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Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder (Review)

Cipriani A, Reid K, Young AH, Macritchie K, Geddes J

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Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD003196.

DOI: 10.1002/14651858.CD003196.pub2.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	9
Figure 1.	10
Figure 2.	13
Figure 3.	14
Figure 4.	16
Figure 5.	18
Figure 6.	20
DISCUSSION	21
AUTHORS' CONCLUSIONS	24
ACKNOWLEDGEMENTS	24
REFERENCES	25
CHARACTERISTICS OF STUDIES	28
DATA AND ANALYSES	43
Analysis 1.1. Comparison 1 Valproate versus placebo, Outcome 1 Study withdrawal due to episode of mood disorder.	46
Analysis 1.2. Comparison 1 Valproate versus placebo, Outcome 2 Participant withdrawal from treatment-any cause.	47
Analysis 1.3. Comparison 1 Valproate versus placebo, Outcome 3 Participant withdrawal from treatment due to intolerance or non-compliance.	47
Analysis 1.4. Comparison 1 Valproate versus placebo, Outcome 4 Adverse events.	48
Analysis 2.1. Comparison 2 Valproate versus lithium, Outcome 1 Study withdrawal due to episode of mood disorder.	49
Analysis 2.2. Comparison 2 Valproate versus lithium, Outcome 2 Number of hospital admissions.	50
Analysis 2.3. Comparison 2 Valproate versus lithium, Outcome 3 New drug treatment for mood episode.	51
Analysis 2.4. Comparison 2 Valproate versus lithium, Outcome 4 Time to relapse (days).	51
Analysis 2.5. Comparison 2 Valproate versus lithium, Outcome 5 Participant withdrawal from treatment-any cause.	52
Analysis 2.6. Comparison 2 Valproate versus lithium, Outcome 6 Participant withdrawal from treatment due to intolerance or non-compliance.	53
Analysis 2.7. Comparison 2 Valproate versus lithium, Outcome 7 Adverse events.	54
Analysis 2.8. Comparison 2 Valproate versus lithium, Outcome 8 GAF-number of participants not responding at 24 months.	55
Analysis 2.9. Comparison 2 Valproate versus lithium, Outcome 9 Quality of life-number of participants not responding at 24 months.	56
Analysis 2.10. Comparison 2 Valproate versus lithium, Outcome 10 DSH-number of participants with at least one episode of deliberate self-harm.	56
Analysis 2.11. Comparison 2 Valproate versus lithium, Outcome 11 Death.	57
Analysis 3.1. Comparison 3 Valproate versus olanzapine, Outcome 1 Study withdrawal due to episode of mood disorder.	57
Analysis 3.2. Comparison 3 Valproate versus olanzapine, Outcome 2 Participant withdrawal from treatment-any cause.	58
Analysis 3.3. Comparison 3 Valproate versus olanzapine, Outcome 3 Participant withdrawal from treatment due to intolerance or non-compliance.	58
Analysis 4.1. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 1 Study withdrawal due to episode of mood disorder.	59
Analysis 4.2. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 2 Number of hospital admissions.	59
Analysis 4.3. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 3 New drug treatment for mood episode.	60
Analysis 4.4. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 4 Participant withdrawal from treatment-any cause.	60

Analysis 4.5. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 5 Participant withdrawal from treatment due to intolerance or non-compliance.	61
Analysis 4.6. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 6 Serious adverse events.	61
Analysis 4.7. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 7 GAF-number of participants not responding at 24 months.	62
Analysis 4.8. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 8 Quality of life-number of participants not responding at 24 months.	62
Analysis 4.9. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 9 DSH-number of participants with at least one episode of deliberate self-harm.	63
Analysis 4.10. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 10 Death.	63
Analysis 5.1. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 1 Study withdrawal due to episode of mood disorder.	64
Analysis 5.2. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 2 Number of hospital admissions.	64
Analysis 5.3. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 3 New drug treatment for mood episode.	65
Analysis 5.4. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 4 Participant withdrawal from treatment-any cause.	65
Analysis 5.5. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 5 Participant withdrawal from treatment due to intolerance or non-compliance.	66
Analysis 5.6. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 6 Serious adverse events.	66
Analysis 5.7. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 7 GAF-number of participants not responding at 24 months.	67
Analysis 5.8. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 8 Quality of life-number of participants not responding at 24 months.	67
Analysis 5.9. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 9 DSH-number of participants with at least one episode of deliberate self-harm.	68
Analysis 5.10. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 10 Death.	68
ADDITIONAL TABLES	68
WHAT'S NEW	71
HISTORY	71
CONTRIBUTIONS OF AUTHORS	71
DECLARATIONS OF INTEREST	71
SOURCES OF SUPPORT	72
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	72
INDEX TERMS	72

Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

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Editorial group: Cochrane Common Mental Disorders Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2013.

Citation: Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD003196. DOI: 10.1002/14651858.CD003196.pub2.

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ABSTRACT

Background

Bipolar disorder is a recurrent illness that is amongst the top 30 causes of disability worldwide and is associated with significant healthcare costs. In the past, emphasis was placed solely on the treatment of acute episodes of bipolar disorder; recently, the importance of episode prevention and of minimisation of iatrogenicity has been recognised. For many years, lithium was the only mood stabiliser in common use, and it remains an agent of first choice in the preventative treatment of bipolar disorder. However, an estimated 20% to 40% of patients may not respond adequately to lithium. Valproate is an anticonvulsant drug that has been shown to be effective in acute mania and is frequently used in maintenance treatment of bipolar disorder. When the acceptability of long-term treatment is considered, together with efficacy, the adverse event profile of a medication is also important. This is an update of a Cochrane review first published in 2001 and last updated in 2009.

Objectives

1. To determine the efficacy of valproate continuation and maintenance treatment:
 - a) in preventing or attenuating manic, depressive and mixed episodes of bipolar disorder;
 - b) in preventing or attenuating episodes of bipolar disorder in patients with rapid cycling disorder; and
 - c) in improving patients' general health and social functioning, as measured by global clinical impression, employment and marital stability.
2. To review the acceptability to patients of long-term valproate treatment, as measured by numbers of dropouts and reasons for dropping out, by compliance and by reference to patients' expressed views regarding treatment.
3. To investigate the adverse effects of valproate treatment (including general prevalence of side effects) and overall mortality rates.

Search methods

Search of the Cochrane Register of Controlled Trials and the Cochrane Depression, Anxiety and Neurosis Group Register (CC-DANCTR) (to January 2013), which includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years), EMBASE, (1974 to date), MEDLINE (1950 to date) and PsycINFO (1967 to date). No language restrictions were applied. Reference lists of relevant papers and previous systematic reviews were handsearched. Pharmaceutical companies marketing valproate and experts in this field were contacted for supplemental data.

Selection criteria

Randomised controlled trials allocating participants with bipolar disorder to long-term treatment with valproate or any other mood stabiliser, or antipsychotic drugs, or placebo. Maintenance treatment was defined as treatment instituted specifically or mainly to prevent further episodes of illness.

Data collection and analysis

Three review authors independently extracted data. A double-entry procedure was employed by two review authors. Information extracted included study characteristics, participant characteristics, intervention details and outcome measures in terms of efficacy, acceptability and tolerability. For dichotomous data, risk ratios were calculated with 95% confidence intervals (CIs). For statistically significant results, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH). For continuous data, mean differences (MDs) or standardised mean differences (SMDs) were calculated along with 95% CIs. MDs were used when the same scale was used to measure an outcome; SMDs were employed when different scales were used to measure the same outcome. The primary analysis used a fixed-effect model. Binary outcomes were calculated on a strict intention-to-treat (ITT) basis; dropouts were included in this analysis. When data were missing and the method of “last observation carried forward” (LOCF) had been used to do an ITT analysis, then the LOCF data were used.

Main results

Six randomised controlled trials (overall 876 participants) lasting 6 to 24 months were included. Two studies (overall 312 participants) compared valproate with placebo, four studies (overall 618 participants) valproate with lithium, one study (overall 23 participants) valproate with olanzapine and one study (overall 220 participants) valproate with the combination of valproate plus lithium. In terms of study quality, most studies reported the methods used to generate random sequence; however, only one study reported enough details on allocation concealment. Four of six included studies described their design as “double blind”, but only two trials reported full details about blinding. Valproate was more effective than placebo in preventing study withdrawal due to any mood episode (RR 0.68, 95% CI 0.49 to 0.93; NNTB 8), but no difference in efficacy was found between valproate and lithium (RR 1.02, 95% CI 0.87 to 1.20). Valproate was associated with fewer participants dropping out of treatment for any cause when compared with placebo or lithium (RR 0.82, 95% CI 0.71 to 0.95 and RR 0.87, 95% CI 0.77 to 0.98, respectively). However, combination therapy with lithium plus valproate was more likely to prevent relapse than was monotherapy with valproate (RR 0.78, 95% CI 0.63 to 0.96). Significant differences in adverse event frequencies were found, and lithium was associated with more frequent diarrhoea, polyuria, increased thirst and enuresis, whereas valproate was associated with increased sedation and infection.

Authors' conclusions

Limited evidence supports the efficacy of valproate in the long-term treatment of bipolar disorder. Clinicians and patients should consider acceptability and tolerability profile when choosing between lithium and valproate-their combination or other agents-as long-term treatment for bipolar disorder.

PLAIN LANGUAGE SUMMARY

Valproate for keeping people with bipolar disorder well, after mood episodes

Bipolar disorder is a common and important disorder that includes episodes of depression, mixed states or mania. Depression includes low mood and energy, as well as lack of enjoyment, often combined with other problems such as sleep disturbance. Mania includes the opposite, with 'too much' energy and problems with high mood or irritation. In mixed states, the symptoms of depression and mania are combined. These mood episodes usually happen several times in an individual's life, so long-term treatment (maintenance treatment) can be very important in preventing relapse and recurrence. As valproate is a drug that may be useful in treating the acute

phase of bipolar disorder, in this review we wanted to answer the following question: Is valproate useful as maintenance treatment for bipolar disorder?

We searched, in a wide-ranging way, for all the useful studies (randomised controlled trials, or RCTs) we could find on long-term treatment of people with bipolar disorder using valproate or any other mood stabiliser, or antipsychotic drugs, or placebo. Three of us looked at RCTs to make sure they were fair experiments. We extracted data from the studies, put all of the evidence together and carried out a statistical analysis to look for significant results.

We conducted these searches to 11 January 2013 and found six studies, including a total of 876 participants. The quality of the studies in terms of design was not good, which means that the effects of some drugs might have been overestimated. All of the trials taken together suggest that valproate might help to prevent relapse in bipolar disorder, especially depressive episodes. However, because of limited available evidence, conclusions on valproate compared with placebo and lithium (or other active drugs) cannot be made with any reliable degree of confidence. Lithium is an important drug to compare with valproate because lithium is already known to be effective in preventing relapses of bipolar disorder. When we combined the findings of all studies comparing valproate with lithium, the evidence did not favour valproate or lithium in terms of efficacy. People taking valproate over a long time were more likely than patients given lithium to keep taking their allocated medication. Clinicians and patients should consider the side effects of valproate, including alopecia, tremor and weight gain.

We also found a study that compared valproate taken alone with valproate combination therapy (two drugs taken at the same time). This study compared people who took lithium only or valproate only with people who took valproate and lithium together. No evidence showed that use of valproate and lithium compared with lithium alone helped to ensure that patients kept taking their allocated medication.

BACKGROUND

Description of the condition

Bipolar disorder (or bipolar affective disorder, or manic depressive disorder) refers to a group of affective disorders that together are characterised by marked mood swings between mania (mood elevation) and depression that cause significant personal distress or social dysfunction, and are not caused by drugs or known physical disorders (Phillips 2013). Bipolar type I disorder is diagnosed when episodes of depression are interspersed with mania. Bipolar type II disorder is diagnosed when depression is interspersed with less severe episodes of elevated mood (hypomania) that do not lead to dysfunction or disability (Müller-Oerlinghausen 2002). Lifetime prevalence rates of bipolar type I disorder range from 0.3% to 1.5% in the general population (Weissmann 1996). Men and women are at similar risk, and mean age at first onset ranges from 19 to 29 years (an average of six years earlier than first onset of major depression). The cause of bipolar disorder is uncertain, although family and twin studies suggest a genetic basis (Craddock 2013). Bipolar disorder is a recurrent illness in which affective episodes of varying form may produce lasting destructive effects on sufferers' psychological, professional and social welfare (Gonzalez-Pinto 2010). Its chronic and recurrent nature places it amongst the top

30 causes of disability worldwide, especially in the age group of 15 to 44 years (Murray 1997). A meta-analysis undertaken to compare observed versus expected rates of suicide in an age- and sex-matched sample of the general population found that the lifetime prevalence of suicide in people with bipolar disorder was about 2%-about 15 times greater than would be expected (Harris 1997).

