Lithium for maintenance treatment of mood disorders (Review)

Burgess SSA, Geddes J, Hawton KKE, Taylor MJ, Townsend E, Jamison K, Goodwin G

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Lithium for maintenance treatment of mood disorders

Sally SA Burgess[2], John Geddes[1], Keith KE Hawton[3], Matthew J Taylor[1], Ellen Townsend[4], K Jamison[5], Guy Goodwin[1]

[1]Department of Psychiatry, University of Oxford, Oxford, UK. [2]Department of Psychiatry of Old Age, Oxfordshire Mental Healthcare NHS Trust, Oxford, UK. [3]University Department of Psychiatry, Warneford Hospital, Oxford, UK. [4]Risk Analysis, Social Processes and Health Group, School of Psychology, University of Nottingham, Nottingham, UK. [5]Oxford, UK

Contact address: John Geddes, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 7JK, UK. john.geddes@psych.ox.ac.uk.

Editorial group: Cochrane Depression, Anxiety and Neurosis Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 18 March 2001.

Citation: Burgess SSA, Geddes J, Hawton KKE, Taylor MJ, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. *Cochrane Database of Systematic Reviews* 2001, Issue 3. Art. No.: CD003013. DOI: 10.1002/14651858.CD003013.

ABSTRACT

Background

Mood disorders are common, disabling and tend to be recurrent. They carry a high risk of suicide. Maintenance treatment, aimed at the prevention of relapse, is therefore of vital importance. Lithium has been used for some years as the mainstay of maintenance treatment in bipolar affective disorder, and to a lesser extent in unipolar disorder. However, the efficacy and effectiveness of prophylactic lithium therapy has been disputed. Low suicide rates in lithium-treated patients have led to claims that lithium has a specific anti-suicidal effect. If so, this is of considerable importance as treatments for mental disorders in general have not been shown convincingly to be effective in suicide prevention.

Objectives

1. To investigate the efficacy of lithium treatment in the prevention of relapse in recurrent mood disorders.

2. To examine the effect of lithium treatment on consumers' general health and social functioning, its acceptability to consumers, and the side-effects of treatment.

3. To investigate the hypothesis that lithium has a specific effect in reducing the incidence of suicide and deliberate self-harm in persons with mood disorders.

Search strategy

The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) and The Cochrane Controlled Clinical Trials Register (CCTR) were searched. Reference lists of relevant papers and major text books of mood disorder were examined. Authors, other experts in the field and pharmaceutical companies were contacted for knowledge of suitable trials, published or unpublished. Specialist journals concerning lithium were hand searched.

Selection criteria

Randomised controlled trials comparing lithium with placebo, where the stated intent of treatment was maintenance or prophylaxis. Participants were males and females of all ages with diagnoses of mood disorder. Discontinuation studies (in which all participants had been stable on lithium for some time before being randomised to either continued lithium treatment or placebo substitution) were excluded.

Data collection and analysis

Data were extracted from the original reports independently by two reviewers. The main outcomes studied were related to the objectives stated above. Data were analysed for all diagnoses of mood disorder and for bipolar and unipolar disorder separately. Data were analysed using Review Manager version 4.0.

Main results

Nine studies were included in the review, reporting on 825 participants randomly allocated to lithium or placebo. Lithium was found to be more effective than placebo in preventing relapse in mood disorder overall, and in bipolar disorder. The most consistent effect was found in bipolar disorder (random effects OR 0.29; 95% CI 0.09 to 0.93). In unipolar disorder, the direction of effect was in favour of lithium, but the result (when heterogeneity between studies was allowed for) did not reach statistical significance. Considerable heterogeneity was found between studies in all groups of patients. The direction of effect was the same in all studies; no study found a negative effect for lithium. Heterogeneity may have been due to differences in selection of participants, and to differing exposures to lithium in the pre-study phase resulting in variable influence of a discontinuation effect. There was little reported data on overall health and social functioning of participants under the different treatment conditions, or on the participants' own views of their treatment. Descriptive analysis showed that assessments of general health and social functioning generally favoured lithium. Small absolute numbers of deaths and suicides, and the absence of data on non-fatal suicidal behaviours, made it impossible to draw meaningful conclusions about the place of lithium therapy in suicide prevention.

Authors' conclusions

This systematic review indicates that lithium is an efficacious maintenance treatment for bipolar disorder. In unipolar disorder the evidence of efficacy is less robust. This review does not cover the relative efficacy of lithium compared with other maintenance treatments, which is at present unclear. There is no definitive evidence from this review as to whether or not lithium has an anti-suicidal effect. Systematic reviews and large scale randomised studies comparing lithium with other maintenance treatments (e.g. anti-convulsants, antidepressants) are necessary. Outcomes relating to death and suicidal behaviour should be included in all future maintenance studies of mood disorder.

PLAIN LANGUAGE SUMMARY

Lithium for maintenance treatment of mood disorders

This systematic review investigated the efficacy of lithium compared to that of placebo in the maintenance treament of mood disorders (unipolar and bipolar disorder). Nine randomised studies (reporting on 825 participants) were included in the review. Lithium was more effective than placebo in preventing relapse in mood disorder overall. Lithium was more effective than placebo in bipolar disorder, though estimates of the size of the effect varied between studies. In unipolar disorder, lithium appeared to be more effective than placebo but the evidence for this was less clear cut.

Lithium should be considered for maintenance treatment in bipolar disorder and, although the evidence is less reliable, it may be considered as one of a range of treatments with possible benefit in preventing relapse in unipolar disorder. When considering lithium maintenance therapy, patients and clinicians should take into account the evidence of efficacy, side effects and the individual's likely adherence to the recommended treatment regimen. Caution should be exercised in abruptly stopping lithium therapy in patients who have been taking it successfully for some time, due to the high risk of relapse.

BACKGROUND

Mood disorders are common, disabling and have a tendency to recur. The defining features of these disorders are disturbances of mood with episodes of depression (lowered mood) and mania (elevated and/ or irritable mood). Categories of mood disorder include bipolar disorder (manic depression), with episodes of both depression and mania or hypomania, and unipolar disorder, with episodes of depression only. Most episodes of illness recover over time and with treatment, but there is a marked tendency for these disorders to be recurrent. It has been estimated that over 50% of

individuals who have an initial episode of major depression and at least 80% who have an episode of mania will have one or more recurrences (Klein 1980; NIMH-NIH 1985; APA 1994). In addition, subclinical depressive symptoms may persist and become chronic. The illnesses vary in severity but share a common potential to cause serious psychological, social and economic suffering. Of particular concern, mood disorder is a major risk factor for suicide, which is 16 to 35-fold more common in those with mood disorders than in the general population (Harris 1997).

Maintenance treatment, or prophylaxis, which aims to prevent or attenuate further episodes of illness, is therefore of vital importance in the management of mood disorders. The maintenance effect of lithium has been recognised since the 1960s (Abou-Saleh 1992). Since then lithium has become the mainstay of preventative treatment in bipolar disorder, and is used in the maintenance treament of other mood disorders. Lithium is also recommended for the treatment of acute mania and for the augmentation of treatment in resistant depression (Gelder 1989; Katona 1995). Its effectiveness as an anti-depressant when used alone has been disputed (Stokes 1971; Fieve 1983). This review focuses on the use of lithium as a maintenance treament .

Maintenance treament of mood disorders is an area of true clinical uncertainty. Lithium is widely used in clinical practice. Its use has been considered "well established" (Guscott 1994) and "one of the most rewarding therapeutic strategies in medical practice" (Abou-Saleh 1982). On the other hand, it has been seriously questioned as "another therapeutic myth" (Blackwell 1968) and "ineffective in the long term outlook of bipolar disorder" (Moncrieff 1997). Abrupt discontinuation of lithium treatment in bipolar patients is known to precipitate episodes of affective illness (Suppes 1991; Goodwin 1994). The early randomised controlled trials that established the use of lithium therapy have been criticised as several of them were of a discontinuation design. It has been suggested that the considerable beneficial effect of lithium found in these studies was due to the operation of such a discontinuation effect. (Moncrieff 1997). In recent years other drugs, namely the anti-convulsants carbamazepine and sodium valproate, have gained wider use in the maintenance treament of bipolar disorder. In unipolar disorder antidepressant drugs are widely used as preventative treatment. The relative efficacy of these agents in comparison to lithium is unknown.

In addition to uncertainty over its efficacy, the effectiveness of lithium in clinical practice has been found to be less than was hoped for (Markar 1989). Patient non-adherence has been suggested as a possible reason for this (Guscott 1994). Lithium treatment is not without its problems, which no doubt affects its acceptability to consumers. Maintenance treament requires prolonged daily tablet taking, and regular blood monitoring is necessary. Lithium has a range of unwanted side effects, including excessive thirst, polyuria, subjective memory disturbances, tremor, weight gain, and long-term effects on the thyroid and kidney. The window between ineffective and toxic doses is narrow and excessive plasma levels can result in potentially fatal neuro-toxicity (Goodwin 1990).

Suicide and deliberate self-harm are currently major public health problems. Suicide and deliberate self-harm are strongly associated with mood disorder (Barraclough 1974; Newson-Smith 1979; Lonnqvist 1995). There is a lack of evidence that modern treatment of mental disorders has had any effect in reducing the incidence of suicide (Gunnell 1994). Lithium may be exceptional in this respect, as it has been suggested that lithium has a specific anti-suicidal effect in mood disorders and also that it reduces rates of deliberate self-harm (Kay 1977; Causemann 1988; Crundwell 1994; Thies-Flechtner 1996; Tondo 1997). This review examines the evidence from randomised controlled trials pertinent to this claim.

