence have already been described and are shown in *Table 78*.

For numerical convenience, we modelled all treatment effects on the log-odds scale, assuming that they are additive to the baseline. To reflect slight differences in recruitment criteria and patient mix, for each type of relapse (manic, depressive or all types) the baseline event rates are assumed to vary randomly around a common mean (i.e. using trial-specific baselines). For the purposes of the cost-effectiveness analysis, manic and depressive relapses were specifically modelled ($x = 1$ for mania and 2 for depression). The model has a regression-like structure with the response γ_{jkx} for trial arm i of study j receiving treatment k derived from a study-specific 'baseline' term (μ_{xj}) and a treatment effect (β_{xjk}):

$$\gamma_{jkx} = \mu_{xj} + \beta_{xjk}$$

The model was implemented as a Bayesian hierarchical model using WinBUGS.[83] In each trial j we observe r_{jkx} episode-specific relapses for the comparator treatments k, in a sample of n_{jkx}.

The likelihood takes the form

$$r_{jkx} \sim \text{Bin}(p_{jkx}, n_{jkx})$$

where p_{jkx} is the probability of relapse under treatment k, specific for both manic and depressive type of relapses.

A fundamental assumption in all meta-analyses is that the true treatment effect is common to all trials (fixed effects), or that the trial-specific treatment differences are derived from a common distribution, which is the same across all sets of trials (random effects). In other words, the key assumption for the fixed effect meta-analysis is that the relative effect of one treatment compared with another is the same across the entire set of trials, whereas the random effect meta-analysis model specifically allows for the existence of between-study heterogeneity as well as the within-study variability.[119] Due to the limited number of trials (only three or less than three trials were available for the majority of treatments), here the treatment effects are modelled as a **fixed treatment-effect model** on the log-odds scale, additive to the baseline probability of relapse. Assuming that treatments effects β_{xjk} are additive to the baseline μ_{xj} on the log-odds scale and that treatment b is the reference treatment in study j, our underlying model is

$$\begin{aligned} \text{logit}(p_{jkx}) &= \mu_{xjb} && \text{if } k = b \\ \text{logit}(p_{jkx}) &= \mu_{xjb} + \delta_{xbk} && \text{for the rest of treatment } k \end{aligned}$$

where $\delta_{xbk} = \beta_{xjk} - \beta_{xjb}$, μ_{xjb} is the log-odds of relapse on treatment b in trial j (a study-specific 'baseline' parameter) for both manic and depressive outcomes x and δ_{xbk} are the log-odds ratios relative to the control treatment b, also for both manic and depressive relapses. For example, if trial j compares treatments B and C, the B arm provides an estimate of $\text{logit}(p_{xjB}) = \mu_{xjB}$, while the C arm estimates $\text{logit}(p_{xjC}) = \mu_{xjB} + \delta_{xBC}$. By default, the most common treatment across all trials (lithium) was used as the control treatment b, followed by the second most common treatment (placebo) when lithium was not present in any of the trial arms, and so on.

As already mentioned, trials reported the number of manic, depressive and/or all types of relapses. We borrowed strength[82] from data reported on all relapses in order to inform the split manic/depressive relapses when this was not explicitly reported in individual trials, using the constraint that the number of all relapses equals the sum of manic and depressive relapses. This assumption was validated using the data provided by those trials which reported the three types of outcomes: manic (1), depressive (2) and all (3) relapses:

$$\text{logit}(p_{1k}) = \mu_{1jb} + \delta_{1bk}$$

$$\text{logit}(p_{2k}) = \mu_{2jb} + \delta_{2bk}$$
$$\text{logit}(p_{3k}) = \min(1, p_{1k} + p_{2k})$$

where the likelihood is

$$r_{jkx} \sim \text{Bin}(p_{jkx}, n_{jkx}) \qquad \text{for } x = 1, 2$$

A full Bayesian analysis requires the specification of prior distributions for unknown parameters. The following vague priors were defined, using the convention of specifying the mean and precision of a normal distribution:

$$\beta_{xjk} \sim \text{Normal}(0, 0.0001)$$
$$\mu_{xj} \sim \text{Normal}(0, 0.0001)$$