Description of the intervention

'Mood stabilisers' are defined as drugs that alleviate the frequency and/or intensity of manic, depressive or mixed episodes in patients with bipolar disorder and, further, do not increase the frequency or severity of any of the subtypes or course variables of bipolar disorder (Bowden 1996). For many years, lithium was the only mood stabiliser in common use, and it remains a first choice in the preventative treatment of bipolar disorder (APA 1994b; CANMAT 2009; Goodwin 2009; Geddes 2013). However, an estimated 20% to 40% of patients may not respond adequately to lithium. In particular, a high incidence of inadequate response has been noted in individuals with rapid cycling disorder (Post 1989), a variant of bipolar disorder associated with greater morbidity and mortality than its classic form, including greater risk of suicide (Fawcett 1990). A search for adjunctive and alternative treatments to lithium has uncovered evidence that other medi-

cations, including anticonvulsant agents (e.g. valproic acid, carbamazepine) and several atypical antipsychotics, have mood-stabilising properties. Valproic acid (together with sodium valproate or valproate sodium, either of which is a sodium salt of valproic acid) is an anticonvulsant that is used also in neurology for the treatment of patients with epilepsy and migraine; in Europe it has been used since 1966 as maintenance treatment for bipolar disorder (Lambert 1966).

How the intervention might work

Valproic acid and its derivatives, hereafter given the generic term 'valproate', are weak blockers of sodium ion channels that produce a weak inhibitor of enzymes that deactivate gamma-aminobutyric acid (GABA) (such as GABA transaminase) (Fawcett 1989). The exact mechanisms that contribute to the efficacy of valproate in treating bipolar disorder remain unclear. However, it seems unlikely that GABAergic transmission is related to the psychotropic action of valproate, as other different molecular mechanisms might be involved, such as serotonergic and glutamatergic transmission, energy metabolism and neuronal membrane lipid synthesis (Winterer 2000). Recently, amongst other potential mechanisms of action, neurotrophic and neuroplastic effects of valproate have been explored (Schloesser 2008). Valproate has a complex pharmacokinetic profile that follows a three-compartment model and shows protein-binding saturation. Monitoring of plasma level is supposedly, therefore, of more limited use than with carbamazepine or lithium. A dose of at least 750 mg/d or a serum level of at least 50 mg/L may be associated with response (Taylor 1997). The therapeutic dose usually ranges between 1000 and 1500 mg/d but can reach a maximum of 2000 mg/d. Valproate is highly protein bound (up to 94%). Other drugs that are highly protein bound can displace valproate from albumin and precipitate toxicity (e.g. aspirin). Valproate is hepatically metabolised and can increase the plasma levels of some drugs, possibly by inhibiting their metabolism (e.g. tricyclic antidepressants, lamotrigine).

Why it is important to do this review

Until the recent millennium, valproate was recommended as a second-line prophylactic agent in bipolar disorder and a first-line choice in rapid cycling disorder in the United States of America and in Great Britain (APA 1994b; Sachs 1996; Maudsley 2001). Notwithstanding its sometimes troublesome side effect profile, valproate is still frequently used in clinical practice (Geddes 2013). Side effects of valproate include neurological symptoms such as tremor, sedation and ataxia (especially with concomitant administration of other anticonvulsants or neuroleptics), alopecia, lethargy, dizziness, haematological dysfunction, hepatic failure and other gastrointestinal complaints. Asymptomatic elevation in hepatic transaminases may occur. Pancreatitis and hepa-

totoxicity are rare but potentially serious and fatal complications. Possible induction of polycystic ovaries and hyperandrogenism with long-term valproate treatment has been reported, especially in young females (Garland 1996; Geller 1998). Teratogenicity has been reported in the form of neural tube defects associated with first trimester use (Jeavons 1982), congenital heart lesions, digital anomalies, oral clefts and craniofacial dysmorphic features (Dukes 1996). It has also been found that the use of valproate in pregnancy was associated with a reduction in cognitive functioning in the children of mothers with epilepsy (Adab 2004a; Adab 2004b; Meador 2009). Concerns regarding teratogenicity led to the recommendation by the United Kingdom National Institute of Clinical Excellence (NICE) that valproate should not be prescribed routinely for women of child-bearing potential (NICE 2006). Over the past decade, the range of agents available for the maintenance treatment of bipolar disorder has expanded, and new efficacy and safety data on the use of valproate have become available. This is an update of a Cochrane review first published in 2001 and last updated in 2009 (Macritchie 2009). In light of recent developments, this re-appraisal of valproate in the maintenance treatment of bipolar disorder is due and timely.

OBJECTIVES

1. To determine the efficacy of valproate continuation and maintenance treatment:
 - i) in preventing or attenuating manic, depressive and mixed episodes of bipolar disorder;
 - ii) in preventing or attenuating episodes of bipolar disorder in patients with rapid cycling disorder; and
 - iii) in improving patients' general health and social functioning, as measured by global clinical impression, employment and marital stability.
2. To review the acceptability to patients of long-term valproate treatment, as measured by numbers of dropouts and reasons for dropping out, by compliance and by reference to patients' expressed views regarding treatment.
3. To investigate the adverse effects of valproate treatment (including general prevalence of side effects) and overall mortality rates.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomised controlled trials (RCTs) comparing valproate maintenance treatment with placebo or alternative drug treatment in bipolar disorder were included in this review. Maintenance treatment was defined as treatment instituted specifically or mainly to prevent further episodes of illness. When trials combined acute treatment and maintenance phases, these data would be analysed separately when possible for the purposes of this review.

Types of participants

The review included participants of both sexes with a primary diagnosis of bipolar disorder corresponding to the *International Classification of Diseases (ICD), Tenth Revision (ICD-10)*, code F31, and the *Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth Edition (DSM-IV)* code 296 (trials with *ICD, Ninth Revision (ICD-9)* and *DSM, Third Edition (DSM-III)/DSM, Third Edition, Revised (DSM-III-R)* diagnoses approximating these codes were included). All subtypes of bipolar disorder (rapid cycling [suffering from four or more affective episodes per year] and types I, II and not otherwise specified) were included.

No age restrictions were applied.

When trials involved heterogeneous groups of participants, in particular, those with schizoaffective disorder and recurrent unipolar depression (diagnoses approximating *ICD-10* code F25 and *DSM-IV* code 295.70; and *ICD-10* code F33 and *DSM-IV* 296.3, respectively), data were separated into diagnostic groups if randomisation had been stratified.

No restrictions on setting were applied.

Excluded were studies with participants who had a concurrent primary diagnosis of an Axis I or II disorder and participants with a serious concomitant medical illness. Participants with cyclothymia were excluded as well.

Types of interventions

Experimental intervention

This intervention consisted of valproate given as monotherapy or in combination with other mood stabilisers. Several formulations of valproate and valproic acid are available, including sodium valproate, valpromide and divalproex. In this review, we refer to these generically as valproate, as this is the term in common usage. However, the precise preparation used in each study was specified (see [Characteristics of included studies](#)), and if heterogeneity was observed, difference in preparation was considered as a potential explanation.

Comparator intervention

- Placebo
- Alternative mood stabiliser (i.e. lithium, carbamazepine)
- Other treatments (e.g. antipsychotics)

See [Data extraction and management](#) below for a list of main comparisons.

Types of outcome measures

Primary outcomes

1. Efficacy of valproate in preventing/attenuating further episodes of affective disorder

1.1 Recurrence of any mood episodes, as measured by:

- study withdrawal due to recurrence of any mood episode;
- admission to hospital: (i) time to next admission; (ii) number of admissions during trial period;

• institution of additional treatment for affective episode and time to institution; and

- number of episodes during the trial period.

We also performed the same analysis for recurrence of manic, mixed or depressive episodes only, if possible.

Secondary outcomes

2. Acceptability of treatments

2.1 Participants dropping out of treatment during the study period.

2.2 Measures of compliance: Completion of the trial was taken as a specific surrogate marker of acceptability.

2.3 Participant reports of satisfaction or otherwise with treatment.

3. Adverse effects

3.1 Numbers of participants experiencing the following.

- Troublesome side effects.
- Gastrointestinal side effects: anorexia, nausea, vomiting, dyspepsia, diarrhoea.

• Neurological complaints: tremor, sedation, ataxia, cognitive impairment.

- Dizziness.
- Alopecia.
- Lethargy.
- Haematological dysfunction.
- Pancreatitis.
- Evidence of hepatic dysfunction and hepatotoxicity.
- Weight gain.
- Menstrual irregularity, polycystic ovaries and hyperandrogenism.

3.2 Cases of teratogenicity.

4. General Health and Social Functioning

4.1 Clinical global impression of the clinician (Global Assessment of Functioning-GAF) (APA 2000).

4.2 Quality of life according to the EuroQol (EQ-5D) questionnaire (Kind 1996).

4.3 Employment during study period.

4.4 Separation/divorce during study period.

5. Mortality rates and deliberate self-harm

5.1 Overall mortality rates during study period.

5.2 Mortality excluding suicide and verdicts of undetermined death.

5.3 Mortality due to hepatic failure.

5.4 Mortality due to pancreatitis.

5.5 Suicide and verdicts of undetermined death.

5.6 Rates of deliberate self-harm.

Search methods for identification of studies

Electronic searches

CCDAN's specialised register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintains two clinical trials registers at its editorial base in Bristol, UK: a references register and a studies-based register. The CCDANCTR-References Register contains more than 31,500 reports of randomised controlled trials in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register, and records are linked between the two registers through the use of unique study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Co-ordinator for further details.

Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950 to date), EMBASE (1974 to date) and PsycINFO (1967 to date); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP), drug companies, and handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCDAN's generic search strategies can be found at the Group's website.

The CCDANCTR-Studies Register was searched using the following terms:

Condition=(bipolar or mani or schizoaffective) and Intervention=(divalproex or valpro*)*

The CCDANCTR-References Register was searched using a more sensitive set of free-text terms to find additional untagged/uncoded references:

(valpro or divalpro*) and (bipolar or mania or manic or hypomani* or psychos* or psychotic or postpsycho* or post-psycho* or "rapid cycling" or schizoaffective)*

The CCDANCTR was searched (all years to 11 January 2013).

Review authors conducted their own searches on EMBASE, MEDLINE, PsycLit and Psynex to May 2012.

International trial registries

The WHO Clinical trials Portal (ICTRP) and ClinicalTrials.gov were searched (January 2013) to identify additional ongoing or unpublished studies. Clinicalstudyresults.org was also searched (to May 2011). This database no longer exists.

Regulatory agencies

Trial databases of the following drug-approving agencies were searched for published, unpublished and ongoing controlled trials: the Food and Drug Administration (FDA) in the USA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the European Medicines Agency (EMA) in the EU. We also searched ongoing trial registers such as International Standard Randomised Controlled Trial Number Register (ISRCTN) and the National Research Register in the UK, Nederland's Trial Register in the Netherlands and European Union Drug Regulating Authorities Clinical Trials (EudraCT) in the EU. These searches were undertaken in February 2012.

Searching other resources

Personal communication

The contact authors of all review papers or trials over the relevant search period were identified from authorship lists. They and other experts in the field were contacted and asked about their knowledge of other studies, published or unpublished, relevant to the review. Pharmaceutical companies marketing valproate products were requested to provide relevant published and unpublished data.

Reference checking

The reference lists of all reviews, identified RCTs, other relevant papers and major English textbooks on mood disorder were checked for published reports and citations of unpublished research.

Data collection and analysis

Selection of studies

Two independent review authors checked to ensure that studies related to valproate generated by the search strategies of the CC-DANCTR References and other complementary searches met the inclusion criteria, first based on the title and abstracts. All studies that were rated as possible candidates by either of the two review authors were added to the preliminary list, and their full texts were retrieved. AC and KM then assessed all of the full text articles in this preliminary list to see whether they met the strict inclusion criteria. If the raters disagreed, the final rating was made by consensus, with the involvement, if necessary, of another member of the review group (JG or AHY).

Data extraction and management

AC and KM extracted data from the included studies. Any disagreement was discussed, and decisions were documented. If necessary, we contacted authors of studies for clarification. We extracted the following data: (i) participant characteristics (age, sex, diagnosis, comorbidity, severity of illness, study setting); (ii) intervention details (intended dosage range, mean daily dosage actually prescribed, co-intervention if any, sponsorship); and (iii) outcome measures of interest from the included studies.

Main comparisons

1. Valproate versus placebo.
2. Valproate versus alternative mood stabiliser.
3. Valproate versus other treatments (e.g. antipsychotics).
4. Valproate plus mood stabiliser versus mood stabiliser alone.
5. Valproate plus mood stabiliser versus valproate alone.

Assessment of risk of bias in included studies

Two review authors independently assessed trial quality in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This set of criteria is based on evidence of associations between effect overestimation and high risk of bias in an article, such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting. Categories are defined as low risk of bias, high risk of bias, and unclear risk of bias.

If the raters disagreed, the final rating was made by consensus with involvement of another member of the review group. Non-congruence in quality assessment was reported as percentage disagreement.

Measures of treatment effect

All comparisons were performed between valproate and comparator drug or placebo as individual compound.