There are various challenges in studying the literature in this area. Firstly, diagnostic classifications have changed over the years. In the past the term 'manic depressive disorder' was used as a single diagnosis, including both unipolar and bipolar disorder. More recent diagnostic classifications have drawn distinctions between these two disorders (WHO 1992; APA 1994). Second, the point at which acute treatment of an episode of mood disorder ends and maintenance treament begins is arbitrary. This causes particular difficulties as lithium is also used as a treatment for acute mania and to augment anti-depressant treatment. Thirdly, as discontinuation relapse has been recognised only relatively recently the earlier studies in the field do not consider whether previous lithium exposure is a cause of possible bias.

OBJECTIVES

The principal objectives were:

1. To determine the efficacy of lithium therapy as a maintenance treament in preventing episodes of mood disorder in persons with bipolar and unipolar mood disorder. To assess whether any such effect operates in the prevention of both manic and depressive episodes.

2. To determine effects of lithium maintenance treament on participants' health and social functioning, with reference to clinician and participant reports, employment and marital stability.

3. To review the acceptability to participants of long-term treatment with lithium, measured by numbers and reasons for dropping out of treatment, compliance, and by reference to participants' expressed views regarding treatment.

4. To investigate the side-effects of lithium treatment, including general prevalence of side-effects and specific unwanted effects namely: excessive thirst, polyuria, subjective cognitive disturbance,

tremor, weight gain, renal and thyroid dysfunction, and lithium induced neurotoxicity.

5. To compare mortality on lithium treatment with mortality on placebo.

6. To test the hypothesis that lithium has an anti-suicidal effect in terms of preventing suicide, deliberate self-harm and other suicidal phenomena (such as the expression of suicidal ideas). To determine if any such anti-suicidal effect is dependant on, or independent of, effectiveness in preventing further episodes of mood disorder.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomised controlled studies.

Types of participants

Males and females of all ages with a diagnosis of mood disorder (primarily bipolar disorder and recurrent unipolar disorder) were included. Studies were divided into three groups on the basis of their participants; studies of participants with mixed diagnoses of mood disorder (bipolar disorder, unipolar disorder and unspecified), studies with bipolar participants only, and studies with unipolar participants only. Trials of participants with mixed diagnoses of mood disorder could include more heterogeneous groups of participants, including some individuals with schizoaffective disorder and dysthymia. These participants were not excluded from the analyses of the effect of lithium maintenance treament in mood disorders as a whole. Where possible, it was noted if bipolar 1 or II (the distinction is that in bipolar 1, full manic episodes occur whereas in bipolar II only hypomanic episodes occur)

Types of interventions

Studies included were those comparing lithium with placebo in the maintenance treament of mood disorders, where follow up was for at least three months. Maintenance treament was defined as treatment instituted primarily to prevent further episodes of affective illness. Discontinuation studies (in which participants stable on lithium therapy were selected, then randomly assigned to continued lithium treatment or placebo substitution) were excluded from the main analyses. We considered these studies to have a high risk of bias due to withdrawal relapse. In addition, they did not address the main clinical question of this review, namely the proportion of patients with mood disorder likely to benefit from lithium treatment. Relapse rates from discontinuation studies were analysed separately, as we felt they provided valuable information on the outcome of sudden discontinuation of lithium treatment. We excluded trials that were confounded by adjunctive treatments i.e. when lithium was combined with another treatment such as an anidepressant or anticonvulsant. However, in factorial trials of lithium, placebo and and antidepressant, we included the lithium v. placebo comparison because the factorial design allows an unconfounded comparison between lithium and placebo.

Types of outcome measures

1. Relapse: in mood disorders overall, and in bipolar disorder and unipolar disorder separately. As measured by:
i).All affective episodes
-admission to hospital
-institution of additional treatment for mood disorder
-relapse- however defined by study authors
ii). Manic episodes
-admission to hospital
-institution of additional treatment for manic disorder
-relapse- however defined by study authors
iii). Depressive episodes
-admission to hospital
-institution of additional treatment for depressive disorder
-relapse- however defined by study authors
2. General health and social functioning
i). Clinical global impression of clinician
ii). Clinical global impression of participant
iii). Employment during study period
iv). Separation/divorce during study period
3. Acceptability of lithium treatment
i). Participants dropping out of treatment during study period
ii). Measures of compliance with treatment
iii). Participant reports of satisfaction or otherwise with treatment
4. Side-effects
ii). Participants reporting any troublesome side-effects
iii). Participants reporting excessive thirst; polyuria; cognitive impairment; tremor; weight gain
iv). Evidence of thyroid dysfunction
v). Evidence of renal disturbance
vi). Incidence of neurotoxicity, excluding incidence of toxicity secondary to lithium overdose
5. Mortality
i). Overall mortality rates during study period
ii). Mortality excluding suicide and verdicts of undetermined death
iii). Mortality due to cardiovascular causes
6. Suicide and non-fatal suicidal behaviour
i). Mortality due to suicide and undetermined death
ii). Deliberate self-harm (self-poisoning and self-injury)
iii). Suicidal ideation

Search methods for identification of studies

See: Collaborative Review Group search strategy
1). Electronic databases
The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) (see Collaborative Review Group search strategy) and The Cochrane Controlled Clinical Trials Register (CCTR) were searched using the following search terms;
LITHIUM OR CAMCOLIT OR CARBOLITH OR DUROLITH OR ESKALITH OR LICARBIUM OR LISKONUM OR LITAREX OR LITHANE OR LITHOCARB OR LITHIZINE OR LITHONATE OR LITHOTABS OR MANIALITH OR PHASAL OR PRIADEL OR QUILONORM OR QUILONUM OR LI-LIQUID
2). Reference checking
The reference lists of all identified randomised controlled trials, other relevant papers and major textbooks on mood disorder were checked.
3). Hand searching
The journals Lithium (1990-1994) and Lithium Therapy Monographs (1987-1991) were hand-searched.
4). Personal communication
The authors of randomised controlled trials included in the review and other recognised experts in the field were contacted and asked if they had knowledge of any other studies, published or unpublished, relevant to the review. Pharmaceutical companies marketing lithium products were requested to provide relevant published and unpublished data (see CCDAN group policy).

Data collection and analysis

Selection of trials and data extraction
Studies generated by the search strategies were checked to ensure they met the previously defined inclusion criteria. Two reviewers independently extracted data concerning participant characteristics, intervention details (including participants' lithium exposure immediately preceding the trial), and outcome measures from the included studies. Any disagreements were resolved by consensus.
Quality assessment
The methodological quality of the included studies was assessed according to the Cochrane criteria for quality assessment (Clarke 1999). On this basis, studies were given a rating of A (adequate randomisation and concealment)) B (unclear) and C (inadequate). In addition, other aspects of methodological quality were assessed using the instrument described by Jadad (Jadad 1996). This is a five-point scale, with points awarded for adequacy of randomisation, double blinding, and reporting of withdrawals and dropouts. Two reviewers (different reviewers to those extracting data) independently assessed the included studies. These reviewers were blind to the authorship and source of the studies. Where there was disagreement, final ratings were made by consensus with the involvement of other members of the review group. In cases where inadequate details of randomisation and other methodologies were provided in published papers, the authors were contacted to obtain further information. Quality ratings were revised in several cases on the basis of information received from authors.
Data analysis
Data were entered into RevMan 4.0 software by two reviewers. Heterogeneity between studies was assessed using the Q statistic (DerSimonian 1986). Heterogeneity refers to the variation observed between the results of the individual studies. Statistically significant heterogeneity is said to be present when more variation between the studies occurs than can be explained by the play of chance alone. For binary efficacy outcomes random (DerSimonian 1986) and fixed (Yusuf 1985) effects odds ratios (with 95% confidence intervals) were calculated. Fixed effect analysis assumes a common underlying treatment effect across studies and random effects assumes a range of treatment effects and incorporates inter-study variation into the pooled odds ratio. When heterogeneity is observed, the random effects approach has some advantages because it takes the variation into account. However, the random effects model also makes a number of assumptions. We therefore present both sets of results to allow an estimation of the sensitivity of the results to the choice of method. When significant heterogeneity is observed, we favoured the random effect model because the uncertainty of the true estimate is reflected in the broader confidence interval. Potential sources of heterogeneity were investigated. Where possible we intended to use intention-to-treat (ITT) data for the primary efficacy analyses. Where ITT data were not available, we used endpoint data for trial completers. Quantitative data that could not be pooled are presented descriptively. We planned to perform a sensitivity analysis excluding data from studies of lower methodological quality, to assess the robustness of the results. However, the data did not allow this analysis. Separate analyses were done for: studies involving participants with mixed diagnoses of mood disorder (unipolar, bipolar and unspecified); studies with bipolar participants only; studies with unipolar participants only. Data from trials including both unipolar and bipolar participants were only included in the respective analysis if the two diagnostic groups had been randomised separately. We also analysed the data for all studies that included unipolar participants and all studies that included bipolar participants. Subgroup analyses were planned for participants with longer duration of illness and multiple previous episodes and for those with shorter duration of illness, but these were not possible.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Eighteen randomised controlled trials comparing lithium with placebo in the maintenance treament of mood disorder were initially identified. All studies led to published reports. Several resulted in multiple publications. Five studies were excluded from the main analyses as they were of a discontinuation design (Baastrup 1970 a; Melia 1970; Cundall 1972; Hullin 1972; Hardy 1997). Relapse rates in these studies were analysed separately. One study was excluded as the diagnoses of mood disorder appeared unsound (Naylor 1974). Three further studies have been categorised as awaiting assessment (Coppen 1981; Dorus 1989; Wilson 1995 b). We have requested further data from the authors of these studies regarding outcome measures of relevance to this review. These data, if received, will be included in future versions of this review. This leaves nine studies that are presently included in the review. These studies report on 825 participants randomly allocated to lithium or placebo. Four of the studies included a mixed group of participants with either bipolar or unipolar disorder (Laurell 1968; Coppen 1971; Prien 1973b; Fieve 1976). One study reported on groups with bipolar disorder and unipolar disorder that were randomised separately (Kane 1982). Two studies included only unipolar participants (Glen 1984; Prien 1984), and two studies only bipolar participants (Prien 1973a; Bowden 2000).