For the extrapolation model, the baseline risk of relapse was not taken from all trials. We decided to select trials with a length of follow-up of 1 year, instead of averaging across all different follow-up periods. Lithium instead of placebo was selected as the baseline treatment as this can be considered to be the standard treatment for prevention of relapse and because doing nothing is not an option for bipolar patients. Other additional criteria for the selection of our baseline trials included that all patients analysed had to be bipolar I patients and stable at randomisation, and that trials reported number of manic and depressive relapses. Only a small number of trials fulfilled the stated criteria. The Bowden study[40] was finally not considered because of its small sample size and because it did not present the right follow-up, and, although an exponential functional adjustment of the annual hazard could have been undertaken, it was decided to use direct evidence instead. For the purposes of the cost-effectiveness model, two baseline risks were considered: Analysis 1 used a baseline risk for patients having experienced a pretrial depressive episode (from Calabrese and colleagues[42], data reported for 12 months' follow-up), whereas Analysis 2 used a baseline risk for patients having experienced a pretrial manic episode (from Tohen and colleagues[77] and Bowden and colleagues[39]). The selection criteria and the final decision on the selection of these three trials were decided in consultation with our clinical experts.

The meta-analysis then provided estimates of the relapse rate for each of the treatments based on all observed comparisons and adjusted for within trial variation, but incorporating the probability of relapse of these three selected lithium trials as the common baseline risk (Analysis 1 and Analysis 2). These estimates were used in the cost-effectiveness model as the absolute probability of experiencing a manic and depressive relapse for patients taking any of the potential pharmacological treatments object of analysis.

Some trials also reported number of relapses defined as requiring hospitalisation. Only for the purpose of estimating the probability of hospitalisation for mania and depression, we recoded all the definitions of relapse into two main categories ($h = 1$ for hospitalisation and 2 for not hospitalisation), assuming that the 'as stated by authors' and 'requiring additional treatment' definitions were equivalent to not requiring hospitalisation when either of them and the hospitalisation definition were reported in the same trial. An extension of our original model (Model 2) was built where the probability of hospitalisation conditional on having a manic or depressive relapse (pH_x) was estimated at the same time as the probability of relapse (p_{xk}). Where appropriate, the probability of having a relapse was multiplied in the model with a probability of hospitalisation, given a relapse:

$$p_{xhk} = p_{xk} \times pH_x \qquad \text{if } h = 1$$
$$p_{xhk} = p_{xk} \times (1 - pH_x) \qquad \text{if } h = 2$$

The likelihood takes the form

$$r_{jk} \sim \text{Bin}(p_{xhk}, n_{jk})$$

where p_{xhk} is the joint probability of being or not hospitalised and having a relapse under treatment k, specific for both manic and depressive type of relapses.

The conditional probability of hospitalisation was assumed to be independent of the treatment, but it was specific to manic or depressive relapses (see the WinBUGS code for the Hospitalisation Model in the next section for further details). However, the probability of relapse obtained from this extended model was not used to inform our cost-effectiveness model, as we decided to use only data from the most common definition ('as stated by authors') and not include different levels of severity in order to estimate the absolute probability of relapse (see Chapter 3, 'Mixed treatment comparison', p. 10).

The evidence synthesis was conducted using WinBUGS version 1.4.[83] A burn-in period of 50,000 simulations was used to allow convergence followed by 50,000 simulations for estimation. As autocorrelation was observed in some of the model parameters, the model was 'thinned' so every fifth simulation was retained. Three chains were

compiled starting from different initial values. The Gelman–Rubin diagnostic plot was checked to ensure that the model converged satisfactorily. A range of uninformative vague priors for the main parameters of interest was also tested to verify that the choice of prior did not have a noticeable impact on the results. The ordering of treatments according to their efficacy in the prevention of manic and depressive relapses did not contradict results from direct treatment comparisons, as specific treatments for treating depressive and manic relapses were appropriately ranked. Results were validated by our clinical experts.