Dichotomous data

For dichotomous, or event-like, data, the risk ratio (RR) was calculated with its 95% confidence interval (CI). For statistically significant results, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) as the inverse of the risk difference.

Continuous data

For continuous data, mean differences (MDs) or standardised mean differences (SMDs) were calculated with 95% CIs. MDs were used when the same scale was used to measure an outcome; SMDs were employed when different scales were used to measure the same outcome. Continuous data on clinical outcomes often are not normally distributed, and skewed data were presented descriptively. If papers reported a mean and a standard deviation (SD), as well as an absolute minimum possible value for the outcome, we divided the mean by the SD. If this value was less than two, then we concluded that some indication of skewness was present. If the value was less than one (i.e. the SD was bigger than the mean), then skewness was almost certainly present. If papers did not report the skewness and simply reported means, SDs and sample sizes, these numbers were used. Because these data may not have been properly analysed and can be misleading, analyses were conducted with and without these studies. If the data were log-transformed for analysis, and the geometric means were reported, skewness was reduced. This is the recommended method for analysis of skewed data (Higgins 2011).

Unit of analysis issues

Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs when an effect (e.g. pharmacological, physiological, psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase, participants can differ systematically from their initial state, even despite a wash-out phase. For this reason, we planned to use only data from the first phase of the cross-over studies. No cross-over studies were identified for this version of the review. Given that cross-over trials for which only first period data are available should be considered to be at risk of bias (Higgins 2011), careful attention will be paid to retrieve only unbiased data available from such studies in the next updates of this review.

Cluster-randomised trials

No cluster randomised trials were found for this version of the review. Should they be identified in a future update, we will attempt to adjust for the effects of clustering using an intraclass correlation coefficient (ICC). In fact this is seldom available in published reports, so a common approach is to use external estimates obtained from similar studies; several resources are available that provide examples of ICC ([Higgins 2011](#)). We will conduct sensitivity analyses to investigate the robustness of our conclusions, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Studies with multiple treatment groups

For a particular multi-arm study, the intervention groups of relevance to a systematic review are all those that could be included in a pair-wise comparison of intervention groups that, if investigated alone, would meet the criteria for inclusion of studies in the review. Each meta-analysis addresses only a single pair-wise comparison, so we first considered whether a study of each possible pair-wise comparison of interventions in the study was eligible for the meta-analysis. Then, several possible approaches to including a study with multiple intervention groups could be used in a particular meta-analysis ([Higgins 2011](#)). For binary outcomes, we decided to combine all relevant experimental intervention groups of the study into a single experimental group, and to combine all relevant control intervention groups into a single control group. For continuous outcomes, we decided to combine means and standard deviations using methods described in Chapter 7 of the *Cochrane Handbook for Systematic Review of Interventions*.

Dealing with missing data

Binary outcomes were calculated on a strict intention-to-treat (ITT) basis: Dropouts were included in this analysis. When data were missing and the method of “last observation carried forward” (LOCF) had been used to do an ITT analysis, then the LOCF data were used. When standard deviations (SDs) were missing, we presented data descriptively. When SDs were not reported, authors were asked to supply the data. When only the standard error (SE) or *t*-statistics or the P value was reported, we calculated SDs in accordance with [Altman 1996](#).

Assessment of heterogeneity

Heterogeneity between studies was investigated by the I^2 statistic ([Higgins 2003](#)) (I^2 equal to or greater than 50% was considered indicative of heterogeneity) and by visual inspection of the forest plots. Given that the value of I^2 depends on the sample size of the included studies, the magnitude and direction of effects and the strength of evidence for heterogeneity, we used this arbitrary threshold to perform a preliminary evaluation. If the I^2 value fell below 50% but the direction and magnitude of treatment effects

were suggestive of important heterogeneity, we investigated the potential sources of heterogeneity.

Assessment of reporting biases

Data from included studies were entered into a funnel plot (trial effect against trial variance) for investigation of small-study effects ([Sterne 2000](#)). We planned to use the tests for funnel plot asymmetry only when at least 10 studies were included in the meta-analysis ([Higgins 2011](#)). Funnel plot asymmetry may be noted for many possible reasons, so when evidence of small-study effects was identified, all possible reasons for funnel plot asymmetry, including publication bias, were investigated.

Data synthesis

All analyses used a fixed-effect model. We decided to use a fixed-effect model as the primary analysis because by including only RCTs with standardised dose regimens, similar clinical management and narrow diagnostic inclusion criteria, we did not expect to see significant clinical heterogeneity. However, the robustness of this summary measure was routinely examined by checking the random-effects model, which has the greatest generalisability in our empirical examination of summary effect measures for meta-analyses ([Furukawa 2002a](#)). Material differences between the models were reported. A P value less than 0.05 and a 95% confidence interval (CI) were considered statistically significant.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for primary outcomes when possible.

1. Studies examining rapid cycling bipolar disorder were to be considered separately. The efficacy of valproate in preventing/attenuating episodes in rapid cycling disorder was measured by recurrence of affective episodes; admission to hospital; institution of additional treatment for mood disorder; and length of the well period, expressed in cycle lengths.

2. Assessment of the effectiveness of valproate treatment in previous mood stabiliser non-responders was considered. Results were interpreted with caution because multiple comparisons can lead to false-positive conclusions ([Oxman 1992](#)). If the CIs of RRs in the groups did not overlap, potential sources of heterogeneity were investigated. Given that no age restrictions were applied in the present review, in the next update we will conduct, if possible, subgroup analyses for age, as important differences between children/adolescents and adults could be seen in terms of clinical presentation.

Sensitivity analysis

The following sensitivity analyses for primary outcomes were planned a priori.

1. We excluded trials with unclear concealment of random allocation and/or unclear double blinding.
2. We excluded trials with a dropout rate greater than 20%.
3. We excluded studies with a discontinuation design. Data from these studies were to be analysed separately for assessment of the effects of valproate discontinuation.
4. The routine application of random-effects and fixed-effect models can be considered an additional form of sensitivity analysis.
5. The use of ITT analyses, when data have been imputed (by you or by the trialists), warrants sensitivity analyses. In future updates, we will undertake sensitivity analysis in the event that we will impute data for ITT analysis.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); and [Characteristics of studies awaiting classification](#).

Results of the search

Initially, we identified 59 new references through the updated search. After the abstracts were read, 30 references were considered relevant for our review and were retrieved for more detailed evaluation (see [Figure 1](#) for PRISMA flow diagram). Although the search was thorough, it is possible that unpublished studies may not have been identified.

Figure 1. Study flow diagram showing study selection process.

Included studies

A total of six studies were identified, with a mean follow-up duration ranging between 6 and 24 months. Attempts to contact trial authors for additional unpublished information were successful in five cases, and additional data were provided by the authors of three studies (Bowden 2000; Calabrese 2005; BALANCE 2010).

Study design

Most studies were reported to be double-blind (Bowden 2000; Calabrese 2005; Findling 2005; Kemp 2009), apart from Altamura 2004 and BALANCE 2010, which were designed as open-label studies. Only two studies were three-arm trials (Bowden 2000; BALANCE 2010), and the remaining four were two-armed studies (Altamura 2004; Calabrese 2005; Findling 2005; Kemp 2009).

Sample Size

Overall, 876 participants were included. The mean sample size per arm was 60.5 participants (range 10 to 187). Four studies recruited fewer than 100 participants (Altamura 2004; Calabrese 2005; Findling 2005; Kemp 2009), and only two studies recruited more than 200 participants overall (Bowden 2000; BALANCE 2010).

Setting/participants

Five trials enrolled only outpatients (Bowden 2000; Altamura 2004; Calabrese 2005; Findling 2005; Kemp 2009), and one study enrolled both inpatients and outpatients (BALANCE 2010). All participants had been given a formal diagnosis of bipolar disorder according to *DSM-IV* (Calabrese 2005; Kemp 2009; BALANCE 2010) or *DSM-III-R* (Bowden 2000; Findling 2005); however, one study (Altamura 2004) recruited a few participants with schizoaffective disorder (3 of 23 randomly assigned participants). One study recruited children and adolescents only (Findling 2005), and two trials randomly assigned only participants with rapid cycling disorder (Calabrese 2005; Kemp 2009). In Kemp 2009, participants had co-occurring substance abuse or dependence. About three-fifths of the participants included in the study recruiting children and adolescents only (Findling 2005) were prescribed concomitant psychostimulants for attention deficit hyperactivity disorder (ADHD) symptoms (35 of 60, 58.3%), but randomisation was stratified on the basis of three factors: age (5 to 11 or 12 to 17 years), presence/absence of rapid cycling and whether the individual had comorbid ADHD. All studies employed a discontinuation design (randomly assigning participants before long-term, relapse prevention treatment was provided).

Interventions and comparators

We found two studies (overall, 312 participants) that compared valproate with placebo (Bowden 2000; Kemp 2009), four studies (overall, 618 participants) comparing valproate with lithium (Bowden 2000; Calabrese 2005; Findling 2005; BALANCE 2010), one study (overall, 23 participants) comparing valproate with olanzapine (Altamura 2004) and one study (overall, 220 participants) comparing valproate with the combination of valproate plus lithium (BALANCE 2010). In the included studies, almost all participants used lithium or valproate within the therapeutic dose range. Valproate or divalproex as orally administered was used in all trials. Blood levels of valproate were monitored in all trials. The tapering discontinuation of medications in the run-up to maintenance treatment was explicitly gradual in Bowden 2000 (two weeks), Calabrese 2005 (average six weeks), Findling 2005 (eight weeks) and Kemp 2009 and BALANCE 2010 (four weeks), presumably to avoid rebound. Altamura 2004 recruited participants who were euthymic at the moment of recruitment, with no run-in phase. Rescue medications were allowed in all studies in accordance with a priori protocols.

Outcomes

Of the included six studies, all reported efficacy data and tolerability or acceptability data that were suitable for meta-analysis. The included studies did not report on all outcomes prespecified in the protocol of this review. Outcomes of clear relevance to patients and clinicians, in particular, patients' and their relatives' attitudes towards treatment, patients' ability to return to work and resume normal social functioning, health-related quality of life measures and costs of health care services, were not reported in the included studies.

Excluded studies

Of the 30 references retrieved for more detailed evaluation, 24 articles did not meet our inclusion criteria and were excluded for one of the following reasons: wrong/non-randomised design (13 articles), review/case series (two articles), wrong comparison (five articles) and wrong diagnosis/population (four articles) (see Figure 1 for PRISMA flow diagram).

Ongoing studies

No ongoing studies were identified.

Studies awaiting classification

Two studies are awaiting classification. Bowden 2012 was identified after the search date, so has not been formally considered for inclusion. If it meets all the inclusion criteria it will be included in a subsequent update of this review. We require further information to assess NCT00071253. If we receive the required information we will be able to consider its eligibility when updating this review.

New studies found at this update

Five new studies were incorporated at this update: [Altamura 2004](#); [Calabrese 2005](#); [Findling 2005](#); [Kemp 2009](#); and [BALANCE 2010](#).

Risk of bias in included studies

See [Included studies](#), [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Altamura 2004	+	?	?	?	?	-	?
BALANCE 2010	+	+	+	+	+	+	?
Bowden 2000	+	?	?	?	+	?	?
Calabrese 2005	+	?	+	?	+	?	+
Findling 2005	+	?	+	?	?	?	?
Kemp 2009	+	?	+	?	?	?	+

Figure 3. Risk of bias graph: review authors' judgements about all risk of bias items presented as percentages across all included studies.

Our judgement about the overall risk of bias in the individual studies is illustrated in [Figure 2](#) and [Figure 3](#). No disagreement between the raters occurred. The methodological quality of these included studies was questionable overall. Even though it is not possible to predict the direction or magnitude of bias associated with lack of adequate sequence generation or adequate allocation concealment ([Odgaard-Jensen 2011](#)), this type of reporting has been associated with an overestimate of the effect of investigational drugs ([Schulz 1995](#)), and this should be considered when the review results are interpreted.

Allocation

In terms of random sequence generation, we found that all included studies were at low risk of bias, and most studies reported that the method of generating random sequence was “a computer originated schedule”. In terms of “allocation concealment”, only one study reported enough details on the allocation concealment procedure ([BALANCE 2010](#)). We were not assured that bias was minimised during the allocation procedure in the other five studies ([Bowden 2000](#); [Altamura 2004](#); [Calabrese 2005](#); [Findling 2005](#); [Kemp 2009](#)), yet the great majority of them reported that participants allocated to each treatment group were “similar”, “the same”, “not significantly different”, “comparable” or “matched”.

Four of six included studies described their design as “double-blind” ([Bowden 2000](#); [Calabrese 2005](#); [Findling 2005](#); [Kemp 2009](#)); however, no tests were conducted to ensure successful blinding. Two studies reported full details about blinding of participants and personnel and were rated at low risk of bias ([Calabrese 2005](#); [Kemp 2009](#)), and two studies had been carried out in an open manner ([Altamura 2004](#); [BALANCE 2010](#)). Blinding of outcome assessment was rated as “unclear” in five studies ([Bowden 2000](#); [Altamura 2004](#); [Calabrese 2005](#); [Findling 2005](#); [Kemp 2009](#)).