Three of the studies included a third group of participants who were allocated to treatment with anti-depressant medication (Laurell 1968; Glen 1984; Prien 1972b). One study included a third arm who were allocated to divalproex, a form of valproic acid which is an anticonvulsant and is used as a mood stabiliser (Bowden 2000). Participants on these other medications were not included in the analyses. Two studies had a factorial design in which patients were allocated to lithium, placebo, imipramine, or lithium + imipramine (Prien 1984; Kane 1981). For the purposes of this review the lithium and lithium + imipramine cells were included as a lithium group, and the placebo + imipramine groups as a placebo group.

In three of the studies all the participants were stabilised on lithium treatment for unstated lengths of time prior to randomisation (Prien 1973a; Prien 1973b; Prien 1984). In the study by Bowden, 34% of the group allocated to lithium and 35% of the group allocted to placebo received lithium as an open treatment prior to randomisation. In this study lithium was discontinued gradually over two weeks in those participants allocated to placebo. In the five remaining studies the participants' use of lithium prior to the study was unstated or unclear. Additional information regarding prior lithium use in these studies is being sought. See Table 1

Table 1. Previous lithium exposure

study	lithium exposure	notes
Coppen 1971	Not stated	
Fieve 1976	Not stated	
Glen 1984	Unclear	Participants gradually changed over from acute treatment to study treatment over 2 weeks
Kane 1982	Unclear	
Laurell 1968	Not stated	
Prien 1973a	Stabilised on lithium prior to randomisation	Length of stabilisation phase unstated. No major diference in results obtained from 1st and 2nd years of the study.
Prien 1973b	Stabilised on lithium or imipramine prior to randomisation	Length of stabilisation phase unstated. Results from months 1-4 and 5-24 presented seperately. 5-24 month results only used in review.
Prien 1984	Stabilised on lithium and imipramine for at least 2 months	

Table 1. Previous lithium exposure (*Continued*)

Bowden 2000	31/90 of lithium group and 32/92 in placebo group taking lithium in 3 month open phase before randomisation	Lithium withdrawn gradually over first 2 weeks of trial. Limited recue medication of lorazepam and haloperidol allowed during first month to early relapse

The studies followed participants from randomisation either until they relapsed or for maximum periods of between 11 months and 4 years. Five of the studies had a two-year follow up period.

The range of lithium levels employed was known for 8 studies and the ranges used were all between 0.5 and 1.4. mmol/l. One study did not report lithium levels (Laurell 1968). See Table 2

Table 2. Lithium levels and doses used in the studies

Study	Target level; mmol/l	Dose used	Level: mmol/l
Coppen 1971	0.8 to 1.2		0.73 - 1.23 (mean 0.93)
Fieve 1976	0.7 to 1.3 or 0.8 to 1.3		
Glen 1984	0.6 to 1.2		
Kane 1982	0.8 to 1.2		
Laurell 1968		900mg	
Prien 1973a	0.5 to 1.4	median 1000mg	median 0.7
Prien 1973b	0.5 to 1.4	median 1250mg	median 0.8
Prien 1984	0.6 to 0.9		0.43 to 1.05, mean 0.66
Bowden 2000	0.8-1.2		mean 1.0 +/- 0.48

Bowden (2000) states that the included participants have bipolar 1 disorder. Although the other trials do not mention the distinction, it is likely that most of the patients in these studies were bipolar 1 because the distinction between I/II post-dates most of the studies. Prien (1973 and 1984) states that, to be rated as bipolar, a patient must have had a manic episode.

Risk of bias in included studies

In accordance with the protocol, the studies were assessed using the Cochrane Criteria for quality assessment (Clarke 1999) and the Jadad scale (Jadad 1996). (See 'methods of review' for details of these quality assessments.) The ratings given to the studies were as below:
Coppen 1971 A 5
Fieve 1976 A 5
Glen 1984 A 5
Kane 1981 B 3

Laurell 1968 B 3
Prien 1973a B 3
Prien 1973b B 3
Prien 1984 A 4
Bowden 2000 A 4
Due to doubts over the validity of the scales used (Juni 1999), and the relative homogeneity of the ratings, we did not carry out sensitivity analysis excluding the studies with lower ratings. However, we did consider that there were significant methodological problems in the studies which had the potential to introduce bias into the results of the review. These issues are discussed below.
1. Randomisation/concealment of allocation
All the studies are described as randomised, but generally little information was given in the published reports regarding the methods used to achieve random allocation. Thus, on the basis of published reports, most of the studies initially received a B rating according to the Cochrane criteria. Additional information was sought from the study authors. Where this information has been received, it indicates mostly that the procedures used were adequate, and Cochrane quality ratings have been upgraded accordingly. The lack of detailed reporting of randomisation methodology seems to be a common feature of studies published in the last 20 years.
2. Lack of intention-to-treat analysis
The data in the included studies were not analysed on an intention-to-treat (ITT) basis, with the exception of the Bowden study (Bowden 2000). Post-hoc ITT analysis was not possible on the basis of data presented in the papers due to inadequacies in reporting. As more participants overall appear to have dropped out of the placebo groups, this may have the effect of biasing the results in favour of placebo.
3. Blinding
Two of the largest studies (Prien 1973a; Prien 1973b) were single blind. In these studies the treating physician (who was responsible for hospitalisation and withdrawal of the patients from the study) was aware of the participants' treatment allocation. As hospitalisation and withdrawal are important outcome measures, this is a source of potential bias.
4. Numbers of participants
All of the included studies were small, and some were very small. This affects their ability to detect treatment differences, especially if such differences are moderate, or the outcomes are rare (e.g. suicide). The use of power calculations to guide sample size is only presented in one study (Bowden 2000) and in this case the aim of the power calculation was not to detect differences between the lithium and placebo groups.

5. Selection of participants
The source and selection of participants varied between the studies. Prien 1973a and Prien 1973bPrien (1973a and b) recruited participants hospitalised for acute mania or depression. In Bowden (2000) the index episodes of mania appear to have been less severe than in the Prien studies, as many participants were not admitted to hospital and some did not even require drug treatment for their index illnesses. The number of previous episodes of illness required for inclusion also varied between studies. Thus the studies may have been investigating groups of participants with different severity of mood disorder. In addition, Bowden (2000) was completed at a time when lithium prophylaxis was in much wider clinical use than it was during the earlier studies. This may have led to bias against inclusion of participants with a history of responding well to lithium, as such persons may have been less willing to enter a study with the possibility of being allocated to placebo. This difference in the selection of participants may have led to heterogeneity between studies results. Overall, however, the heterogeneous nature of the participants in the studies broadens the applicability of the results of the review.
6. Diagnosis of affective disorder
Standardised diagnostic tools and operationally defined diagnostic classifications were not used in several of the earlier studies. The criteria that were used to diagnose mood disorder in these studies were generally sparsely reported, reflecting the custom of the time.
7 . Discontinuation effects
It is now widely accepted that abrupt withdrawal of established lithium therapy may precipitate early (especially manic) relapse in bipolar disorder (Suppes 1991; Goodwin 1994). Such an effect would be expected to lead to an increased number of early relapses in placebo-treated groups in lithium discontinuation studies (studies in which patients stable on lithium therapy are randomly allocated to continued lithium treatment, or substitution of lithium with placebo). For this reason, such discontinuation studies have been excluded from the review. However, in three of the included studies participants were stabilised on lithium for an unknown length of time before randomisation, in one study approximately 35% of participants were taking lithium prior to randomisation, and in the five remaining studies previous lithium use was either unstated or unclear. It is not known if persons taking lithium for short periods or for acute treatment are at risk of discontinuation relapse. In some of the studies lithium was discontinued slowly, which would be expected to reduce any such effect. However, none of the studies are known with certainty to have been free of the possibility of bias from discontinuation relapse.
8. Treatment of early relapse
Several of the included studies have been previously criticised (Moncrieff 1997) because the treating physicians were allowed to increase the dose of study medication in the face of either inadequate serum levels or impending relapse. We did not consider these criticisms to be justified. Dose adjustment to maintain serum levels within the therapeutic range is necessary in prophylactic treatment. Such adjustments occurred in both lithium and placebo groups, as fictitious serum levels were presented for the placebo treated participants. Dosages could also be increased due to impending relapse, and thus participants receiving lithium could be considered to be receiving active treatment for early relapse

whereas placebo-treated participants were not. This view presupposes that lithium is effective in the treatment of early relapse. Again, such dose adjustments were made in both the lithium and placebo groups and can be considered an element of good practice in prophylactic treatment. We consider that such dose adjustments were part of the treatment condition being evaluated.