Finally, we tested the model fitting using the deviance information criteria (DIC) tool.[120] Although, as expected, the fixed treatment effect model was found to fit the data slightly less well than the random effects model (e.g. for Analysis 1, deviance 392.9, DIC 429.7 compared with deviance 379.7, DIC 410.4 for the equivalent random effect model), we decided to use the former for the reasons of limited trial evidence stated above. Results for the random and fixed treatment effect models were also compared for both manic and depressive relapses, but only very minor differences could be observed.

The WinBUGS code is reproduced below.

WinBUGS code for mixed treatment comparison model

Analysis 1: pre-trial depressive episode

```
Model

{

for(i in 1:N)

      {
      logit(p[1,i])<-mu[1,s[i]]+delta[1,i]*(1-equals(t[i],b[i]))    #MODEL – logit link for prob. of response
      logit(p[2,i])<-mu[2,s[i]]+delta[2,i]*(1-equals(t[i],b[i]))
      p[3,i]<-min(1,p[1,i]+p[2,i])                                  #Functional constraint

      r[i]~dbin(p[type[i],i], n[i])                                 #BINOMIAL LIKELIHOOD

      for(x in 1:2)
            {
            delta[x,i]<-md[x,i]                                     #Fixed effect model

            md[x,i]<-d[x,t[i]]-d[x,b[i]]                            #Relative treatment effect
            }
      }

for (j in 1: NS)
      {
      for(x in 1:2)
            {
            mu[x,j]~dnorm(0,0.0001)                                 #Unconstrained baseline
            }
      }

for(x in 1:2)
      {
      logit(pext[x])<-muext[x]                                      #External common baseline
      muext[x]<-mu[x,17]
```

```
    d[x,1]<-0
    for (k in 1:NT)
        {
        logit(T[x, k])<-muext[x]+d[x, k]          #Absolute prob. of relapse (episode specific)
        rk[x,k]<-rank(T[x,1:NT],k)                #Ranking and prob. treatment k is best
        best[x,k]<-equals(rk[x,k],1)              #OR compared against lithium
        OR[x,k]<-exp(d[x,k])
        d[x,k]~dnorm(0,0.0001)
        }

    for (c in 1:(NT-1))
        {
        for (k in (c+1):NT)
            {
            ORpair[x,c,k]<-exp(d[x,k]-d[x,c]) #All pairwise O.R.
            }
        }

    }
    pext[3]<-min(1,pext[1]+pext[2])
    for(k in 1:NT)
        {
        T[3,k]<-min(1,T[1,k]+T[2,k])
        }

    }
```

Analysis 2: pre-trial manic episode

```
Model

{

for(i in 1:N)

    {
    logit(p[1,i])<-mu[1,s[i]]+delta[1,i]*(1-equals(t[i],b[i]))   #MODEL – logit link for prob. of response
    logit(p[2,i])<-mu[2,s[i]]+delta[2,i]*(1-equals(t[i],b[i]))
    p[3,i]<-min(1,p[1,i]+p[2,i])                                 #Functional constraint

    r[i]~dbin(p[type[i],i], n[i])                                #BINOMIAL LIKELIHOOD

    for(x in 1:2)
        {
        delta[x,i]<-md[x,i]                                      #Fixed effect model

        md[x,i]<-d[x,t[i]]-d[x,b[i]]                             #Relative treatment effect
        }
    }

for (j in 1: NS)
    {
    for(x in 1:2)
        {
        mu[x,j]~dnorm(0,0.0001)                                  #Unconstrained baseline
        }
    }
```

```
for(x in 1:2)
      {
      logit(pext[x])<-muext[x]                    #External common baseline (average two
                                                  trials)
      muext[x]<-(mu[x,1]+mu[x,2])/2

      d[x,1]<-0
      for (k in 1:NT)
            {
            logit(T[x, k])<-muext[x]+d[x, k]      #Absolute prob. of relapse (episode specific)
            rk[x,k]<-rank(T[x,1:NT],k)            #Ranking and prob. treatment k is best
            best[x,k]<-equals(rk[x,k],1)          #OR compared against lithium
            OR[x,k]<-exp(d[x,k])
            d[x,k]~dnorm(0,0.0001)
            }

      for (c in 1:(NT-1))
            {
            for (k in (c+1):NT)
                  {
                  ORpair[x,c,k]<-exp(d[x,k]-d[x,c]) #All pairwise O.R.
                  }
            }

      }
      pext[3]<-min(1,pext[1]+pext[2])
      for(k in 1:NT)
            {
            T[3,k]<-min(1,T[1,k]+T[2,k])
            }

      }
```