Incomplete outcome data

Only three studies were rated as at “low risk” of bias ([Bowden 2000](#); [Calabrese 2005](#); [BALANCE 2010](#)). Total dropout rate was high overall, ranging from 20.9% ([BALANCE 2010](#)) to 90% ([Findling 2005](#)). In four studies, the total dropout rates were higher than 50% ([Bowden 2000](#); [Calabrese 2005](#); [Findling 2005](#); [Kemp 2009](#)). Two studies used a proper ITT analysis and were rated as “low risk” ([Calabrese 2005](#); [BALANCE 2010](#)), and the remaining four did not provide clear information about analysis and were rated “unclear” ([Bowden 2000](#); [Altamura 2004](#); [Findling 2005](#); [Kemp 2009](#)).

Blinding

Selective reporting

Two studies were rated as “low risk” (Calabrese 2005; BALANCE 2010) and one as “high risk” (Altamura 2004). The study protocol was available for only one study (BALANCE 2010), and some trials did not report in the published paper SDs for mean changes as continuous outcomes (Findling 2005; Kemp 2009).

Other potential sources of bias

One study was sponsored by a valproate manufacturer (Bowden 2000), one study reported no information about funding (Altamura 2004) and all remaining studies were funded by grants from independent bodies (e.g. the National Institutes of Health, the Stanley Medical Research Institute, or the Stanley Foundation, and the Nina Rahn Fund). In three of these studies, medications were provided by Abbott Laboratories or Abbott Pharmaceuticals, the manufacturer of valproate (Calabrese 2005; Findling 2005; Kemp 2009), and in the fourth study, all study drugs (both lithium carbonate and valproate semisodium) were donated by sanofi-aventis (BALANCE 2010).

Effects of interventions

All six included studies contributed usable data for the efficacy, acceptability and tolerability analyses, but only one reported data about quality of life and global functioning (BALANCE 2010). No studies assessed other general health and social functioning issues, such as employment or separation/divorce, and no information about costs of healthcare services was provided in the included studies. All included studies excluded women who were pregnant (or were planning to become pregnant) and fertile women not on adequate contraceptive methods. No cases of teratogenicity were

signalled. The results of the present systematic review are reported by comparison and by outcome, in accordance with the original review protocol. The forest plots are organised according to relevance of outcomes, as reported in the review protocol. For tolerability, adverse events are reported only when statistically significant (non-statistically significant results about adverse events are presented in Table 1).

Comparison 1: valproate versus placebo

Primary outcome

1.1 Efficacy in preventing/attenuating further episodes of affective disorder

Valproate was more effective than placebo in preventing study withdrawal due to any mood episode (RR 0.68, 95% CI 0.49 to 0.93; $P = 0.02$; NNTB 8, 95% CI 5 to 50; 2 RCTs, 312 participants) or to a depressive episode alone (RR 0.46, 95% CI 0.24 to 0.89; $P = 0.02$; NNTB 13, 95% CI 7 to 100; 2 RCTs, 312 participants) (Analysis 1.1; Figure 4). No strong evidence suggested that valproate was superior to placebo in reducing study withdrawals due to manic episodes (RR 0.77, 95% CI 0.48 to 1.25; $P = 0.29$; 2 RCTs, 312 participants) (Analysis 1.1; Figure 4). When study data were analysed using the random-effects model, valproate was still seen to more effective than placebo in preventing study withdrawal due to any mood episode, but results were no more statistically significant (RR 0.71, 95% CI 0.49 to 1.02; $P = 0.07$).

Figure 4. Forest plot of comparison: I Valproate versus placebo, outcome: I.1 Study withdrawal due to episode of mood disorder.

Secondary outcomes

1.2 Acceptability of treatments

Valproate was more effective than placebo in preventing all-cause study withdrawal (RR 0.82, 95% CI 0.71 to 0.95; $P = 0.01$; NNTB 8, 95% CI 5 to 34; 2 RCTs, 312 participants) (Analysis 1.2), but it was associated with a greater number of participants dropping out of treatment as the result of intolerance or non-compliance (RR 1.87, 95% CI 1.01 to 3.47; $P = 0.05$; NNTB 10, 95% CI 6 to 100; 1 RCT, 281 participants) (Analysis 1.3). No data were provided about participant reports of satisfaction or otherwise with treatment.

1.3 Adverse effects

People allocated to valproate were more likely to have tremor (RR 2.41, 95% CI 1.58 to 3.67; $P < 0.0001$; NNTB 10, 95% CI 6 to 34; 2 RCTs, 312 participants; $I^2 = 90\%$) (Analysis 1.4), weight gain (RR 2.04, 95% CI 1.07 to 3.86; $P = 0.03$; NNTB 4, 95% CI 3 to 7; 2 RCTs, 312 participants; $I^2 = 80\%$) and alopecia (RR

2.51, 95% CI 1.15 to 5.51; NNTB 10, 95% CI 6 to 34; $P = 0.02$; 2 RCTs, 312 participants). However, the differences in tremor and weight gain disappeared when the random-effects model was used (RR 1.85, 95% CI 0.54 to 6.33; $P = 0.33$ and RR 1.25, 95% CI 0.19 to 7.94; $P = 0.82$, respectively).

1.4 General health and social functioning

No studies reported on this outcome for this comparison.

1.5 Mortality rates and deliberate self-harm

No data about mortality or suicide were reported.

Comparison 2: valproate versus lithium

Primary outcome

2.1 Efficacy in preventing/attenuating further episodes of affective disorder

No strong evidence indicated that valproate was inferior or superior to lithium in preventing study withdrawals due to episodes of mood disorder (any mood episode or manic, depressive hypomanic or mixed episode alone) ([Analysis 2.1](#); [Figure 5](#)). One study ([BALANCE 2010](#)) reported detailed information about other dichotomous efficacy outcomes, such as number of hospital admissions ([Analysis 2.2](#)) or new treatment for mood episode ([Analysis 2.3](#)). No difference was found between valproate and lithium on these outcomes, with the exception of “new treatment for de-

pressive episode”, for which valproate was noted to be inferior to lithium (RR 1.43, 95% CI 1.02 to 2.01; $P = 0.04$; NNTH 8, 95% CI 4 to 100; 1 RCT, 220 participants) ([Analysis 2.3](#)). Another study reported the continuous outcome “time to relapse” ([Findling 2005](#)), but we do not know whether valproate was better than lithium in terms of time to median survival (as measured in days) for participants who relapsed because of the presence of mood symptoms (MD -2.00, 95% CI -7.24 to 3.24; $P = 0.45$; 1 RCT, 60 participants) ([Analysis 2.4](#)).

Figure 5. Forest plot of comparison: 2 Valproate versus lithium, outcome: 2.1 Study withdrawal due to episode of mood disorder.

Secondary outcomes

2.2 Acceptability of treatments

When compared with lithium, valproate was associated with a lesser number of participants dropping out of treatment for any cause (RR 0.87, 95% CI 0.77 to 0.98; $P = 0.02$; 4 RCTs, 618 participants) (Analysis 2.5) and because of intolerance or non-compliance (RR 0.67, 95% CI 0.49 to 0.93; $P = 0.02$; 4 RCTs, 618 participants) (Analysis 2.6).

2.3 Adverse effects

People allocated to valproate were less likely to have diarrhoea (RR 0.74, 95% CI 0.55 to 0.99; NNTB 10, 95% CI 5 to ; $P = 0.04$; 2 RCTs, 338 participants), polyuria (RR 0.31, 95% CI 0.16 to 0.58; $P = 0.0003$; NNTB 7, 95% CI 5 to 15; 2 RCTs, 338 participants; $I^2 = 63\%$), increased thirst (RR 0.32, 95% CI 0.15 to 0.65; $P = 0.002$; NNTB 9, 95% CI 6 to 25; 2 RCTs, 338 participants) or enuresis (RR 0.22, 95% CI 0.05 to 0.94; $P = 0.04$; NNTB 5, 95% CI 3 to 20; 1 RCT, 60 participants) but were more likely to have sedation (RR 1.45, 95% CI 1.00 to 2.10; $P = 0.05$; NNTH 9, 95% CI 5 to 100; 2 RCTs, 338 participants; $I^2 = 59\%$) or infection (RR 2.07, 95% CI 1.16 to 3.68; $P = 0.01$; NNTH 8, 95% CI 5 to 20; 1 RCT, 278 participants) (Analysis 2.7). However, the differences for sedation and polyuria disappeared when the random-effects model was used (RR 0.93, 95% CI 0.20 to 4.44; $P = 0.93$ and RR 0.21, 95% CI 0.02 to 1.89; $P = 0.16$, respectively).

2.4 General Health and Social Functioning

Only one study (BALANCE 2010) reported data about quality of life and global functioning, but the results were inconclusive (Analysis 2.8; Analysis 2.9).

2.5 Mortality rates and deliberate self harm

Only one study (BALANCE 2010) reported data about mortality and deliberate self-harm (DSH). We do not know whether valproate was worse than lithium in terms of DSH (RR 2.50, 95% CI 0.50 to 12.61; $P = 0.27$; 1 RCT, 220 participants; Analysis 2.10) or number of deaths (RR 1.50, 95% CI 0.26 to 8.80; $P = 0.65$; 1 RCT, 220 participants) (Analysis 2.11). None of the deaths was caused by suicide.

Comparison 3: valproate versus olanzapine

Primary outcome

3.1 Efficacy in preventing/attenuating further episodes of affective disorder

We do not know whether valproate was better than olanzapine in terms of numbers of participants experiencing syndromic recurrence of any mood episode (meeting *DSM-IV* criteria) (RR 0.74, 95% CI 0.30 to 1.85, $P = 0.52$; 1 trial, 23 participants) (Analysis 3.1). No strong evidence suggested that valproate was inferior or superior to olanzapine in preventing study withdrawals due to episodes of mood disorder (manic or depressive episodes) (Analysis 3.1).

Secondary outcomes

3.2 Acceptability of treatments

In the included study (Altamura 2004), all dropouts left the study because of side effects, and all belonged to the olanzapine group. However, it is unclear whether there was a difference between valproate and olanzapine in terms of numbers of participants withdrawing from treatment (RR 0.18, 95% CI 0.01 to 3.16, $P = 0.24$; 1 trial, 23 participants) (Analysis 3.2; Analysis 3.3).

3.3 Adverse effects

No clear data were available in the paper that reported only that adverse events causing premature discontinuation for three participants allocated to olanzapine were weight gain and sedation.

3.4 General Health and Social Functioning

No studies reported on this outcome for this comparison.

3.5 Mortality rates and deliberate self harm

No deaths during the treatment period were reported in the included study (Altamura 2004).

Comparison 4: valproate plus lithium versus lithium alone

Primary outcome

4.1 Efficacy in preventing/attenuating further episodes of affective disorder

There was no evidence that valproate plus lithium was superior to lithium alone in preventing study withdrawals due to episodes of mood disorder (Analysis 4.1). No differences were found between valproate plus lithium and lithium alone in terms of hospital admission or new drug treatment for mood episode (Analysis 4.2; Analysis 4.3).

Secondary outcomes

4.2 Acceptability of treatments

Even though it was not clear whether there was a difference between the combination of lithium and valproate and lithium alone in terms of all-cause dropout (Analysis 4.4), lithium alone was associated with dropout from treatment of a lesser number of participants as the result of intolerance or non-compliance when compared with lithium and valproate, but results were inconclusive (RR 1.83, 95% CI 0.70 to 4.78; $P = 0.22$; 1 RCT, 220 participants) (Analysis 4.5).

4.3 Adverse effects

No evidence indicates that valproate plus lithium differed from lithium alone in causing serious adverse events (Analysis 4.6).

4.4 General health and social functioning

No difference was found between lithium and valproate in terms of quality of life or global functioning (Analysis 4.7; Analysis 4.8).

4.5 Mortality rates and deliberate self-harm

Fewer participants in the lithium alone group committed DSH, but the results were inconclusive (RR 2.00, 95% CI 0.37 to 10.70; $P = 0.42$; 1 RCT, 220 participants) (Analysis 4.9). Three participants died: one in the combination arm and two in the lithium alone arm (Analysis 4.10).

Comparison 5: valproate plus lithium versus valproate alone

Primary outcome

5.1 Efficacy in preventing/attenuating further episodes of affective disorder

Valproate plus lithium was superior to valproate alone in prevention of study withdrawals due to episodes of mood disorder (RR 0.78, 95% CI 0.63 to 0.96; $P = 0.02$; NNTB 7, 95% CI 4 to 34; 1 RCT, 220 participants) (Analysis 5.1; Figure 6); this combination also resulted in lesser numbers of participants who required new treatment for any mood episode (RR 0.77, 95% CI 0.62 to 0.96; $P = 0.02$; NNTB 7, 95% CI 4 to 34; 1 RCT, 220 participants) or for mania alone (RR 0.61, 95% CI 0.42 to 0.89; $P = 0.009$; NNTB 6, 95% CI 4 to 20; 1 RCT, 220 participants) (Analysis 5.3). The combination of lithium and valproate was also more effective than valproate alone in terms of hospital admissions or new drug treatments for depression, but these results were inconclusive (Analysis 5.2; Analysis 5.3).