9. Publication bias

Funnel graphs were plotted to assess the possibility of publication bias (the selective publishing of studies showing positive treatment effects). No evidence of major publication bias was found, but the number of studies was too small for it to be excluded unequivocably.

Effects of interventions

1). Relapse

Relapse was defined in various ways in the studies. We therefore categorised it in three ways: i) admission to hospital, ii) prescription of non-study medication for mood disorder, and iii) relapse-however defined by study authors ("relapse however defined").

Mixed diagnoses of mood disorder

Overall, there was evidence that lithium was more efficacious than placebo in preventing relapse in groups of participants with mixed diagnoses of mood disorder. No single study found a negative effect for lithium on any of the three main outcomes relating to relapse. Although the direction of effect was the same in all the studies, there was statistically significant heterogeneity between the studies (chi-square 33.92, df 8, p<0.0001). We therefore considered the random effects odds ratio to be the best estimate of treatment effect, because this method does not assume a constant underlying effect, and takes inter-study variation into account. However, both random and fixed effect (Peto) odds ratios are quoted because comparisons between them can be informative. For admission to hospital (random effects odds ratio (OR) 0.24, 95% confidence interval (CI) 0.14 to 0.40; Peto OR 0.26, 95% Cl 0.16 to 0.42; 2 studies, 286 participants) and relapse however defined (random effects OR 0.21, 95% CI 0.10 to 0.43; Peto OR 0.30, 95% Cl 0.23 to 0.40; 9 studies, 825 participants) the estimate of the treatment effect was robust to the choice of method. For prescription of non-study medication, when a random effects model was used, the confidence interval broadened to include the point of no effect (random effects OR 0.32, 95% CI 0.09 to 1.20; Peto OR 0.41 95% Cl 0.24 to 0.7; 3 studies, 351 participants).

When manic and depressive relapses were considered separately, using the broad definition of relapse however defined, lithium was more effective than placebo in preventing depressive relapses (random effects OR 0.43, 95% CI 0.21 to 0.86; Peto OR 0.51, 95% Cl 0.34 to 0.76; 5 studies, 484 participants). For manic relapses, the trend was towards lithium preventing relapses, but the results did not reach statistical significance (random effects OR 0.67, 95% CI 0.40 to 1.13; Peto OR 0.65, 95% Cl 0.39 to 1.08; 5 studies, 484 participants).

Bipolar disorder

There were three studies which included only bipolar participants or had separately randomised bipolar groups (Prien 1973a; Kane 1982; Bowden 2000) (212 participants). There was significant heterogeneity between the results of the studies (chi-square 10.06, df 2, p<0.01), so random effects odds ratios were again primarily considered. In bipolar disorder, lithium was more effective than placebo in preventing relapse when considering the broadest outcome of relapse however defined (random effects OR 0.29, 95% CI 0.09 to 0.93; Peto OR 0.35, 95% OR 0.23 to 0.51). The results were in the same direction when manic and depressive relapses were considered separately although they did not exclude the point of no effect (manic relapse random effects OR 0.85, 95% CI 0.43 to 1.69; Peto OR 0.83, 95% Cl 0.42 to 1.63, 2 studies, 107 participants), (depressive relapse random effects OR 0.50, 95% CI 0.22 to 1.11; Peto OR 0.51, 95% CL 0.24 to 1.09, 2 studies, 107 participants).

A sensitivity analysis was performed including all the studies that included participants with bipolar disorder (the three exclusively bipolar studies plus four studies concerning participants with a mixture of affective disorder diagnoses). This analysis showed a similar result for overall relapses as that including only bipolar patients (random effects OR 0.20, 95% CI 0.09 to 0.45; Peto OR 0.27, 95% CL 0.2 to 0.38, 7 studies, 629 participants).

Unipolar disorder

Three studies included only unipolar patients or had separately randomised unipolar groups, (Glen 1984; Prien 1984; Kane 1982) (196 participants). There was significant heterogeneity between the results of these studies (chi-square 9.36, df 2, p<0.01), with Kane 1982 and Glen 1984 finding a positive treatment effect and Prien 1984 showing little effect. For relapse however defined, the direction of the effect was in favour of lithium, but the results did not exclude the point of no effect when the random effects model was used (random effects odds ratio 0.14, 95% CI 0.02 to 1.27; Peto OR 0.40, 95% Cl 0.23 to 0.70). The findings for depressive relapse were similar, again with significant heterogeneity between studies (random effects OR 0.16, 95% CI 0.02 to 1.34; Peto OR 0.46, 95% Cl 0.26 to 0.8, 3 studies 196 participants). There were few manic relapses in patients with unipolar disorders (9 out of 196 participants) and so the estimate of effect is imprecise (random effects OR 0.48, 95% CI 0.12 to 1.86; Peto OR 0.46, 95% Cl 0.12 to 1.75, 3 studies, 196 participants).

We performed a sensitivity analysis including all the studies that included participants with unipolar disorder (all studies excluding the two concerning solely bipolar participants). This analysis showed a result more favourable to lithium than that including only unipolar patients only (random effects OR 0.15, 95% Cl 0.05-0.42; Peto OR 0.26, 95% Cl 0.18 to 0.39, 7 studies, 413 participants).

Discontinuation studies

As an addition to the main objectives of the review, we analysed relapse rates in the five discontinuation studies identified by the

search strategy. In these studies the participants had been stable on lithium therapy for periods between 9 months and seven years. In each of the studies the participants were randomly allocated to continuation of lithium therapy or double-blind placebo substitution. Analyses of the outcome 'relapse however defined' found significant heterogeneity between the studies. Participants whose lithium therapy was withdrawn were significantly more likely to relapse than those whose lithium was continued (random effects OR 0.18, 95% Cl 0.04 to 0.74; Peto OR 0.14, 0.07 to 0.28).

2. General health and social functioning

We had hoped to compare the general health and social functioning of participants receiving lithium maintenance treament with those receiving placebo. Few studies included such outcome measures, and where they did, the actual data collected were often absent or inadequately reported. The data that were recorded in this area were not directly comparable across the studies and could not be combined numerically. In general the data presented favoured lithium over placebo on a variety of measures. The Bowden study (Bowden 2000) was an exception to this generality with participants assigned to placebo showing less worsening on global assessment and depression rating scales over the period of the study than lithium participants.

i). Clinical global impression of clinician

Six studies included some kind of global assessment made by clinicians. These assessments varied in their scope. They assessed overall experience of affective disorder, affective symptoms, behaviour, functioning and treatment preferences. Details of these global ratings are given below.

Bowden 2000

This study included outcome measures of mean change from baseline scores in the Global Assessment Scale (GAS), Depressive Syndrome score (DSS), and Mania Rating Scale (MRS). It is unclear how often these assessment scales were administered. GAS and DSS scores worsened less for the placebo than the lithium group, GAS (F(1,325) =4.92, P=0.027), DSS (F91,358) =5.20, P =0.023). MRS scores showed small mean changes which did not differ significantly between the treatment groups.

Coppen 1971

Global assessment by psychiatrists and social workers made at the end of study period was compared with a similar assessment of affective disturbance in the two years before the study. Psychiatrists' and social workers' ratings showed high levels of concordance (Kendall's tau 0.942: p<0.001). Analysis of psychiatrists' ratings showed patients on lithium did better than those on placebo. 86% of patients on lithium showed no conspicuous affective disturbance or a moderate improvement over the previous two years compared with 8% on placebo. NB Lithium use in two years prior to study not known.

Fieve 1976

Participants were assessed for manic and depressive symptoms using a modified Hamilton Depression Rating Scale at four-weekly intervals. Severity of depressive episodes was also rated on a three point 'global' scale. Ratings of severity of depressive episodes were lower in the lithium treated group than in the placebo group. This result reached statistical significance in the unipolar sub-group (Lithium: mean 1.87 (S.D 0.18); Placebo: 2.17(S.D 0.38) p<0.05), but not in the bipolar sub-group.

Prien 1973a, 1973b

The treating physician (non-blind) completed the Global Affective Scale (GAS) every four weeks. This scale rated affective symptoms on a seven point scale. The GAS ratings indicated that in the 1973a (bipolar study) 55 of 58 relapse-free patients on lithium were asymptomatic or had mild symptoms only, compared with 19 of 20 relapse-free participants on placebo. In the 1973b (bipolars and unipolars) study 42% episode-free completers in the lithium group had prolonged periods of mild or moderate symptoms. There were only three episode-free completers on placebo: one had prolonged mild symptoms and the other two were asymptomatic. Social workers carried out a global assessment of affective episodes every six months following home visits and interviews with the participant and their family. These assessments indicated that in the 1973a (bipolar) study 29% of the lithium group and 67% of the placebo group had at least one severe/moderately severe affective episode (chi-squared =24.3; p<0.001). A further 18% of the lithium group and 7% of placebo participants had mild episodes. 54% of the lithium group compared with 27% of placebo participants had no episodes (chi-squared =13.3; p<0.001). In the 1973b (bipolars and unipolars) study, participants in the lithium group had less severe/moderately severe episodes than those in the placebo group. This difference reached statistical significance in the sub-group of participants with unipolar disorder, but not in the sub-group with bipolar disorder (Fisher's exact test). These studies also used the Inpatient Multidimensional Psychiatric Scale and the Katz Adjustment Scale, but no results were reported.