Hospitalisation model

```
model

{

for(i in 1:N)
      {
      logit(p[1,i])<-mu[1,s[i]]+delta[1,i]*(1-equals(t[i],b[i]))
      logit(p[2,i])<-mu[2,s[i]]+delta[2,i]*(1-equals(t[i],b[i]))
      p[3,i]<-min(1,p[1,i]+p[2,i])

      for(x in 1:2)
            {
            delta[x,i]<-md[x,i]
            md[x,i]<-d[x,t[i]]-d[x,b[i]]
            }
      }

for(i in 1:N)
      {
      psplit[1,1,i]<-p[1,i]*phosp[1,t[i]]
      psplit[1,2,i]<-p[1,i]*(1-phosp[1,t[i]])
      psplit[2,1,i]<-p[2,i]*phosp[2,t[i]]
```

```
        psplit[2,2,i]<-p[2,i]*(1-phosp[2,t[i]])
        psplit[3,1,i]<-psplit[1,1,i]+psplit[2,1,i]
        psplit[3,2,i]<-psplit[1,2,i]+psplit[2,2,i]
        r[i]~dbin(psplit[type[i],hosp[i],i],n[i])
        }

for (x in 1:2)
        {
        for (k in 1:NT)
                {
                phosp[x,k]~dbeta(hospa[x],hospb[x])
                }
        hospa[x]~dexp(0.01)
        hospb[x]~dexp(0.01)
        hospav[x]<-hospa[x]/(hospa[x]+hospb[x])
        }

for (j in 1: 3)
        {
        for(x in 1:2)
                {
                mu[x,j]~dnorm(muext[x],tauext)
                }
        }

for (j in 4: NS)
        {
        for(x in 1:2)
                {
                mu[x,j]~dnorm(0,0.0001)
                }
        }

sdext~dunif(0,2)
tauext<-1/pow(sdext,2)

for(x in 1:2)
        {
        logit(pext[x])<-muext[x]
        muext[x]~dnorm(0,0.0001)

        d[x,1]<-0
        for (k in 1:NT)
                {
                logit(T[x, k])<-muext[x]+d[x, k]
                rk[x,k]<-rank(T[x,1:NT],k)
                best[x,k]<-equals(rk[x,k],1)
                ORbis[x,k]<-exp(d[x,k])
                }

for (k in 2:NT)
                {
                OR[x,k]<-(T[x,k]/(1-T[x,k]))/(T[x,1]/(1-T[x,1]))
                d[x,k]~dnorm(0,0.0001)
                }
        }
        pext[3]<-min(1,pext[1]+pext[2])
```

```
    for(k in 1:NT)
        {
        T[3,k]<-min(1,T[1,k]+T[2,k])
        }

}
```

Mixed treatment comparison sensitivity analysis

Sensitivity analysis data are given in *Table 115*.