Figure 6. Forest plot of comparison: 5 Valproate plus lithium versus valproate alone, outcome: 5.1 Study withdrawal due to episode of mood disorder.

Secondary outcomes

5.2 Acceptability of treatments

Even though it was not clear whether there was a difference between the combination of lithium and valproate and valproate

alone in terms of all-cause dropout ([Analysis 5.4](#)), valproate alone was associated with lesser numbers of participants dropping out of treatment as the result of intolerance or non-compliance when compared with the combination of lithium and valproate, but the results were inconclusive (RR 2.75, 95% CI 0.90 to 8.37; $P = 0.07$; 1 RCT, 220 participants) ([Analysis 5.5](#)).

5.3 Adverse effects

No evidence indicated that valproate plus lithium was more likely than valproate alone to cause serious adverse events ([Analysis 5.6](#)).

5.4 General health and social functioning

No difference between combination lithium plus valproate and valproate alone was noted in terms of quality of life or global functioning ([Analysis 5.7](#); [Analysis 5.8](#)).

5.5 Mortality rates and deliberate self-harm

Fewer participants in the combination group died, but the results were inconclusive (RR 0.33, 95% CI 0.04 to 3.16; $P = 0.34$; 1 RCT, 220 participants) ([Analysis 5.10](#)). Nine participants committed DSH: four in the combination arm and five in the valproate alone arm ([Analysis 5.9](#)).

Subgroup analyses

1) Rapid cycling bipolar disorder

We did not find enough studies to investigate the issue about rapid cycling disorder as reported in the review protocol because, of the two small trials randomly assigning participants with rapid cycling disorder only, one compared valproate as add-on treatment with placebo ([Kemp 2009](#)), and the second compared valproate as monotherapy with lithium ([Calabrese 2005](#)).

2) Effectiveness of valproate treatment in previous mood stabiliser non-responders

Information about participants who did not respond to other mood stabilisers, as reported in the included studies, was not sufficient to allow a proper statistical analysis.

Funnel plot analysis

For all comparisons, the presence of publication bias was not examined because trials were insufficient to allow meaningful formal assessment with the use of funnel plots.

Sensitivity analyses

1) Excluding trials with unclear concealment of random allocation and/or unclear double blinding

This sensitivity analysis was not performed because only one study reported clear details on concealment of random allocation ([BALANCE 2010](#)), and of four double-blind studies, two studies reported full details on blinding, but one compared valproate with lithium ([Calabrese 2005](#)) and the other one compared valproate with placebo ([Findling 2005](#)).

2) Excluding trials whose dropout rate was greater than 20%

This sensitivity analysis was not performed because in all studies, the dropout rate was greater than 20%.

3) Excluding trials with a discontinuation design

This sensitivity analysis was not performed because five of six included studies had a discontinuation design, and only [Altamura 2004](#) recruited participants who were euthymic at the moment of recruitment with no run-in phase.

DISCUSSION

Summary of main results

This systematic review of six randomised controlled trials comparing valproate with placebo or other active drugs in the maintenance treatment of bipolar disorder showed that valproate is more effective than placebo in preventing study withdrawals due to an episode of mood disorder (especially, depressive episode), but it is not materially different from lithium in terms of overall efficacy. However, only two studies compared valproate with placebo, and in the study that had the larger sample, valproate was no better than placebo on the primary efficacy measure. No reliable evidence suggested a difference between valproate and lithium (pooled RR 1.02, 95% CI 0.87 to 1.20), although the confidence interval is consistent with a 13% relative reduction in the risk in favour of valproate and a 20% reduction in the risk consistent with lithium. No statistically significant difference was noted between valproate and lithium in terms of prevention of manic episodes (RR 1.14, 95% CI 0.90 to 1.44) or depressive episodes (RR 1.12, 95% CI 0.84 to 1.49). In both cases, however, the direction of the effect favoured lithium, and a post hoc sensitivity analysis, including or excluding [Findling 2005](#) (which used slightly different definitions of outcome), had no material effect on the overall estimate. The apparent benefit of valproate compared with placebo was of a similar size to the advantage of valproate plus lithium compared

with lithium monotherapy. Taken together, these suggest that valproate has some preventative efficacy in bipolar disorder. However, when compared with combination therapy with lithium, valproate alone did not show any clinical advantage, as combination therapy was more likely to prevent relapse than was monotherapy with valproate. Even though it was associated with a higher incidence of adverse events such as alopecia, tremor and weight gain than placebo, valproate was more acceptable than lithium, as it was associated with a lower risk for participants to withdraw from treatment.

Overall completeness and applicability of evidence

Retrieved randomised evidence compared valproate with a selection of possible comparator drugs, but only a few studies were found per comparison. The evidence that valproate is more effective than placebo was derived from only one moderately sized RCT and one very small RCT. By contrast, for the comparison between valproate and lithium, results were numerically more robust, as we found four RCTs. The identified studies were sufficient to address many, but not all, of the outcomes originally specified in the review protocol.

In this review, we included only RCTs, and one of the main limitations of efficacy trials involves including participants far from the “real world”. Proper randomisations and reliable inclusion and exclusion criteria may help create two or more groups that do not differ. However, the external validity of study findings might be limited (Cipriani 2009a). Generalisability of these findings can be extended only to patients who are likely to be enrolled in a randomised trial, and results from systematic reviews of RCTs should be integrated with available high-quality observational evidence, which may inform better about the adverse events that cannot be fully assessed in RCTs only.

Quality of the evidence

With summary statistics, the quality of information is important for interpreting results and for usefulness of results in practice. Use of high-quality research evidence is relevant for reviewing results and facilitating the translation of research in a way that can answer clinically relevant questions. However, the quality of RCTs is not easy to assess. Despite the fact that randomised clinical trials provide the best research design by which to answer questions about efficacy and acceptability of treatments (Cipriani 2009b), the six studies included in this review (876 participants overall) failed to report key methodological issues. For example, a great majority of trials still do not report adequate information about allocation concealment. Meta-analyses of poor-quality studies may be seriously misleading (Ioannidis 2005) because the bias associated with defects in the conduct of primary studies can seriously affect over-

all estimates of intervention. Even though reporting of outcomes in the included studies was sometimes unclear or incomplete (only graphs, no SDs), and the figures used for the analyses were not immediately understandable, the scant information about allocation concealment may be more a matter of reporting in the text than of real defects in study design.

Potential biases in the review process

- Although the search was thorough, it is possible that unpublished studies have not been identified, but the small number of trials identified per comparison hinders the detection of any publication bias. We are also aware that a number of further randomised controlled trials comparing valproate with other drugs are currently being conducted and will be included in future updates of the review.

- For several comparisons, the data came from just one study (e.g. valproate vs olanzapine, valproate plus lithium vs valproate alone), and results from this review should be interpreted with caution.

- We found only one large placebo-controlled RCT that investigated the efficacy and acceptability of valproate maintenance treatment in bipolar disorder. This study (Bowden 2000) is one of the largest trials of maintenance therapy in bipolar disorder ever undertaken; however, the results are equivocal. The practical difficulties caused by the inclusion of a placebo-treated group led to the inclusion of a less severely affected group of participants than is generally found in clinical practice. A higher relapse rate was anticipated than was actually found, which meant that the study had insufficient power to detect reliably a moderate, but clinically important, treatment effect. Moreover, a 52-week follow-up was probably rather short for a maintenance study. Despite its short duration, a large number of participants withdrew from the study, especially in the lithium group. Finally, during the up to 3-month run-in phase, the index manic episode was treated at the discretion of the investigator, and 117 participants had been treated with valproate only (31.5%), 124 with lithium only (33.3%), 50 with both drugs (usually sequentially) (13.4%) and 81 with neither drug (21.8%). Given that 187 participants were subsequently randomly assigned to valproate, 91 to lithium and 94 to placebo (2:1:1 randomisation scheme), and that participants taking valproate or lithium on the day of randomisation had the drug gradually withdrawn over a 2-week time, this design might have favoured valproate over placebo and lithium. The primary analysis used in Bowden 2000 was a comparison of survival curves in the treatment arms. This primary analysis found no significant differences between treatment groups, although the comparison between lithium and valproate tended to favour the latter. In our analysis, without access to individual participant data, we simply used the number of participants leaving the

study because of recurrence during the study. We found a statistically significant benefit for valproate compared with placebo. This result is rather surprising because the time-to-event analysis is more efficient. In other words, because it makes fuller use of the data, other things being equal, it is more likely to detect an effect should one exist. It is possible that the discrepancy is explained by the large number of dropouts, which occurred at different rates in each arm, and the number of censored observations. Therefore, although our analysis suggests that valproate is more efficacious than placebo in preventing mood episodes, the effect is not robust to the choice of analysis, and the true efficacy of valproate therefore remains uncertain.

- According to review protocol, we included non-blind studies (Altamura 2004; BALANCE 2010). As all RCTs used an open-label design, outcome assessment should be done very carefully to reduce the risk of performance and ascertainment biases. In BALANCE 2010, this risk was managed by restriction of randomisation to participants for whom there was no strong treatment preference on the part of the participant or the clinician and by careful verification of outcomes: All outcome events were considered by the trial management team, who were masked to treatment assignment, and in the case of any doubt, a description of the event was sent to an independent adjudication team.

- We considered the all-cause discontinuation rate as a measure of acceptability of treatment. Even though it has been employed in many other systematic reviews in the field of long-term treatment for bipolar disorder (Cipriani 2009d; Cipriani 2010) and also for unipolar depression (Nakagawa 2009; Cipriani 2009c; Omori 2010; Watanabe 2011; Cipriani 2012), this choice might be questioned. We believe that early drug discontinuation is highly clinically relevant from a clinical point of view because it is one of the most important things the psychiatrist wants to know when starting the prescription of an effective long term treatment.

- Our decision to use fixed-effect meta-analysis could have introduced a bias in the review process, as there was some visual indication of heterogeneity, although this was rarely statistically significant and so could simply indicate random error. Overall, we believe that the fixed-effect average is probably the best estimate for guiding clinical practice. The two largest studies (Bowden 2000; BALANCE 2010) reported conflicting estimates, which contributed to the final heterogeneity ($I^2 = 25\%$). However, this result was robust to the choice of statistical method because no material differences were noted between the random-effects models and the fixed-effect models.

- The relative risk of serious adverse events or death between valproate and other agents or placebo was not significant; however, included trials were not powered to detect any mortality difference. Because of the low numbers of events,

random error is substantial, and estimates of treatment effect are consequently unstable with wide confidence intervals. Systematic reviews of randomised controlled trials may increase statistical power, but absolute numbers of participants who have rare adverse events such as completed or attempted suicide are low (Cipriani 2005a), and a few events in one direction or another can completely change the overall outcome (Cipriani 2005b).

- It is known that Axis I and Axis II psychiatric comorbidity is of clinical interest, especially for bipolar disorder and borderline personality disorder (Bassett 2012). However, evidence suggests that bipolar disorder and borderline personality disorder are most likely separate disorders and that benefits of mood stabilisers are more predictable in bipolar disorder than in borderline personality disorder (Paris 2007). Therefore, we decided to exclude studies that recruited participants with Axis II comorbidity. Even though our inclusion criteria were aimed at higher internal validity (Cipriani 2009a), our choice might have limited the external validity of review findings because in clinical practice, patient populations are usually highly heterogeneous.

- We found no reports of teratogenic effects, but randomised controlled trials are not intended or designed to evaluate this very important aspect of treatment. Treatment guidelines recommend that valproate should not be routinely used in women of child-bearing potential in primary or secondary care (Goodwin 2009). If no effective alternative treatment to valproate can be used, then the patient should be made aware of the risks of taking valproate in pregnancy, and effective contraception should be used (NICE 2006).

Agreements and disagreements with other studies or reviews

Despite the increasingly widespread use of valproate in bipolar disorder (Hayes 2011), only one systematic review about the long-term treatment of bipolar disorder has been published in the scientific literature since the first publication of the present review in 2001. The review by Soares and colleagues was published in 2007 and included a total of seven randomised or quasi-randomised trials that investigated the efficacy of valproate (Soares-Weiser 2007). Three studies included in Soares-Weiser 2007 were excluded from the present review because we specifically included only randomised trials with a relapse prevention design, which did not recruit acutely ill patients for long-term treatment. Notwithstanding these differences in inclusion/exclusion criteria, results from these two systematic reviews are consistent overall. Valproate was found to be effective as maintenance therapy for the prevention of relapse in bipolar disorder, but it was possibly more efficacious for the prevention of depressive relapses rather than manic relapses.