Prien 1984

A Global Assessment Scale (GAS) evaluating affective symptoms and functional impairment on a scale of 0 (severely incapacitated) to 100 (no symptoms or impairment) was completed by a psychiatrist at each clinic visit. A GAS score of less than 60 was one of the criteria for defining a relapse. GAS scores were not otherwise reported. Several other rating scales for affective symptoms were also used but the results were not reported.

ii). Clinical global impression of participant

Three studies included some form of self-rating by participants. The details of these self-assessments are given below.

Prien 1973a, 1973b

A self-report mood scale was completed by participants every three months. Results were not reported

Prien 1984

A social adjustment self-report questionnaire completed at each visit. Results were not reported.

iii). Employment during the study period

None of the studies made reference to participants' employment.

iv). Separation/divorce during study period

No references to marriage, separation or divorce were found in any of the studies.

3). Acceptability of lithium treatment

We assessed the acceptability of long-term lithium treatment to participants by various outcome measures.

i). Participants dropping out of treatment during study period

Drop-out rates were reported in six studies (Coppen 1971, Prien 1973a and b, Fieve 1976, Glen 1984, Bowden 2000). These data are of limited use in determining the acceptability and tolerability of lithium treatment as rates were estimated from various time-points into the studies. Several of the studies included stabilisation periods on open lithium treatment prior to randomisation. One of these studies (Prien 1984) reported high levels of participant attrition (54%) during this preliminary phase. In other studies participants prior exposure to lithium treatment is unstated or unclear. Thus, it appears that participants unable to tolerate lithium treatment may have been excluded before commencement of the study periods. Incomplete information was given regarding the reasons for participants dropping out during the trials. The most common reason appeared to be due to treatment failure. Analysis of drop-out rates shows participants to have dropped out of placebo treatment more often than lithium treatment (random effects OR 0.30, 95% Cl 0.13-0.71; Peto OR 0.34, 95% Cl 0.25-0.48; 6 studies, 646 participants). This result was not consistent across the studies. Two studies showed more participants dropping out of lithium treatment (Glen 1984, Bowden 2000). Attempts to examine drop-out rates on an intention-to-treat basis were not possible due to inadequate reporting.

ii). Compliance with treatment

Reports of lithium levels achieved in the studies indicate that not all participants were compliant with treatment. In some studies participants with low lithium levels indicating poor compliance were excluded from the analysis. No other measures of compliance (such as participant or observer reports or tablet counts) were reported.

iii). Participant reports of satisfaction or otherwise with treatment

As reported above there was very little information regarding the participants' own views on their treatment.

4). Side effects

Six studies made some reference to side effects (Coppen 1971, Prien 1973a and b, Glen 1984, Prien 1984, Bowden 2000). Due to drop-out in pre-study open treatment phases, participants with poor tolerance of lithium may have been excluded from some of the studies. Differing methods of recording and reporting side effect data limited possibilities for pooling data. Four studies (458 participants) reported overall rates of side effects (Prien 1973a, Prien 1973b, Glen 1984, Prien 1984). Side effects were found to be more common in the lithium-treated participants than those treated with placebo (random effects OR 2.35, 95% CI 1.57-3.53; Peto OR 2.32 95% Cl 1.57-3.43). Only two participants (one in each treatment group) are reported to have dropped out of the studies due to side effects. Three studies gave rates of hypothyroidism (Prien 1973a, 1973b, Glen 1984). Seven of 158 participants on lithium (5%) developed hypothyroidism compared with none of 152 participants on placebo (random effects OR 5.09, 95% CI 0.85-30.51; Peto OR 7.19, 95% Cl 1.6-32.32). There were insufficient data on other specific side effects to allow meta-analysis. The details of data on side effects reported in the various studies are summarised below.

Bowden 2000

Lithium participants experienced significantly more tremor than placebo participants, and had significant increases in white blood cell counts and serum calcium.

Coppen 1971

One participant on placebo dropped out due to eczema, which he believed was caused by medication.

Glen 1984

Presence or absence of nine different side effects recorded. 7/12 (58%) lithium participants experienced side effects compared with 3/9 (33%) placebo participants. 7/12 (58%) lithium participants had their treatment modified due to side effects compared with 2/9 (22%) placebo participants.

Prien 1973a, 1973b

Side-effect check list completed by treating physician (non-blind) at each clinic visit. In the 1973a (bipolar) study over 60% of the lithium group experienced side effects. Diarrhoea, nausea, tremor, hyperactive deep tendon reflexes and somnolence were most common. 24% of the reactions were severe enough to warrant temporary discontinuation/dosage reduction. One participant taking lithium had to have treatment permanently discontinued. Four lithium participants developed hypothyroidism. One-third of the placebo participants reported side effects. In the 1973b (bipolar and unipolar) study 69% of the lithium group experienced side effects (diarrhoea, tremor, muscle weakness, anorexia, somnolence). 18% of participants had treatment temporarily withdrawn or reduced due to side effects. 49% of the placebo group reported side effects.

Prien 1984

Side effect rates for the different treatment groups were as follows: Lithium + imipramine 84%; lithium alone 79%; placebo 76%. Rates of participants reporting side effects of greater than mild severity for at least 2 clinic visits: Lithium + imipramine 36%; lithium alone 14%; placebo 3%. Most common lithium side effects were dry mouth, fine tremor headache and lethargy. One participant on combined lithium and imipramine had treatment discontinued due to loss of memory and fine hand tremor.

5). and 6). Mortality, suicide, deliberate self-harm and suicidal ideation.

Four studies made reference to mortality (Coppen 1971; Prien 1973a; Prien 1973b; Glen 1984). Overall mortality was low. Seven out of 189 (4%) participants on placebo died during the studies compared with 2 out of 186 (1%) on lithium (random effects OR 0.36, 95% CI 0.08-1.61; Peto OR 0.43, 95% Cl 0.09-1.27). The five non-suicide deaths in participants on placebo were reported

as due to 'causes not associated with affective disorder'. The two deaths in the lithium group were also recorded as due to 'causes not associated with affective disorder'. No further detail as to the causes of, or events leading up to, the deaths of these participants was given.

No participants taking lithium committed suicide compared with two on placebo (random effects OR 0.31, 95% CI 0.03-3.02; Peto OR 0.13, 95% Cl 0.01-2.04). There was no other information regarding the participants who committed suicide. There was no reported data on suicide attempts, deliberate self-harm or suicidal ideation. Additional information has been sought from the study authors.

DISCUSSION

EFFICACY

This systematic review of nine randomised controlled trials comparing lithium with placebo in the maintenance treament of mood disorder shows that for mixed diagnoses of mood disorder and in bipolar disorder lithium is more efficacious than placebo in preventing relapse over periods of up to four years. There remains uncertainty over the value of lithium maintenance treament in unipolar disorder. The number of participants in the studies is small (835 participants) and the included studies have various methodological shortcomings. The results should be interpreted in light of this. The modest number of participants has also meant that sub-groups analyses (for example analysing efficacy in participants with longer or shorter histories of mood disorder) have not been possible.

There was evidence of quantitative heterogeneity between studies in all groups of participants. In other words, there was more variation between the results of individual studies than one would expect by chance. Accordingly, our discussion of efficacy will focus on the random effects odds ratios, which are likely to be more conservative. For some of the outcome measures relating to relapse, the pooled estimates of effect were sensitive to the choice of statistical method (random or fixed effects odds ratios), and did not exclude the point of no effect when random effects methods were used. However there was no qualitative heterogeneity, in that no single study found lithium to be less effective than placebo.

When the results were pooled for trials including participants with all types of mood disorder (unipolar, bipolar and unspecified) lithium was found to be more effective than placebo in preventing relapse in two of the three outcomes relating to relapse (admission to hospital and relapse however defined). For the outcome of 'relapse however defined' (on which data was available for the greatest number of participants) the random effects odds ratio was 0.21, 95% Cl 0.10-0.43 (9 studies, 825 participants). It may be considered that such analyses of mixed groups of patients with mood disorder are of limited clinical use, as a clinician considering lithium prophylaxis for an individual will generally have some diagnostic indication as to whether their patient suffers from bipolar or unipolar disorder. However, as earlier diagnostic classifications made less distinction between bipolar and unipolar disorder, and notwithstanding a degree of clinical overlap between the two conditions, we felt that analysis of mixed groups was relevant in examining the maximum amount of data available regarding the role of lithium prophylaxis in mood disorder.

The relative efficacy of lithium in preventing manic relapses and depressive relapses continues to be an area of clinical uncertainty. Some reviewers have considered lithium to be more effective against mania than depression (Prien 1979). Our findings do not support this view. This may be because we have excluded discontinuation design studies from our analyses. Rapid discontinuation of lithium is thought to predispose to mainly manic relapses (Suppes 1991; Goodwin 1994) so previous reviews, which included discontinuation studies, may have found a higher rate of manic relapses in their placebo groups.