TABLE 115 *Main results of MTC sensitivity analysis: probability of relapse for patients with pretrial acute depressive episode (Analysis 1) and pretrial acute manic episode (Analysis 2)*

	Analysis 1			Analysis 2		
	Best case	**Worst case**	**BPII + olanzapine[a] responders**	**Best case**	**Worst case**	**BPII + olanzapine[a] responders**
Type of relapse: all						
Lithium	0.46	0.46	0.46	0.27	0.36	0.29
Placebo	0.71	0.76	0.73	0.50	0.60	0.50
Divalproex/valproate	0.36	0.41	0.38	0.28	0.32	0.27
Imipramine	0.57	0.65	0.64	0.65	0.68	0.65
Lamotrigine	0.44	0.47	0.44	0.37	0.44	0.37
Olanzapine	0.49	0.57	0.54	0.22	0.28	0.24
Carbamazepine	0.87	0.94	0.93	0.83	0.83	0.85
Lithium + imipramine	0.42	0.44	0.41	0.37	0.44	0.36
Type of relapse: depression						
Lithium	0.38	0.38	0.38	0.07	0.12	0.08
Placebo	0.56	0.60	0.58	0.16	0.21	0.18
Divalproex/valproate	0.27	0.32	0.28	0.05	0.07	0.05
Imipramine	0.26	0.30	0.30	0.05	0.08	0.06
Lamotrigine	0.30	0.32	0.30	0.06	0.09	0.06
Olanzapine	0.45	0.54	0.50	0.13	0.16	0.13
Carbamazepine	0.68	0.76	0.74	0.34	0.42	0.35
Lithium + imipramine	0.28	0.29	0.27	0.05	0.08	0.05
Type of relapse: mania						
Lithium	0.08	0.08	0.08	0.19	0.24	0.20
Placebo	0.14	0.15	0.14	0.33	0.38	0.32
Divalproex/valproate	0.08	0.09	0.09	0.22	0.24	0.22
Imipramine	0.30	0.35	0.33	0.59	0.60	0.58
Lamotrigine	0.13	0.14	0.13	0.31	0.35	0.31
Olanzapine	0.04	0.03	0.04	0.08	0.12	0.10
Carbamazepine	0.26	0.37	0.38	0.57	0.48	0.60
Lithium + imipramine	0.13	0.14	0.13	0.31	0.35	0.31

[a] Inclusion of trials with BPII patients only and one olanzapine responders trial.[78]

Appendix 9

Quality assessment of economic evaluations reviewed

Quality assessment of the NICE economic evaluation

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.

Study question	Answer	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	Three pharmacological agents: lithium 1000 mg/day, valproate 1250 mg/day, olanzapine 10 mg/day
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	NHS
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	?	Other pharmacological agents for long-term treatment of patients with bipolar disorder are available. No treatment/placebo was considered
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	Average dosages described
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	Alternatives chosen on the basis of the available clinical evidence. Only clinical evidence obtained from RCTs was included
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	Cost-effectiveness and cost–utility analyses
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 evidence was based on a meta-analysis of RCTs
10. Effectiveness data from RCT or review of RCTs	✓	Inclusion criteria for RCT were the use of relapse rate as main clinical outcome reported separately for acute/mixed and depressive episodes
11. Potential biases identified (especially if data not from RCTs)	NA	
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)	✓	Since the majority of the trials included placebo in one of the treatment arms, relative risks of manic and depressive relapses for all pharmacological treatments were estimated in comparison with placebo
Costs		
13. All the important and relevant resource use included	×	Resource use and costs associated with the treatment of adverse events of long-term medications not included

continued

Study question	Answer	Comments
14. All the important and relevant resource use measured accurately (with methodology)	?	The majority of resource use was based on experts' opinion given the lack of published data
15. Appropriate unit costs estimated (with methodology)	✓	Unit costs based on standard UK sources
16. Unit costs reported separately from resource use data	✓	Resource use and unit costs were reported separately for all items
17. Productivity costs treated separately from other costs	NA	Not relevant given the perspective of the study
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	The price year was 2004/2005. All costs were estimated from UK sources
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	Number of patients remaining stable, number of days free from acute episodes and QALYs
20. Methods to value health states and other benefits are stated (e.g. TTO)	✓	Utility values were based on published studies that used both the visual analogue scale and the standard gamble approach
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	✓	Patients with bipolar disorder in stable state
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	Markov model with a time-horizon of 5 years and yearly cycles. Structure and assumptions of the model reported
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	Some model parameters are based on assumptions and experts' opinion
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance (3.5% for costs and benefits, or based on historical approaches – 1.5–2% for benefits; 6% for costs)?	✓	3.5% for both costs and benefits
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and CIs are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	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?	✓	Key parameters were varied in the probabilistic sensitivity analysis
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	?	Type of distributions reported and appropriate, but no other details given (mean, SD, etc.)
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)	×	