AUTHORS' CONCLUSIONS

Implications for practice

A key clinical question is whether valproate or lithium should be favoured as the first-line therapy in the prevention of recurrence in bipolar disorder. Given the lack of clear findings of this review and the limited amount of evidence obtained, conclusions on the efficacy and acceptability of valproate compared with placebo and lithium cannot be made with any degree of confidence. The evidence of efficacy for valproate versus placebo (in terms of both total participants randomised and independently replicated results) is less robust when compared with the more substantial evidence for the efficacy of lithium versus placebo (Burgess 2001). Clinicians should always individualise the best maintenance drug treatment for each patient, in accordance with the efficacy and tolerability of long-term treatments of documented efficacy. However, in making such clinical decisions, clinicians and patients may wish to consider evidence from a related review that highlights other important factors. These may include differences in the efficacy of drugs in acute treatment of mania (Cipriani 2011) and the relative acceptability and tolerability of valproate and lithium. In terms of safety, lithium and valproate had different side effect profiles. Our analysis suggests that valproate may be better tolerated than lithium, but comparatively high lithium levels were used in the trial, and it has been shown that informed management of lithium plasma levels may ensure both improved utility and improved outcomes (Mahli 2012). Moreover, a combination therapy with lithium plus valproate may be an option if the patient can tolerate the combination; however, this suggestion is based on evidence from a single study.

Implications for research

Longer-term and larger sample size RCTs, with clinically appropriate designs, are needed, preferentially conducted independent of the manufacturer, to examine the relative efficacy and acceptability of valproate in the maintenance treatment of bipolar disorder. The review of lithium in maintenance therapy concluded that, although the total number of participants randomly assigned was rather small, reasonable evidence for the efficacy of lithium

was found (Burgess 2001). We would therefore argue that it is unnecessary for future studies to include a placebo arm: The ethical and practical costs of doing so outweigh the possible benefits. Future trials need to compare valproate with other mood-stabilising agents that have not been compared with valproate so far (e.g. carbamazepine, atypical antipsychotics) and must be of sufficient duration to inform real-life clinical decision making. Good-quality trials of valproate are needed: Analysis should be conducted on an intention-to-treat basis, and power calculations should be undertaken by using realistic estimates of recurrence rates. Trial outcomes should include measures that are meaningful to patients and clinicians, and recorded side effects should reflect the concerns of patients. Finally, although it is unclear whether valproate exhibits discontinuation effects similar to those exhibited by lithium, trial design should avoid rapid discontinuation of any mood stabiliser.

Even though two of the included studies focused on rapid cycling disorder, they were very small, and there remains a need for additional evidence on the use of valproate in such populations of patients.

ACKNOWLEDGEMENTS

We thank the CCDAN Trials Search Co-ordinator for assistance in developing the search strategy for the review and for conducting several of the database searches. We thank those authors who supplied us with their time and information when contacted. We thank Miss Ana Stefanovic for her help in translating an Azerbaijani trial from Russian.

CRG Funding Acknowledgement:

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Depression, Anxiety and Neurosis Group.

Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, the NHS or the Department of Health.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Altamura 2004

Methods	6-Month, open-label, randomised, controlled study
Participants	<p>23 participants</p> <p>Drug formulation: valproate</p> <p>Age: at baseline, mean age of 40.2 (± 13.5) years for olanzapine group and 51.0 (± 13.9) years for valproate group</p> <p>Diagnosis (Structured Clinical Interview for <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i>, Axis I): 6 participants with a diagnosis of bipolar disorder I (5 in olanzapine group and 1 in valproate group), 11 of bipolar disorder II (2 in olanzapine group and 9 in valproate group) and 3 of schizoaffective disorder bipolar type (olanzapine group)</p> <p>Exclusion criteria: patients taking concomitant psychotropic compounds except for benzodiazepines or with medical or physiological conditions (pregnant women, fertile women not on adequate contraceptive methods, and breast-feeding women) contraindicating the administration of olanzapine or valproate</p>
Interventions	<p>Olanzapine and valproate doses adjusted according to clinical needs</p> <p>Olanzapine final mean dosage: 9 (± 3.2) mg</p> <p>Valproate final mean dosage: 415 (± 16.39) mg. At the end of the study, mean valproate plasma level of 62.7 (± 19.5) microg/mL; therapeutic level of 50 microg/mL required</p> <p>Duration of trial: 6 months</p>
Outcomes	<p>Percentage of participants who relapsed during follow-up (relapse defined as a participant fulfilling <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i>, criteria for a major mood episode: depressive, manic or mixed</p> <p>Brief Psychiatric Rating Scale (administered by blind raters)</p> <p>Clinical Global Impression (administered by blind raters)</p>
Notes	In this study, authors compared percentage of participants who relapsed during follow-up with that of the 6-month period before the beginning of the study, during which participants did not take any mood stabiliser

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned". Probably done
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "open-label fashion"

Altamura 2004 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Twenty outpatients (9 males and 11 females) completed the study. Three patients assigned to OLZ group prematurely discontinued the study because of the occurrence of side effects (weight gain, sedation)." No information about analysis reported at all
Selective reporting (reporting bias)	High risk	Study report (journal letter) fails to include results for some outcomes that would be expected to have been reported for such a study
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

BALANCE 2010

Methods	Randomised, open-label, controlled, parallel-group trial
Participants	<p>330 men and women Drug formulation: valproate semisodium Age: 16 years and older Diagnosis: clinical diagnosis of bipolar I disorder (on the basis of a previous episode of mania meeting <i>Diagnostic and Statistical Manual-IV</i> criteria) Eligibility for entry into the run-in phase</p> <ul style="list-style-type: none"> • Written informed consent was given • Individual was not having an acute episode, and long-term drug therapy was clinically indicated to prevent relapse • Combination therapy with lithium plus valproate was considered clinically reasonable for the individual by the clinician • No medical disorder or condition contraindicated either of the investigational drugs (e.g. pregnancy) • Individual was normally resident in one country and had a residential address <p>Eligibility for randomisation</p> <ul style="list-style-type: none"> • No clear treatment preference for either investigational drug was apparent • Lithium plasma concentration was between 0.4 and 1.0 mmol/L • Valproate dose was at least 750 mg, or valproic acid serum concentration was at least 50 µg/mL • Combination of lithium and valproate was tolerated at trial doses • Adherence during the run-in phase was judged by the investigator to be at least 70%

Interventions	During the run-in, participants received 4 to 8 weeks of treatment with both lithium carbonate, at doses producing a serum concentration of 0.4 to 1.0 mmol/L, and valproate semisodium, at least 750 mg per day, with a target daily dose of 1250 mg or the highest dose tolerated. Low doses of valproate were allowed if needed for tolerability, and if the serum concentration was at least 50 µg/mL before randomisation After run-in, participants were randomly allocated to one of three groups <ul style="list-style-type: none">• Combination therapy with lithium and valproate• Lithium monotherapy (valproate withdrawn and lithium continued)• Valproate monotherapy (lithium withdrawn, valproate continued) Allocated drugs were continued at the dose established during the run-in. In monotherapy groups, the discontinued drug was withdrawn over 4 weeks to reduce risk of relapse associated with abrupt discontinuation. Doses of investigational drugs could be increased if the serum concentration fell below the minimum threshold (measurement of serum concentrations after randomisation was performed at the discretion of the investigator) and decreased (within the trial ranges) if side effects became troublesome Duration of trial: 2 years	
Outcomes	Time to new intervention for an emerging mood episode, including drug treatment (commencement of a new drug, increase in dose of concurrent drug, restarting of a discontinued drug, or increase in the investigational drug dose in response to an emergent mood episode) or admission to hospital Time to new intervention for an emerging depressive or manic episode (including mixed and cycling) Global assessment of functioning Episodes of deliberate self-harm Quality of life according to the EuroQol (EQ-5D) questionnaire Adverse events including both emergent serious adverse events and participant-reported adverse effects Withdrawal from study treatment Adherence to study treatment as estimated by investigator	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The computerised randomisation program included a minimisation algorithm to ensure balanced allocation of participants across the intervention groups for six prognostic factors: (1) nature of most recent episode (mania or non-mania); (2) number of previous psychiatric admissions (<two or ≥two); (3) previous maintenance treatment (yes or no); (4) age (<35 years or ≥35 years); (5) sex; and (6) region"

Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was via the 24-h telephone service at the Clinical Trial Service Unit, University of Oxford, UK. Investigators telephoned the service and logged the patient as eligible for randomisation. The investigator was then informed of the treatment allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators and participants were aware of treatment allocation because of the complexities of masking of lithium therapy and the concern that concealment would restrict participation and generalisability. The consequent risk of performance and ascertainment biases was managed by restriction of randomisation to patients for whom there was no strong treatment preference on the part of the patient or clinician and by careful verification of outcomes. All outcome events were considered by the trial management team, who were masked to treatment assignment. In the case of any doubt, a description of the event was sent to an independent adjudicator"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators and participants were aware of treatment allocation because of the complexities of masking of lithium therapy and the concern that concealment would restrict participation and generalisability. The consequent risk of performance and ascertainment biases was managed by restriction of randomisation to patients for whom there was no strong treatment preference on the part of the patient or clinician and by careful verification of outcomes. All outcome events were considered by the trial management team, who were masked to treatment assignment. In the case of any doubt, a description of the event was sent to an independent adjudicator"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Analysis was by intention to treat, and followed a detailed, prespecified plan. Time to first event during the scheduled follow-up was compared between the three groups. Follow-up was censored at the last available assessment in patients who were lost to follow-up without having an event."

BALANCE 2010 (Continued)

		Time from randomisation to event was summarised by Kaplan-Meier curves, and compared with the log rank test. Hazard ratios (HRs) with 95% CIs were calculated with Cox's regression to estimate size of the treatment effect. The proportional hazards assumption was tested formally with analysis of Schoenfeld residuals. An analysis adjusting for minimisation factors was also done. Because BALANCE had very specific hypotheses and only one outcome of primary importance, we made no formal adjustment for multiple significance testing. We used Stata (version 10) for all power calculations and analyses"
Selective reporting (reporting bias)	Low risk	Quote: "The primary outcome was time to new intervention for an emerging mood episode, including drug treatment (commencement of a new drug, increase in dose of concurrent drug, restarting of a discontinued drug, or increase in the investigational drug dose in response to an emergent mood episode) or admission to hospital. Secondary outcomes were time to new intervention for an emerging depressive episode, time to new intervention for an emerging manic episode (including mixed and cycling), global assessment of functioning, 25 episodes of deliberate self-harm, quality of life according to the EuroQol (EQ-5D) questionnaire, adverse events including both emergent serious adverse events and participant-reported adverse effects, withdrawal from study treatment, and adherence to study treatment estimated by investigator"
Other bias	Unclear risk	None.

Bowden 2000

Methods	Randomised double-blind placebo-controlled parallel-group trial
Participants	372 participants Drug formulation: divalproex Age: 18 to 75 years Diagnosis: <i>DSM-III-R</i> criteria for bipolar affective disorder with at least one manic episode in the past 3 years

	<p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of intolerance to lithium or valproate • Alcohol abuse within the previous 6 months, current substance dependence or positive results on urine toxicology tests • Potentially confounding concomitant drug treatment • Disorders of the nervous system or uncontrolled systemic disorders • Serious suicidal risk • Ongoing psychotherapy • Poor compliance with open-phase treatment • Pregnancy
Interventions	<p>Open phase: up to 3 months</p> <p>Index episode treated according to clinical judgement. No depot neuroleptic or E.C.T.</p> <p>All drugs other than lithium and valproate discontinued before randomisation</p> <p>Discontinuation of first-phase mood stabilisers could occur in protocol</p> <p>Randomly assigned to valproate, lithium or placebo</p> <p>Doses adjusted to reach serum trough levels: valproate 71 to 125 micrograms/mL and lithium 0.8 to 1.2 mEq/L</p> <p>Rescue medication:</p> <ul style="list-style-type: none"> • Lorazepam up to 6 mg/d for maximum of 14 days in first month and for up to 7 days for remainder of study • Haloperidol up to 10 mg/d allowed in second week of first month after 1 week of lorazepam <p>Participants with DSS scores greater than or equal to 25 treated with sertraline or paroxetine: data censored from analyses of time to mania relapse on the day antidepressant treatment began</p> <p>Duration of trial: 52 weeks</p>
Outcomes	<ul style="list-style-type: none"> • Time to affective episode • Time to manic or depressive episode • Average change in baseline scores on Mania Rating Scale, Depression Syndrome Scale and Global Assessment Scale during maintenance treatment
Notes	<p>For the purposes of this review, we used withdrawal from the study because of the occurrence of an episode of mood disorder as the main outcome measure. This was not the primary outcome measure used in the original study, which is now discussed in detail. In the original study, the primary outcome measure was time to next mood episode. Secondary outcome measures were time to manic episode, time to depressive episode and average change from baseline in scores on the Mania Rating Scale, the Depression Syndrome Scale and the Global Assessment Scale during maintenance treatment. As the trial progressed, the initial outcome measures were revised at the suggestion of reviewers. A manic episode was defined as being represented by a Mania Rating Scale of 16 or greater, or requiring hospital admission. A depressive episode was defined as one requiring antidepressant use or premature discontinuation of the study because of symptoms. Patients with Depression Syndrome Scale scores of 25 or higher were treated with sertraline or paroxetine, and their data were censored from the analyses of time to mania relapse on the day that antidepressant treatment began. The Schedule of Affective Disorders and the Schizophrenia-Change version, augmented by the addition of eleven items to the Mania Rating Scale, were used to measure symptom severity</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised". Probably done
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No clear information reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All randomised patients were evaluated for safety and reasons for premature discontinuation. Comparability of groups at baseline was assessed by one-way analysis of variance and Kruskal-Wallis tests. Differences between treatment groups in categorical measures were examined with Cochran-Mantel-Haenszel and Fisher exact tests. Survival analyses of time to occurrence of a manic or depressive episode were performed for the intent-to-treat sample (all patients receiving at least one dose of study drug)"
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