This review shows that lithium is more effective than placebo in preventing relapse in patients with bipolar disorder. However, the estimate of the size of the effect varied between individual studies. In Prien (1973a), the number needed to treat to prevent one relapse during the first year of follow-up was 4 (95% CI 3 to 6). In Bowden et al (2000), the number needed to treat to prevent one relapse in the same time-period was 14 (95% CI 4 to infinity). The reasons for this heterogeneity between studies cannot be conclusively identified from our analysis. However, two factors - the selection of participants, and a possible variable influence of lithium discontinuation - may be of importance. The authors of Bowden (2000) suggest that the inclusion and exclusion criteria in their study led to the recruitment of more mildly ill patients than those participating in earlier studies. This is supported by the fact that in this study the 12-month relapse rate in the placebo group was only about half that observed in the Prien (1973a) study. The inclusion of a more mildly ill group of patients, with a lower baseline risk of relapse, may explain the divergence of Bowden's findings from those of previous studies, because less severely ill patients may be expected to derive less relative benefit from treatment. We attempted to reduce the possibility of bias due to discontinuation relapse by excluding studies of a purely discontinuation design. However, possible influence from this effect has not been eliminated, because participants in the individual studies had variable exposure to lithium in the pre-study period. In Bowden (2000) only a proportion of participants were treated with lithium in the pre-trial phase, and open treatment was withdrawn gradually over two weeks. In Prien (1973a) all participants were stabilised on open lithium treatment, which was then stopped abruptly in the placebo group. Thus, discontinuation relapse in the placebo group may have played a greater part in Prien (1973a) than in Bowden (2000), increasing the apparent treatment effect of lithium

in the Prien study. Although a discontinuation effect may have contributed to the difference in effect size seen between these two studies, it is unlikely to account for it fully. If it was the full explanation for the large effect size observed in Prien (1973a), then one would expect a larger difference between lithium and placebo in the early stages of the trial. In fact, there was no major difference between year 1 and year 2 of the study. It is possible that further analysis of the individual patient data from these studies using survival techniques may help to elucidate this issue further. However, despite the differences in effect size found in the different studies, the overall result of this review suggests that lithium is an effective treatment in the average patient with bipolar disorder for whom maintenance treatment is indicated.

In unipolar disorder, evidence for a treatment benefit of lithium in preventing relapse is more equivocal. The three unipolar studies are small, involving only 196 patients in total. There was heterogeneity in the estimates of effect in preventing relapse between the studies. Two very small studies (Kane 1982, Glen 1984) showed a considerable beneficial effect of lithium, and one larger study (Prien 1984) showed a lesser effect. The pooled estimate was sensitive to the choice of method, with the confidence interval of the random effects estimate including the point of no effect. However, lithium was not found to be less effective than placebo for any of the outcomes relating to relapse. It is possible that the heterogeneity between the studies can be explained by differences in participants in these trials, by effects of lithium discontinuation or different criteria for defining relapse. A further confounding factor adding to the uncertainty of these analyses is that two of these trials (Kane 1982, Prien 1984) were of a factorial design. In these studies approximately half the participants in the placebo group also received imipramine, as did approximately half the participants in the lithium group. As imipramine is also used as a prophylactic treatment in unipolar depression, the effect of imipramine in these studies may be to reduce the rate relapse in both placebo and control groups, thus lessening the possibility of detecting a treatment difference attributable to lithium. Overall, this review suggests that whilst lithium may be of benefit in preventing relapse in unipolar affective disorder, there remains uncertainty about its value in this regard. In view of the clearer benefit of lithium maintenance treament in bipolar disorder, it could be speculated that lithium might be effective in a sub-group of patients with unipolar disorder that share features (such as a family history, or a more "melancholic" form of depression) with bipolar disorder, or those with apparent unipolar disorder that subsequently go on to suffer a manic illness.

The studies included in this review employed lithium levels ranging between 0.5 and 1.4mmol/l. This review has not addressed the question of the relative efficacy of higher or lower lithium levels. In future versions we hope to address this question by systematic review of randomised controlled trials comparing higher and lower levels of lithium.

Five discontinuation studies were analysed separately from the main review and indicate that patients stable on lithium therapy are at increased risk of relapse for periods of up to 2 years if their lithium is abruptly discontinued. We do not consider that this analysis constitutes a systematic review of the effects of lithium withdrawal, as we included only discontinuation studies that had follow up periods of longer than three months. We anticipate extending the objectives of this review in future versions to include a full systematic review of the effect of lithium discontinuation.

EFFECTIVENESS

This systematic review gives limited information about the proportion of unselected patients with mood disorder that might be expected to benefit from lithium therapy. Later studies have suggested poorer outcomes in clinical settings than would be anticipated from the results of the early clinical trials (Markar 1989). The discontinuation design of earlier studies may have inflated estimates of the apparent therapeutic efficacy of lithium. Such studies have been excluded from this review. Poor compliance has been suggested as a possible cause of the apparent gap between the efficacy and effectiveness of lithium. Some of the studies included in the review showed high rates of participant attrition during open lithium treatment prior to randomisation, thus persons unable to tolerate lithium treatment may not have participated in the studies. This may have resulted in a greater treatment effect in the studies than that seen in clinical practice. In general, the studies were not analysed according to intention-to-treat, and the reasons for participants dropping out of treatment were poorly reported. The "real-world" effectiveness of lithium treatment is therefore unclear.

ACCEPTABILITY

We were intending to investigate the acceptability of lithium treatment in terms of the numbers of participants prematurely discontinuing treatment, measures of adherence to treatment and participant reports of their satisfaction or otherwise with treatment. Lack of intention-to-treat data made quantitative estimates of the proportion of participants who prematurely discontinued treatment impossible. However, it appears from the number of drop-outs, both during the trials and in pre-trial open lithium treatment, that there was a significant proportion of participants that were unwilling or unable to continue with long-term lithium treatment. With the exception of monitoring lithium levels, there is no indication of measures being taken to monitor or ensure adherence. There was very little self-reported data of participants' experiences and attitudes to lithium treatment, or their reasons for discontinuing it. The review shows overall adverse effect rates to have been significantly higher in lithium groups than placebo groups, but few participants were reported to have dropped out specifically because of adverse effects. It should also be noted, however, that the adverse-effect data relates to the selected group of participants who reached the stage of inclusion and analysis in the studies, rather than those

who discontinued at an early stage. There was little information as to the incidence of specific adverse effects, or which of these were particularly troublesome to the participants. There were also few reports of the occurrence of more serious and long-term adverse effects such as lithium toxicity, and thyroid and renal disturbance.

The literature on lithium adherence has been reviewed by Goodwin 1990. Non-adherence to medication regimes is a general problem. It has been found to be especially common in outpatients, chronic relapsing conditions, and when the patient is asymptomatic for a long time. Prophylactic treatment for mood disorder is a treatment susceptible to poor adherence. Rates of lithium non-adherence have been estimated at between 18 and 53% of those receiving treatment. No demographic variables have consistently been found to be predictive of lithium adherence, although some studies have suggested that older age, female gender and being married are each associated with adherence. Co-morbidity, especially with substance misuse is likely to adversely affect adherence. Reasons given by patients and clinicians for poor adherence include psychological factors and adverse effects. Psychological factors include a dislike of medication controlling mood, a dislike of the idea of chronic illness symbolised by lithium, feeling well and seeing no need for medication, and missing the 'highs' of hypomania. The particular adverse effects leading to noncompliance are not necessarily those which are most common. Of the somatic effects, weight gain, problems with coordination and tremor have been found most likely to lead to noncompliance. Cognitive effects such as mental confusion, poor concentration and memory problems have also been found to be important. The issue of treatment adherence is of particular importance in lithium maintenance therapy due to the risk of discontinuation relapse. Taking lithium for a time and then stopping may have a net worse effect than not taking it at all (Goodwin 1994).

In addition to being a considerable clinical problem, non-adherence is a potentially significant source of bias in research studies. Interpretation of treatment efficacy is predicated on having reliable measures of adherence. Guidelines have been put forward to detect and minimise noncompliance in lithium treatment. (Goodwin 1990). There is little evidence of any serious attempts being made to measure and take account of non-adherence in the studies included in this review. It is extremely unlikely that all participants in these studies were compliant with treatment. This is supported by reports of inadequate lithium levels achieved by some participants. Poor treatment adherence therefore may be a source of bias in this review, reducing the estimation of treatment efficacy.

ANTI-SUICIDAL EFFECT

An anti-suicidal effect of lithium treatment in affective disorders has been proposed by several authors. (Kay 1977; Causemann 1988; Thies-Flechtner 1996; Tondo 1997). If this effect occurs, it is of considerable clinical importance. It has been estimated that 15% of persons with severe affective disorder seen by psychiatric services end their lives by suicide, a 30-fold increase in risk compared with the general population (Guze 1970). More recent reviews have confirmed these findings (Goodwin 1990). Early evidence in support of an anti-suicidal effect of lithium prophylaxis came from open follow-up studies of patients receiving lithium, in which lower than expected suicide rates were found (Kay 1977). Alternative explanations for the low rates found have been put forward. These include a more general effect of the regular, specialised medical care that these patients recieved, and also the possiblity of a selection bias in that patients who adhere to a treatment programme may be at less risk of suicide than those who do not. In a review of 28 studies of various methodologies addressing this issue, Tondo and colleagues calculated a risk of suicide and attempted suicide of 0.37 per 100 patient years in patients with affective disorder taking lithium, compared with 3.2 per 100 patient years in those not taking it (Tondo 1997).