continued

Study question	Answer	Comments
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	Univariate sensitivity analysis
35. The choice of variables for sensitivity analysis is justified	×	Only some model parameters that had been based on assumptions were varied
36. The ranges over which the variables are varied are stated	✓	However, ranges were based again on assumptions
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	Incremental ratios calculated. Alternative dominated by absolute or extended dominance excluded
38. Major outcomes are presented in a disaggregated as well as aggregated form	×	Mean costs and mean utilities reported by each strategy. Disaggregated data on costs per treatment option not reported
39. Applicable to the NHS setting	✓	

Quality assessment of the cost-effectiveness model submitted by Chisholm and colleagues[88]

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.

Study question	Answer	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	Lithium compared with valproic acid, alone and in combination with psychosocial treatment
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	Healthcare system
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	?	Other pharmacological agents for long-term treatment of patients with bipolar disorder are available
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	×	Average/optimal dosage for valproic acid not described
6. The rationale for choosing the alternative programmes or interventions compared is stated	×	Lithium chosen on the basis of proven efficacy in the acute and prophylactic treatment of both manic and depressive episodes. Selection criteria relaxed in order to choose a comparator which evidence exists only for prophylactic effect, but the reason why valproic acid was selected among other available mood stabilisers is unclear
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	?	It is not clear whether a cost-effectiveness analysis was the best analytical option given the aim of the study
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	

continued

Study question	Answer	Comments
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	✓	Treatment effect limited to reduction of time length with episodes and a reduction of the suicidal rate ascribed only to lithium
11. Potential biases identified (especially if data not from RCTs)	×	Potential biases and generalisability of studies to global subregions not discussed
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	✓	Resource use assumed to be the same among all the 14 global subregions as the same level of coverage is being modelled (50%)
14. All the important and relevant resource use measured accurately (with methodology)	✓	Estimates based on earlier modelling studies (developed countries[91,92]) and on a multinational Delphi consensus panel (for developing countries[93])
15. Appropriate unit costs estimated (with methodology)	?	Not reported. Details of subregional unit costs on WHO-CHOICE website
16. Unit costs reported separately from resource use data	?	Not reported. Details of subregional unit costs on WHO-CHOICE website
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	International dollars (I$), price year 2000
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	DALYs averted
20. Methods to value health states and other benefits are stated (e.g. TTO)	×	Composite disability weight for untreated patients estimated based on data on time spent with episodes before receiving treatment (50%[121]), adjusted by time spent in depressive vs manic.[8] The method to estimate the disability weight for treated patients is not clear
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)	✓	It can be inferred that it is a Markov model type
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	?	The model is based on very strong assumptions, especially regarding the way in which the authors have estimated the treatment effect of the interventions compared

continued

Study question	Answer	Comments
24. All model outputs described adequately	×	Benefits expressed as age-weighted population health gain of DALYs averted annually by first-line treatment of bipolar disorder. The outcome measure is difficult to interpret. Cost-effectiveness results expressed as average cost-effectiveness ratios per treatment
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance (3.5% for costs and benefits, or based on historical approaches – 1.5–2% for benefits; 6% for costs)?	×	Costs and benefits discounted at an annual rate of 3%, no source referenced
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and CIs are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	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?	?	Not reported
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	?	Not clear
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)	✓	Multivariate sensitivity analysis of best- and worst-case scenarios were derived according to lower and upper 95% CIs to the unit costs, the proportion of cases using hospital services and number of psychosocial treatment sessions. One-way sensitivity analysis on parameters related to discount rates, treatment effect (mortality, disability weights and adherence to therapy), among others
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	One-way and multivariate sensitivity analysis
35. The choice of variables for sensitivity analysis is justified	✓	Costs and suicide rate are the key drivers of results
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	×	Average cost-effectiveness ratios reported for all interventions instead of ICERs
38. Major outcomes are presented in a disaggregated as well as aggregated form	×	
39. Applicable to the NHS setting	×	Results calculated based on 14 WHO epidemiological subregions