Calabrese 2005

Methods	Randomised double-blind placebo-controlled parallel-group trial
Participants	60 participants Drug formulation: divalproex Age: mean age of 36 years Diagnosis: <i>DSM-IV</i> Bipolar I or II disorder Inclusion criteria <ul style="list-style-type: none"> • Rapid cycling disorder in the previous 12 months • Hypomanic, manic or mixed episode in previous 3 months, in good physical health Exclusion criteria from maintenance phase

	<ul style="list-style-type: none">• Previous concurrent lithium and valproate treatment• Intolerance• Pregnancy or planned pregnancy• Exogenous steroids• Drug or alcohol misuse in the previous 6 months• Suicidality• Refractory affective episode in stabilisation phase afterward	
Interventions	Open-label stabilisation phase of between 12 and 24 weeks to stabilise and to establish treatment on concurrent valproate and lithium; all other psychotropic medications tapered off before randomisation Randomly assigned to monotherapy valproate or lithium under double-blind conditions Doses adjusted to reach serum trough levels: minimum 0.8 mEq/L for lithium and 50 microgrammes/L for valproate, down-titrated for side effects Rescue medication: unclear Duration of trial: 20 months	
Outcomes	Study withdrawal due to episode of mood disorder Adverse events Withdrawal due to adverse events	
Notes	None	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned". Probably done
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, double-substitution methodology was used to transition patients from open-label combination therapy with both medications to double-blind monotherapy. Patients were started on equal numbers of capsules of double-blind active lithium 300-mg capsules and matching (in colour, taste, and size) lithium placebo capsules, and equal numbers of double-blind active valproate in 250-mg capsules and matching valproate placebo capsules.... Patients randomly assigned to monotherapy had one blinded active capsule replaced with a matching placebo capsule once every 2 weeks for as long as necessary. The process of tapering to monotherapy took place over an average of 6 weeks if

		patients were taking 1200 mg of lithium or 1500 mg of valproate-longer if the doses of either were higher and more quickly if the doses of either were lower. After the taper was completed, matching placebo for the drug that was discontinued was discontinued for the rest of the maintenance phase. This slow, gradual process of transitioning patients to monotherapy obscured the progress of the taper until completed. The maintenance phase began at the beginning of the taper, and the survival analysis began at that time as well. After the taper was completed, the number of capsules of active compound and placebo was unchanged for the rest of the maintenance phase, except for adjustments made to both by the unblinded medical monitor when blood levels decreased to less than 0.8 meq/liter for lithium and 50 $\mu\text{g/mL}$ for valproate"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The intent-to-treat population included all patients who were randomly assigned to a study treatment condition. Kaplan-Meier methodology was used to plot the survival data, and median survival times were calculated. A log-rank test at an alpha = 0.05 level of significance was employed to evaluate differences between survival curves. A Cox regression was performed evaluating the following predictors of outcome: treatment arm assignment, type of bipolar diagnosis (bipolar I or bipolar II), and index episode at study entry"
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	None

Findling 2005

Methods	Randomised double-blind placebo-controlled parallel-group trial	
Participants	60 youths Drug formulation: divalproex Age: 5 to 17 years Diagnosis: Bipolar I or II disorder by <i>DSM-IV</i> semi-structured interview Inclusion criteria for maintenance phase: <ul style="list-style-type: none">• Medically healthy• Manic or hypomanic episode in past 3 months Exclusion criteria for maintenance phase: <ul style="list-style-type: none">• Requirement for treatment outside protocol in stabilisation phase• Intolerance of therapeutic serum concentrations in stabilisation phase (trough 0.6 mmol/L Li, 0.5 microgramme/L valproate)• Previous lithium-resistant mania confirmed while trough serum Li > 0.6 mmol/L• Pregnancy, breast-feeding, risk of pregnancy• Pervasive developmental disorder or learning disability	
Interventions	Stabilisation phase prescribed open-label concurrent valproate and lithium for up to 20 weeks, including tapering of other psychotropic medication, except ADHD medications. Need for antidepressants or antipsychotic medications led to dropout before phase 2. Serum trough lithium maintained between 0.6 and 1.2 mmol/L lithium, and 50 to 100 microgramme/L valproate Duration of trial: up to 76 weeks, which included a gradual weaning off of other medication over 8 weeks	
Outcomes	Total study withdrawal by end of trial Adverse events Withdrawal due to adverse events Withdrawal due to lack of treatment response Withdrawal due to mania/hypomania/mixed state Time to discontinuation for any reason Time to relapse	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “randomised”. Probably done
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind”. Probably done (double-dummy pills were used)

Findling 2005 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No clear information about analysis and dealing with missing data was reported
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Unclear risk	A single-site study

Kemp 2009

Methods	Randomised double-blind placebo-controlled parallel-group trial
Participants	<p>31 participants Drug formulation: divalproex Age: average age approx 40 years Diagnosis: Bipolar I or II disorder by structured <i>DSM-IV</i> interview Inclusion criteria</p> <ul style="list-style-type: none"> Alcohol, cannabis or cocaine abuse within the past 3 months or dependence in the past 6 months by <i>DSM-IV</i> structured interview Rapid cycling in the previous 12 months by structured <i>DSM-IV</i> interview At least one hypomanic, mixed or manic episode in the 3 months preceding study entry by structured <i>DSM-IV</i> interview A persistent bimodal response to combined treatment with lithium and divalproex. Lithium minimum trough level 0.8 mmol/L, valproate minimum serum level of 0.5 microgramme/L. Participants weaned off other psychotropic medications gradually; this was complete by at least four weeks before the comparison phase Good physical health <p>Exclusion from maintenance phase</p> <ul style="list-style-type: none"> Pregnant or planning pregnancy Taking exogenous steroids or anticoagulants Suicidality Previous intolerance to lithium or valproate <p>Discontinuation from valproate would therefore occur in the protocol</p>
Interventions	<p>Participants randomly assigned either to continuing combined lithium and valproate or to lithium monotherapy and valproate placebo under double-blind conditions. During this phase, lorazepam up to 2 mg per day was permitted as needed for agitation, and zolpidem up to 10 mg per night was permitted for insomnia Duration of trial: 6 months</p>
Outcomes	<p>Total study withdrawal Study withdrawal due to mood disorder (any/manic/depressive) Adverse effects</p>
Notes	None

Kemp 2009 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised". Probably done
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No clear information about analysis and dealing with missing data reported
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	Low risk	

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bristol-Myers Squibb 2006	Wrong design (not relapse prevention study-participants acutely manic)
Oquendo 2011	Not randomised at the point of maintenance
Pfizer 2006	Wrong design (not relapse prevention study-participants acutely manic)
Revicki 2005	Randomised controlled double-blind trial; not randomised at the point of maintenance
Tohen 2003	Not randomised at the point of maintenance therapy

Characteristics of studies awaiting assessment [ordered by study ID]

Bowden 2012

Methods	Randomised double-blind placebo-controlled parallel-group trial
Participants	86 participants randomized in the maintenance phase Age: 40.7 ± 12.4 years. Diagnosis: Bipolar I or II disorder with major depressive episode (<i>DSM-IV</i> interview) To be eligible for randomization in the maintenance phase, participants had to achieve control of both depressive and manic symptoms during an open phase that included both lamotrigine and divalproex (up to 8 weeks)
Interventions	Maintenance phase: Lamotrigine + placebo (45 participants); lamotrigine + divalproex (41 participants) Mean daily maintenance phase dosage for lamotrigine alone was 207 mg/day (range, 50-400) and 92 mg/day (range, 12.5-200 mg) for lamotrigine in combination with divalproex. The mean daily dosage for divalproex was 1382 mg/day (range, 250-2500 mg) Dosage did not differ significantly by site. The daily mean plasma concentration for valproate was 500 IU (range, 182-917) Duration of trial: 8 months
Outcomes	Time to relapse - depressive episode
Notes	Study included an open phase (164 patients) and a maintenance phase (86 patients); the study was conducted at two sites - the lead San Antonio site and Raleigh, North Carolina This study was identified after the search date, so has not been formally considered for inclusion. If it meets all the inclusion criteria it will be included in a subsequent update of this review

NCT00071253

Methods	Randomised double-blind placebo-controlled parallel-group trial
Participants	Estimated Enrollment: 180 Age: 18 - 65 years Inclusion Criteria: <ul style="list-style-type: none"> • DSM-IV-TR primary diagnosis of Bipolar I Disorder as confirmed by the SCID • Outpatient receiving treatment with a combination of Depakote plus olanzapine for their bipolar illness and considered clinically stable (e.g., no more than minimal symptoms, no psychiatric hospitalizations, no increase in intensity of clinical interventions) for the preceding 4 months • Identified at Screening a most bothersome side effect listed in the UKU which makes switching to monotherapy desirable • MRS total score < 12 on two consecutive ratings, separated by at least 5 days (Screening and Day 1) • DSS score < 13 on two consecutive ratings, separated by at least five days (Screening and Day 1) • CGI-S score < 3 on two consecutive ratings, separated by at least five days (Screening and Day 1) • Serum valproate level > 45 mcg/mL, and a maximum allowable dose of Depakote of 3000 mg/day at Screening • Olanzapine dose between 5 and 20 mg/day at screening
Interventions	Depakote (divalproex sodium) plus olanzapine, vs. Depakote monotherapy and olanzapine monotherapy in stable subjects during the maintenance phase of bipolar illness

[NCT00071253](#) (Continued)

Outcomes	Primary Outcome Measures: CGI-s, CGI-i, MRS, DSS, SADS-C
Notes	Status of trial on ClinicalTrials.gov = terminated We are seeking more information regarding this trial.

DATA AND ANALYSES

Comparison 1. Valproate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Study withdrawal due to episode of mood disorder	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Any mood episode	2	312	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.49, 0.93]
1.2 Manic episode	2	312	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.48, 1.25]
1.3 Depressive episode	2	312	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.24, 0.89]
2 Participant withdrawal from treatment-any cause	2	312	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.71, 0.95]
3 Participant withdrawal from treatment due to intolerance or non-compliance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Alopecia	2	312	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [1.15, 5.51]
4.2 Tremor	2	312	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [1.58, 3.67]
4.3 Weight gain	2	312	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.07, 3.86]

Comparison 2. Valproate versus lithium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Study withdrawal due to episode of mood disorder	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Any mood episode	4	618	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.20]
1.2 Manic episode	4	618	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.90, 1.44]
1.3 Depressive episode	4	618	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.84, 1.49]
1.4 Hypomanic episode	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.18, 2.61]
1.5 Mixed state	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 8.95]
2 Number of hospital admissions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 New drug treatment for mood episode	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Any mood episode	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Mania	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Depression	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Time to relapse (days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Participant withdrawal from treatment-any cause	4	618	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
6 Participant withdrawal from treatment due to intolerance or non-compliance	4	618	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.49, 0.93]
7 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

7.1 Diarrhoea	2	338	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 0.99]
7.2 Sedation	2	338	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.00, 2.10]
7.3 Polyuria	2	338	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.16, 0.58]
7.4 Increased thirst	2	338	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.15, 0.65]
7.5 Infection	1	278	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [1.16, 3.68]
7.6 Enuresis	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 0.94]
8 GAF-number of participants not responding at 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Quality of life-number of participants not responding at 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 DSH-number of participants with at least one episode of deliberate self-harm	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Valproate versus olanzapine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Study withdrawal due to episode of mood disorder	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Any mood episode	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Manic only	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Depressive only	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Participant withdrawal from treatment-any cause	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Participant withdrawal from treatment due to intolerance or non-compliance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Valproate plus lithium versus lithium alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Study withdrawal due to episode of mood disorder	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of hospital admissions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 New drug treatment for mood episode	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Any mood episode	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Mania	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Depression	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Participant withdrawal from treatment-any cause	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

5 Participant withdrawal from treatment due to intolerance or non-compliance	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Serious adverse events	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 GAF-number of participants not responding at 24 months	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Quality of life-number of participants not responding at 24 months	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 DSH-number of participants with at least one episode of deliberate self-harm	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Death	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Valproate plus lithium versus valproate alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Study withdrawal due to episode of mood disorder	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of hospital admissions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 New drug treatment for mood episode	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Any mood episode	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Mania	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Depression	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Participant withdrawal from treatment-any cause	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Participant withdrawal from treatment due to intolerance or non-compliance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 GAF-number of participants not responding at 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Quality of life-number of participants not responding at 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 DSH-number of participants with at least one episode of deliberate self-harm	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Valproate versus placebo, Outcome 1 Study withdrawal due to episode of mood disorder.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 1 Valproate versus placebo

Outcome: 1 Study withdrawal due to episode of mood disorder

Analysis 1.2. Comparison 1 Valproate versus placebo, Outcome 2 Participant withdrawal from treatment—any cause.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 1 Valproate versus placebo

Outcome: 2 Participant withdrawal from treatment—any cause

Analysis 1.3. Comparison 1 Valproate versus placebo, Outcome 3 Participant withdrawal from treatment due to intolerance or non-compliance.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 1 Valproate versus placebo

Outcome: 3 Participant withdrawal from treatment due to intolerance or non-compliance

Analysis 1.4. Comparison 1 Valproate versus placebo, Outcome 4 Adverse events.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 1 Valproate versus placebo

Outcome: 4 Adverse events

Analysis 2.1. Comparison 2 Valproate versus lithium, Outcome 1 Study withdrawal due to episode of mood disorder.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 1 Study withdrawal due to episode of mood disorder

(Continued ...)