Two studies included in this review reported on suicides. In another two studies it can be inferred reliably that no suicides occurred. In the remaining four studies, suicide was not reported. It is tempting to assume that if suicides had occurred in these studies they would have been reported, but such an assumption may be invalid. No studies reported on the incidence of deliberate self-harm or suicidal ideation. Further information has been sought from the authors on this issue and, if received, will be included in future versions of this review.

If only those studies in which suicide was reported as an outcome are included, the proportion of all participants committing suicide was 2/375 participants (0.5 %). If all studies are included, the proportion drops to 2/825 (0.2%). Due to uncertainty over the length of time participants remained in the studies it is not possible to calculate suicide rates per year to compare with Tondo's figures with any degree of accuracy. However, if the very broad assumption is made that participants remained in the studies for one year (the majority of the studies were of a two-year duration; overall number of participants reported as dropping out was 323 out of total 646 (50%)), the suicide rate for all participants in these randomised controlled trials was between 0.2 and 0.5% per year. This rate appears to be low. This could reflect the selection of participants for clinical trials in that those with significant suicide risk tend to be omitted. Alternatively, it may lend support to the notion that regular, specialised medical care is important in the reduction of suicide in persons with affective disorder.

The two suicides that were reported were both of placebo-treated participants. No participants allocated to lithium committed suicide. Whilst this finding is in line with the hypothesis that lithium has an anti-suicidal effect, the number of suicides is too small for reliable conclusions to be drawn.

AUTHORS' CONCLUSIONS

Implications for practice

Lithium should continue to be considered for maintenance treatment in mood disorders. There is adequate evidence of its efficacy in preventing relapse in bipolar disorder. The relative efficacy of lithium and other mood stabilisers such as valproate and carbamazepine is unknown. In unipolar disorder, the evidence of efficacy is less robust and may vary between patient subgroups, but lithium can be considered as one of a range of treatments that may be beneficial in preventing relapse. When considering lithium maintenance therapy, patients and clinicians should take into account the evidence of efficacy, the side effects and the individual's likely adherence to the recommended treatment regimen. Caution should be exercised in abruptly stopping lithium therapy in patients who have been taking it successfully for some time, due to the high risk of relapse.

Implications for research

There remain several clinically important, unanswered questions about the place of lithium therapy in the maintenance treatment of affective disorders. The following steps are required to resolve these issues:

1. Systematic reviews comparing lithium with other treatments that are used in the maintenance treament of affective disorder (e.g. anti-convulsants, antidepressants). Cochrane reviews of sodium valproate and carbamazepine in the maintenance treatment of bipolar disorder are currently underway.

2. Large-scale randomised trials comparing lithium with other maintenance treatments in unselected groups of subjects with bipolar and unipolar affective disorder. These studies will need to be designed to avoid rapid discontinuation of lithium before or, particularly, after randomisation. Outcomes should include meaningful measures of relapse, such as hospital admission or institution of additional treatment for affective disorder. Adverse effects, simple replicable measures of general health and social functioning, and patients' own views of treatment should be recorded. Outcomes relating to death, suicide and other suicidal phenomena should be assessed and reported in all long-term treatment studies of affective disorder. Analysis should be primarily by intention-to-treat to provide the most clinically meaningful estimates of the effectiveness of the treatments.

3. Research on concordance with treatment, and the factors affecting it, particularly the effect of lithium clinics and differences in levels of patient education, monitoring and support.

4. Systematic review of all evidence concerning the effect of lithium on suicide, including non-randomised and open trials.

ACKNOWLEDGEMENTS

This review was carried out under the auspices of the Depression, Anxiety and Neurosis Group of the Cochrane Collaboration (CCDAN). We thank Hugh McQuire (CCDAN Trials Search Co-ordinator) for assistance in developing the search strategy for this review.

REFERENCES

References to studies included in this review

Baastrup 1970 a *{published data only}*

* Baastrup PC, Poulsen JC, Schou M, Thomsen K, Amdisen A. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet* 1970;**2**(668): 326–30.

Schou M, Baastrup PC. Lithium prophylaxis in recurrent affective disorders. *British Journal of Psychiatry* 1971;**118**(542):133–4.

Bowden 1995 *{published and unpublished data}*

Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, et al.A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Archives of General Psychiatry* 2000;**57**(5):481–9.

* Bowden CL, Swann AC, Calabrese JR, McElroy SL, Morris D, Petty F, et al.Maintenance clinical trials in bipolar disorder: Design implications of the divalproex-lithium-placebo study. *Psychopharmacology Bulletin* 1997;**33**(4):693–9.

Coppen 1971 *{published data only}*

* Coppen A, Noguera R, Bailey J, et al.Controlled Trial. *The Lancet* 1971;**2**(719):275–279.

Cundall 1972 *{published data only}*

* Cundall RL, Brooks PW, Murray LG. A controlled evaluation of lithium prophylaxis in affective disorders. *Psychological Medicine* 1972;**2**:308–11.

Glen 1984 *{published data only}*

Glen A, Johnson A, Shepherd M. Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a randomized, double-blind controlled trial. *Psychological Medicine* 1984;**14**(1):37–50.

* Medical Research Council Drug Trials Subcommittee. Preliminary report. Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a controlled clinical trial. *Psychological Medicine* 1981;**11**(2):409–16.

Hardy 1997 *{published data only}*

* Hardy BG, Shulman KI, Zucchero C. Gradual discontinuation of lithium augmentation in elderly patients with unipolar depression. *Journal of Clinical Psychopharmacology* 1997;**17**(1):22–6.

Hullin 1972 *{published data only}*

* Hullin RP, McDonald R, Allsopp MN. Prophylactic lithium in recurrent affective disorders. *Lancet* 1972;**1**(7759):1044–6.

Laurell 1968 *{published data only}*

* Laurell B, Ottosson J. Prophylactic lithium?. *Lancet* 1968;**2** (7580):1245–6.

Melia 1970 *{published data only}*

Melia P, O'Sullivan D, Barry D. Lithium and rapid-cycling affective disorder: A report on six cases. *Irish Journal of Psychological Medicine* 1988;**5**(2):79–83.

* Melia PI. Prophylactic lithium: A double-blind trial in recurrent affective disorders. *British Journal of Psychiatry* 1970;**116**(535): 621–4.

Mendlewicz 1972 *{published data only}*

Dunner DL, Stallone F, Fieve RR. Lithium carbonate and affective disorders V. A double blind study of lithium prophylaxis of depression in bipolar illness. *Archives of General Psychiatry* 1976;**33** (1):117–20.

Dunner DL, Stallone F, Fieve RR. Prophylaxis with lithium carbonate-an update. *Archives of General Psychiatry* 1982;**39**(11): 1344–5.

Fieve RR, Dunner DL, Kumbaraci T, Stallone F. Lithium carbonate in affective disorders IV. A double-blind study of prophylaxis in unipolar recurrent depression. *Archives of General Psychiatry* 1975; **32**(12):1541–5.

Fieve RR, Dunner DL, Kumbaraci T, Stallone F. Lithium carbonate prophylaxis of depression in three subtypes of primary affective disorder.. *Pharmakopsychiatrie Neuropsychopharmakologie* 1976;**9** (3):100–7.

Fieve RR, Kumbaraci T, Dunner DL. Lithium prophylaxis of depression in bipolar I, bipolar II and unipolar patients. *American Journal of Psychiatry* 1976;**133**(8):925–9.

Mendlewicz J, Fieve RR, Stallone F. Relationship between the effectiveness of lithium therapy and family history. *American Journal of Psychiatry* 1973;**130**(9):1011–3.

Mendlewicz J, Fieve RR, Stallone F, Fleiss JL. Genetic history as a predictor of lithium response in manic depressive illness. *Lancet* 1972;**1**(750):599–600.

Mendlewicz J, Stallone F. Genetic factors and lithium response in manic-depressive illness. *Modern Problems of Pharmacopsychiatry* 1975;**10**(1):23–9.

Shelley EM, Mendlewicz J, Fieve RR. Affective disease health maintenance organization. Patterns of lithium response. *New York State Journal of Medicine* 1974;**74**(10):1766–8.

Stallone F, Shelley E, Mendlewicz J, Fieve RR. The use of lithium in affective disorders III: A double-blind study of prophylaxis in bipolar illness. *American Journal of Psychiatry* 1973;**130**(9): 1006–10.

Prien 1973a *{published data only}*

Caffey E, Prien R. The VA-NIMH study of lithium in affective disorders. *Psychosomatics,* 1970;**11**(5):409–412.

Pokorny A, Prien R. Lithium in the treatment and prevention of affective disorder. *Diseases of the Nervous System,* 1974;**35**:327–333.

Prien R, Caffey E, Klett J. Factors associated with treatment success in lithium carbonate prophylaxis. *Archives of General Psychiatry,* 1974;**31**:189–192.

* Prien R, Caffey E, Klett J. Prophylactic efficacy of lithium carbonate in manic-depressive illness. *Archives of General Psychiatry* 1973;**28**:337341.

Prien R, Klett J, Caffey E. Lithium prophylaxis in recurrent affective illness. *American Journal of Psychiatry* 1974;**131**:198–202.

Prien 1973b *{published data only}*

Caffey E, Prien R. The VA-NIMH study of lithium in affective disorders. *Psychosomatics,* 1970;**11**(5):409–412.

Pokorny A, Prien R. Lithium in the treatment and prevention of affective disorder. *Diseases of the Nervous System,* 1974;**35**:327–333.