Quality assessment of cost-effectiveness of relapse-prevention cognitive therapy for bipolar disorder: 30-month study, Lam and colleagues[94]

Study question	Answer	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	Cognitive therapy + standard care compared against standard care
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	×	Viewpoint is not clearly stated; however, it appears to be society
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	?	It is not clear from the paper whether or not there are other relevant alternatives that should also be compared
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	?	The details are not fully described; however the reader is directed towards other papers where the details of the study have been reported
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	×	It is not clear why there is no attempt to attach utilities to the health states in order to allow better comparison with other studies
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)	✓	Single study
10. Effectiveness data from RCT or review of RCTs	✓	Single RCT
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	✓	A broad range of services was included, although others such as informal care from family and friends, and participant time, were not costed
14. All the important and relevant resource use measured accurately (with methodology)	✓	The authors recognise the potential limitations of collecting information via self-reporting and hospital records
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	×	Not costed
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	Single UK study
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	Number of days with bipolar episodes

continued

Study question	Answer	Comments
20. Methods to value health states and other benefits are stated (e.g. TTO)	NA	Health states not valued
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	See above
Decision modelling	NA	No decision model used
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	×	May be due to short period of analysis – 12 and 30 months
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	See above
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and CIs are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	✓	CEACs generated from a bootstrapping exercise
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)	✓	Sensitivity analysis conducted around the cost of giving cognitive therapy
Stochastic analysis of decision models	NA	
30. Are all appropriate input parameters included with uncertainty?		
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (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	NA	
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	×	Although net-benefit analysis is presented, ICERs are not
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	Cost and effectiveness statistics presented separately with costs broken down
39. Applicable to the NHS setting	✓	

Appendix 10

Sensitivity analyses – cost-effectiveness analysis

Sensitivity analysis data are given in *Tables 116–125*.

TABLE 116 *Best-case (Analysis 1)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	96,839	13.93	D	0.07	0.02	0.02
Valproate	57,135	14.70	–	9.16	2.59	0.78
Imipramine	85,355	14.44	D	0.01	0.00	0.00
Lamotrigine	64,630	14.64	D	4.41	1.96	0.78
Lithium	62,622	15.35	8,501	40.18	44.48	44.74
Olanzapine	65,592	14.40	D	0.15	0.02	0.00
Lithium + imipramine	65,016	15.43	29,332	46.02	50.93	53.68

D, dominated.

TABLE 117 *Best-case (Analysis 2)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	103,366	14.24	D	0.08	0.02	0.00
Valproate	55,870	15.00	D	2.42	0.27	0.02
Imipramine	98,444	14.58	D	0.00	0.00	0.00
Lamotrigine	69,111	14.88	D	0.16	0.01	0.00
Lithium	56,908	15.75	9,985	80.85	89.46	89.82
Olanzapine	49,588	15.01	–	7.48	0.52	0.00
Lithium + imipramine	71,022	15.64	D	9.01	9.72	10.16

TABLE 118 *Worst-case (Analysis 1)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	89,943	14.01	D	0.12	0.06	0.04
Valproate	52,891	14.79	–	24.43	9.65	3.89
Imipramine	78,132	14.55	D	0.21	0.07	0.02
Lamotrigine	62,283	14.68	D	4.20	2.09	1.11
Lithium	62,684	15.34	ED	22.70	31.32	34.39
Olanzapine	61,395	14.55	D	0.12	0.04	0.01
Lithium + imipramine	63,401	15.45	15,800	48.22	56.77	60.54

ED, extended dominated.