Analysis 2.2. Comparison 2 Valproate versus lithium, Outcome 2 Number of hospital admissions.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 2 Number of hospital admissions

Analysis 2.3. Comparison 2 Valproate versus lithium, Outcome 3 New drug treatment for mood episode.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 3 New drug treatment for mood episode

Analysis 2.4. Comparison 2 Valproate versus lithium, Outcome 4 Time to relapse (days).

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 4 Time to relapse (days)

Analysis 2.5. Comparison 2 Valproate versus lithium, Outcome 5 Participant withdrawal from treatment—any cause.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 5 Participant withdrawal from treatment—any cause

Analysis 2.6. Comparison 2 Valproate versus lithium, Outcome 6 Participant withdrawal from treatment due to intolerance or non-compliance.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 6 Participant withdrawal from treatment due to intolerance or non-compliance

Analysis 2.7. Comparison 2 Valproate versus lithium, Outcome 7 Adverse events.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 7 Adverse events

(Continued ...)

Analysis 2.8. Comparison 2 Valproate versus lithium, Outcome 8 GAF-number of participants not responding at 24 months.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 8 GAF—number of participants not responding at 24 months

Analysis 2.9. Comparison 2 Valproate versus lithium, Outcome 9 Quality of life-number of participants not responding at 24 months.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 9 Quality of life—number of participants not responding at 24 months

Analysis 2.10. Comparison 2 Valproate versus lithium, Outcome 10 DSH-number of participants with at least one episode of deliberate self-harm.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 10 DSH – number of participants with at least one episode of deliberate self-harm

Analysis 2.11. Comparison 2 Valproate versus lithium, Outcome 11 Death.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 2 Valproate versus lithium

Outcome: 11 Death

Analysis 3.1. Comparison 3 Valproate versus olanzapine, Outcome 1 Study withdrawal due to episode of mood disorder.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 3 Valproate versus olanzapine

Outcome: 1 Study withdrawal due to episode of mood disorder

Analysis 3.2. Comparison 3 Valproate versus olanzapine, Outcome 2 Participant withdrawal from treatment-any cause.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 3 Valproate versus olanzapine

Outcome: 2 Participant withdrawal from treatment—any cause

Analysis 3.3. Comparison 3 Valproate versus olanzapine, Outcome 3 Participant withdrawal from treatment due to intolerance or non-compliance.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 3 Valproate versus olanzapine

Outcome: 3 Participant withdrawal from treatment due to intolerance or non-compliance

Analysis 4.1. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 1 Study withdrawal due to episode of mood disorder.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 1 Study withdrawal due to episode of mood disorder

Analysis 4.2. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 2 Number of hospital admissions.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 2 Number of hospital admissions

Analysis 4.3. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 3 New drug treatment for mood episode.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 3 New drug treatment for mood episode

Analysis 4.4. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 4 Participant withdrawal from treatment-any cause.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 4 Participant withdrawal from treatment—any cause

Analysis 4.5. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 5 Participant withdrawal from treatment due to intolerance or non-compliance.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 5 Participant withdrawal from treatment due to intolerance or non-compliance

Analysis 4.6. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 6 Serious adverse events.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 6 Serious adverse events

Analysis 4.7. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 7 GAF-number of participants not responding at 24 months.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 7 GAF—number of participants not responding at 24 months

Analysis 4.8. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 8 Quality of life-number of participants not responding at 24 months.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 8 Quality of life—number of participants not responding at 24 months

Analysis 4.9. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 9 DSH-number of participants with at least one episode of deliberate self-harm.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 9 DSH—number of participants with at least one episode of deliberate self-harm

Analysis 4.10. Comparison 4 Valproate plus lithium versus lithium alone, Outcome 10 Death.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 4 Valproate plus lithium versus lithium alone

Outcome: 10 Death

Analysis 5.1. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 1 Study withdrawal due to episode of mood disorder.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 1 Study withdrawal due to episode of mood disorder

Analysis 5.2. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 2 Number of hospital admissions.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 2 Number of hospital admissions

Analysis 5.3. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 3 New drug treatment for mood episode.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 3 New drug treatment for mood episode

Analysis 5.4. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 4 Participant withdrawal from treatment—any cause.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 4 Participant withdrawal from treatment—any cause

Analysis 5.5. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 5 Participant withdrawal from treatment due to intolerance or non-compliance.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 5 Participant withdrawal from treatment due to intolerance or non-compliance

Analysis 5.6. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 6 Serious adverse events.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 6 Serious adverse events

Analysis 5.7. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 7 GAF-number of participants not responding at 24 months.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 7 GAF—number of participants not responding at 24 months

Analysis 5.8. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 8 Quality of life-number of participants not responding at 24 months.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 8 Quality of life—number of participants not responding at 24 months

Analysis 5.9. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 9 DSH-number of participants with at least one episode of deliberate self-harm.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 9 DSH—number of participants with at least one episode of deliberate self-harm

Analysis 5.10. Comparison 5 Valproate plus lithium versus valproate alone, Outcome 10 Death.

Review: Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder

Comparison: 5 Valproate plus lithium versus valproate alone

Outcome: 10 Death

ADDITIONAL TABLES

Table 1. Adverse events

Adverse event	Study	Valproate		Comparator		Risk Ratio, Fixed [95% CI]
		Events	Total	Events	Total	
Valproate vs placebo						
Acne	Kemp 2009	0	15	2	16	0.21 [0.01, 4.10]
Akathisia	Bowden 2000	1	187	1	94	0.50 [0.03, 7.95]
Blurred vision	Kemp 2009	2	15	1	16	2.13 [0.22, 21.17]
Cognitive dysfunction	Kemp 2009	2	15	2	16	1.07 [0.17, 6.64]
Diarrhoea	Bowden 2000; Kemp 2009	69	202	34	110	1.11 [0.78, 1.56]
Dry mouth	Kemp 2009	3	15	0	16	7.44 [0.42, 132.95]
Fatigue	Kemp 2009	5	15	1	16	5.33 [0.70, 40.54]
Increased appetite	Kemp 2009	0	15	2	16	0.21 [0.01, 4.10]
Infection	Bowden 2000	51	187	18	94	1.42 [0.88, 2.29]
Nausea	Bowden 2000; Kemp 2009	81	202	32	110	1.32 [0.94, 1.86]
Polydipsia	Kemp 2009	6	15	5	16	1.28 [0.49, 3.33]
Polyuria	Bowden 2000	15	187	9	94	0.84 [0.38, 1.84]
Sedation	Bowden 2000	78	187	33	94	1.19 [0.86, 1.64]
Sexual dysfunction	Kemp 2009	2	15	2	16	1.07 [0.17, 6.64]
Tachycardia	Bowden 2000	1	187	1	94	0.50 [0.03, 7.95]
Thirst	Bowden 2000	11	187	7	94	0.79 [0.32, 1.97]
Tinnitus	Bowden 2000	12	187	1	94	6.03 [0.80, 45.69]
Valproate vs lithium						

Table 1. Adverse events (Continued)

Akathisia	Bowden 2000	1	187	4	91	0.12 [0.01, 1.07]
Alopecia	Bowden 2000 ; Calabrese 2005 ; Findling 2005	30	245	9	153	1.74 [0.85, 3.56]
Balance problems	Calabrese 2005	2	28	1	32	2.29 [0.22, 23.88]
Cognitive difficulties	Calabrese 2005	0	28	1	32	0.38 [0.02, 8.95]
Decreased appetite	Findling 2005	3	30	3	30	1.00 [0.22, 4.56]
Dry eyes	Bowden 2000	0	187	3	91	0.07 [0.00, 1.34]
Fever	Findling 2005	1	30	4	30	0.25 [0.03, 2.11]
Gastrointestinal discomfort	Calabrese 2005	2	28	5	32	0.46 [0.10, 2.17]
Haematological dyscrasia	Findling 2005	1	30	0	30	3.00 [0.13, 70.83]
Headache	Calabrese 2005 ; Findling 2005	11	58	4	62	2.64 [0.96, 7.24]
Nausea	Bowden 2000 ; Findling 2005	81	217	46	121	0.89 [0.68, 1.18]
Serious adverse events	BALANCE 2010	7	110	5	110	1.40 [0.46, 4.28]
Sore throat	Findling 2005	3	30	1	30	3.00 [0.33, 27.23]
Speech	Calabrese 2005	0	28	1	32	0.38 [0.02, 8.95]
Stomach pain	Findling 2005	7	30	3	30	2.33 [0.67, 8.18]
Tachycardia	Bowden 2000	1	187	4	91	0.12 [0.01, 1.07]
Tremor	Bowden 2000 ; Calabrese 2005 ; Findling 2005	83	245	53	153	0.86 [0.65, 1.14]
Upper respiratory congestion	Findling 2005	3	30	2	30	1.50 [0.27, 8.34]

Table 1. Adverse events (Continued)

Visual impairment	Calabrese 2005	0	28	3	32	0.16 [0.01, 3.02]
Vomiting	Findling 2005	3	30	9	30	0.33 [0.10, 1.11]
Weight gain	Bowden 2000 ; Calabrese 2005	41	215	13	123	1.60 [0.89, 2.85]

WHAT'S NEW

Date	Event	Description
4 September 2013	New citation required but conclusions have not changed	Methodology updated and new studies incorporated
4 September 2013	New search has been performed	Searches updated

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 3, 2001

Date	Event	Description
31 December 1999	New citation required and major changes	previous version of this review

CONTRIBUTIONS OF AUTHORS

Andrea Cipriani identified studies, contacted trial and review authors and pharmaceutical companies, extracted data, assessed study quality and drafted the review. Keith Reid identified studies, contacted trial and review authors and pharmaceutical companies, extracted data, drafted the first review and contributed to drafting of the updated review. Karine Macritchie extracted data, drafted the first review and contributed to drafting of the updated review. John Geddes identified studies, assessed study quality, commented on data extraction and contributed to drafting of the review. Allan H Young extracted data and contributed to drafting of the review.

DECLARATIONS OF INTEREST

Andrea Cipriani participated in the BALANCE trial as Italy's chief investigator.

Keith Reid declares no conflicting interests.

Allan H Young has sat on advisory boards and has received honoraria for lectures from sanofi-aventis, makers of a form of valproate, and also participated in the BALANCE trial, for which sanofi-aventis donated study medications.

Dr Karine Macritchie has worked on a project supported by an award NS-EU-166 from the Translational Medicine Research Collaboration. This consortium comprises the Universities of Aberdeen, Dundee, Edinburgh and Glasgow, the four associated NHS Health Boards (Grampian, Tayside, Lothian and Greater Glasgow and Clyde), Scottish Enterprise and Pfizer (formerly Wyeth). Several pharmaceutical companies have paid her institution for lectures, educational presentations/material and research.

John Geddes currently receives research funding from the UK Medical Research Council, the UK Economic and Social Research Council, the National Institute for Health Research, and the Stanley Medical Research Institute. He was expert witness for Dr Reddy's Laboratories, he is Chief Investigator on the CEQUEL trial to which GlaxoSmithKline has contributed and for which it has supplied investigational drugs and placebo. He is also the chief investigator of the BALANCE trial.

SOURCES OF SUPPORT

Internal sources

- University of Oxford, UK.
- University of Verona, Italy.
- University of Newcastle, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Rate of deliberate self-harm was added as an outcome measure, and the order of the outcome measures was changed.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimanic Agents [*therapeutic use]; Benzodiazepines [therapeutic use]; Bipolar Disorder [*drug therapy; prevention & control]; Drug Therapy, Combination [methods]; Lithium Compounds [therapeutic use]; Olanzapine; Randomized Controlled Trials as Topic; Secondary Prevention; Valproic Acid [*therapeutic use]

MeSH check words

Humans