TABLE 119 *Worst-case (Analysis 2)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	99,749	14.19	D	0.35	0.11	0.02
Valproate	60,290	14.94	ED	12.05	3.82	1.00
Imipramine	100,637	14.53	D	0.00	0.00	0.00
Lamotrigine	74,740	14.80	D	0.84	0.22	0.01
Lithium	66,145	15.61	16,098	49.79	74.99	80.82
Olanzapine	55,304	14.94	–	23.24	4.50	0.43
Lithium + imipramine	77,729	15.55	D	13.73	16.36	17.72

TABLE 120 *Additional trials (Analysis 1)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	97,132	13.94	D	0.04	0.02	0.01
Valproate	54,442	14.76	–	16.65	5.80	1.99
Imipramine	83,795	14.45	D	0.02	0.00	0.00
Lamotrigine	62,582	14.68	D	4.14	1.81	0.87
Lithium	62,761	15.34	ED	25.51	31.72	33.28
Olanzapine	64,199	14.46	D	0.00	0.00	0.00
Lithium + imipramine	62,916	15.46	12,075	53.64	60.65	63.85

TABLE 121 *Additional trials (Analysis 2)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	105,902	14.21	D	0.10	0.06	0.01
Valproate	55,835	15.00	ED	4.31	0.52	0.03
Imipramine	98,021	14.58	D	0.00	0.00	0.00
Lamotrigine	68,885	14.88	D	0.25	0.00	0.00
Lithium	58,933	15.72	10,478	76.11	84.29	84.44
Olanzapine	51,376	15.00	–	5.53	0.31	0.02
Lithium + imipramine	70,621	15.65	D	13.70	14.82	15.50

TABLE 122 *Alternative discount rate (Analysis 1)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	69,110	19.14	D	0.00	0.00	0.00
Valproate	39,412	20.21	–	0.00	0.00	0.00
Imipramine	59,069	19.86	D	0.00	0.00	0.00
Lamotrigine	45,415	20.11	D	0.03	0.00	0.00
Lithium	43,190	21.49	2,943	43.89	40.70	38.77
Olanzapine	46,824	19.75	D	0.00	0.00	0.00
Lithium + imipramine	44,626	21.62	11,162	56.08	59.30	61.23

TABLE 123 *Alternative discount rate (Analysis 2)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	73,715	19.52	D	0.00	0.00	0.00
Valproate	40,132	20.55	D	0.00	0.00	0.00
Imipramine	70,341	19.98	D	0.00	0.00	0.00
Lamotrigine	50,290	20.38	D	0.00	0.00	0.00
Lithium	40,223	22.02	2,897	89.86	89.18	88.55
Olanzapine	36,018	20.57	–	0.00	0.00	0.00
Lithium + imipramine	50,494	21.87	D	10.14	10.82	11.45

TABLE 124 *No additional mortality benefit for lithium strategies (Analysis 1)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	102,004	14.65	D	0.13	0.10	0.11
Valproate	59,409	15.46	–	48.20	47.42	46.54
Imipramine	87,753	15.20	D	0.38	0.50	0.57
Lamotrigine	67,588	15.39	D	15.62	16.65	17.48
Lithium	62,649	15.34	D	7.42	6.40	5.83
Olanzapine	69,114	15.12	D	1.25	1.01	0.88
Lithium + imipramine	64,602	15.44	D	27.00	27.92	28.59

TABLE 125 *No additional mortality benefit for lithium strategies (Analysis 2)*

Treatment	Mean cost (£)	Mean QALYs	ICER (£)	Probability cost-effective for max. WTP (%)		
				£20,000	£30,000	£40,000
Carbamazepine	108,920	14.94	D	0.75	0.71	0.68
Valproate	60,591	15.73	D	15.27	16.57	17.78
Imipramine	104,175	15.30	D	0.00	0.00	0.00
Lamotrigine	74,792	15.61	D	1.58	1.84	2.10
Lithium	58,657	15.72	D	8.53	9.21	9.63
Olanzapine	53,060	15.74	–	70.59	68.17	66.09
Lithium + imipramine	72,954	15.62	D	3.28	3.50	3.72

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