* Prien R, Klett J, Caffey E. Lithium carbonate and imipramine in prevention of affective episodes. *Archives of General Psychiatry,* 1973;**29**:420–425.

Prien R, Klett J, Caffey E. Lithium prophylaxis in recurrent affective illness. *American Journal of Psychiatry* 1974;**131**:198–202.

Prien 1984 *{published and unpublished data}*

Frank E, Prien R, Kupfer D, Alberts L. Implications of non-compliance on research in affective disorders. *Psychopharmacology Bulletin* 1985;**21**(1):37–42.

Greenhouse J, Stangl D, Kupfer D, Prien R. Methodologic issues in maintenance therapy clinical trials. *Archives of General Psychiatry* 1991;**48**(4):313–8.

* Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, et al.Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. *Archives of General Psychiatry,* 1984; **41**(11):1096–104.

Quitkin 1978 *{published data only}*

* Kane JM, Quitkin FM, Rifkin A, Ramos-Lorenzi JR, Nayak DD, Howard A. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: A prospective, placebo-controlled comparison. *Archives of General Psychiatry,* 1982;**39**(9):1065–9.

Quitkin FM, Kane JM, Rifkin A, Ramos-Lorenzi JR, Saraf K, Howard A, et al.Lithium and imipramine in the prophylaxis of unipolar and bipolar II depression: A prospective, placebo-controlled comparison. *Psychopharmacology Bulletin* 1981;**17**(1): 142–4.

References to studies excluded from this review

Naylor 1974 *{published data only}*

* Naylor G, Mcdonald J, Le Poidevin D, Reid A. A double-blind trial of long-term lithium therapy in mental defectives. *British Journal of Psychiatry* 1974;**124**(578):52–7.

References to studies awaiting assessment

Coppen 1981 *{published data only}*

* Coppen A, Abou-Saleh MT, Milln P, Bailey J, Metcalfe M, Burns BH, et al.Lithium continuation therapy following electroconvulsive therapy. *British Journal of Psychiatry* 1981;**139**:284–7.

Dorus 1989 *{published data only}*

* Dorus W, Ostrow DG, Anton R, Cushman P, Collins JF, Schaefer M, et al.Lithium treatment of depressed and non-depressed alchoholics. *JAMA* 1989;**262**(15):1646–52.

Wilson 1995 b *{published data only}*

* Wilson KC, Scott M, Abou-Saleh MT, Burns R, Copeland JR. Long-term effects of cognitive-behavioural therapy and lithium therapy on depression in the elderly. *British Journal of Psychiatry* 1995;**167**:653–8.

Additional references

Abou-Saleh 1982
Abou-Saleh M. Lithium. In: Paykel E editor(s). *Handbook of Affective Disorders*. Edinburgh: Churchill Livingstone, 1982:369.

Abou-Saleh 1992
Abou-Saleh M.T. Lithium. *Handbook of Affective Disorders*. 2nd Edition. Edinburgh: Churchill Livingstone, 1992.

APA 1994
American Psychiatric Association. *Diagnostic and Statistical Manual of mental disorders DSM-IV*. 4th Edition. Washington DC: American Psychiatric Association, 1994.

Barraclough 1974
Barraclough B, Bunch J, Nelson B, Sainsbury P. A hundred cases of suicide: Clinical aspects. *British Journal of Psychiatry* 1974;**125**: 355–73.

Blackwell 1968
Blackwell B, Shepherd M. Prophylactic lithium: Another therapeutic myth?. *Lancet* 1968;**1**(7549):968–71.

Causemann 1988
Causemann B, Muller-Oerlinghausen B. Does lithium prevent suicides and suicide attempts?. In: Birch NJ editor(s). *Lithium: Inorganic pharmacology and psychiatric use*. Oxford: IRL Press, 1988:23–4.

Clarke 1999
Clarke M, Oxman AD. *Cochrane Reviewers' Handbook 4.0*. Oxford: Cochrane Collaboration, 1999.

Cochran 1988
Cochran S, Gitlin M. Attitudinal correlates of lithium compliance in bipolar affective disorders. *Journal of Nervous and Mental Disorders* 1988;**176**(8):457–64.

Coppen 1991
Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. Does lithium reduce the mortality of recurrent mood disorders?. *Journal of Affective Disorders* 1991;**23**(1):1–7.

Crundwell 1994
Crundwell J. Lithium and its potential benefit in reducing increased mortality due to suicide. *Lithium* 1994;**5**(4):193–204.

DerSimonian 1986
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

DOH 1992
Department of Health. *The health of the nation: a strategy for health in England*. London: HMSO, 1992.

Fieve 1983
Fieve R, Peselow E. Lithium: clinical applications. In: Burrows GD, Norman TR, Davies B editor(s). *Antidepressants. Drugs in Psychiatry 1*. Amsterdam: Elsevier, 1983:277–321.

Gelder 1989
Gelder M, Gath D, Mayou R. *Oxford Textbook of Psychiatry*. 2nd Edition. Oxford: Oxford University Press, 1989:666–7.

Goodwin 1990
Goodwin F, Jamison K. *Manic depressive illness*. New York: Oxford University Press, 1990.

Goodwin 1994
Goodwin G. Recurrence of mania after lithium withdrawal. *British Journal of Psychiatry* 1994;**164**:149–52.

Gunnell 1994
Gunnell D, Frankel S. Prevention of suicide: aspirations and evidence. *BMJ* 1994;**308**(6938):1227–33.

Guscott 1994
Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness: efficacy, effectiveness and efficiency. *British Journal of Psychiatry* 1994;**164**:741–6.

Guze 1970
Guze S, Robins E. Suicide and primary affective disorders. *British Journal of Psychiatry* 1970;**117**:437–8.

Harris 1997
Harris E, Barraclough B. Suicide as an outcome for mental disorders. *British Journal of Psychiatry* 1997;**170**:205–28.

Jadad 1996
Jadad A, Moore A, Carroll D, Jenkinson C, Reynolds D, Gavaghan D, et al.Assessing the quality of reports of randomised clinical trials: Is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1–12.

Juni 1999
Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;**282**(11): 1054–60. [MEDLINE: 1999420947]

Katona 1995
Katona C. Refractory depression: a review with particular reference to the use of lithium augmentation. *European Neuropsychopharmacology* 1995;**5**(Suppl):109–13.

Kay 1977
Kay D, Petterson U. VI. Mortality in: U Petterson: Manic-depressive illness: A clinical social and genetic study. *Acta Psychiatrica Scandanavica* 1977;**Supplementum 269**:55–60.

Klein 1980
Klein D, Gittelman R, Quitkin F, Rifkin A. *Diagnosis and drug treatment of psychiatric disorders: adults and children*. Baltimore: Williams and Wilkins, 1980.

Lonnqvist 1995
Lonnqvist J, Henriksson M, Isometsa E, Marttunen M, Heikkinen M, Aro H, et al.Mental disorders and suicide prevention. *Psychiatry and Clinical Neurosciences* 1995;**49**(Suppl 1):111–6.

Markar 1989
Markar H, Mander A. Efficacy of lithium prophylaxis in clinical practice. *British Journal of Psychiatry* 1989;**155**:496–500.

Moncrieff 1997
Moncrieff J. Lithium: evidence reconsidered. *British Journal of Psychiatry* 1997;**171**:113–9.

Newson-Smith 1979
Newson-Smith J, Hirsch S. Psychiatric symptoms in self-poisoning patients. *Psychological Medicine* 1979;**9**(3):493–500.

NIMH-NIH 1985
NIMH-NIH Consensus Development Conference Statement. Mood disorders: Pharmacologic prevention of recurrences. *American Journal of Psychiatry* 1985;**142**(4):469–72.

Prien 1979

Prien R. Lithium in the prophylactic treatment of affective disorders. *Archives of General Psychiatry* 1979;**36**(8 Spec No):847–8.

Stokes 1971

Stokes P, Shamoian C, Stoll P, Patton MJ. Efficacy of lithium as an acute treatment of manic-depressive illness. *Lancet* 1971;**1**(7713): 1319–25.

Suppes 1991

Suppes T, Ross J, Baldessarini R, Faedda G, Tohen M. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Archives of General Psychiatry* 1991;**48**(12): 1082–8.

Thies-Flechtner 1996

Thies-Flechtner K, Muller-Oerlinghausen B, Seibert W, Walther A, Greil W. Effect of prophylactic treatment on suicide risk in patients with major affective disorders. *Pharmacopsychiatry* 1996;**29**(3): 103–7.

Tondo 1997

Tondo L, Jamison K, Ross J, Baldessarini R. Effect of lithium maintenance on suicidal behaviour in major mood disorders. *Annals of the New York Academy of Sciences* 1997;**836**:339–51.

WHO 1992

World Health Organisation. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: WHO, 1992.

Yusuf 1985

Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomised trials. *Progress in Cardiovascular Diseases* 1985;**27**(335):371.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baastrup 1970 a

Methods	Discontinuation study Excluded from main analyses
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Bowden 1995

Methods	Double-blind, randomised controlled trial 1 year follow-up
Participants	Bipolar I disorder (185) Outpatients meeting DSM-III-R criteria for bipolar disorder Episode of mania in 3 months preceeding randomisation, plus one other episode in preceeding 3 years Those with high suicide risk excluded
Interventions	Lithium (0.8-1.2 mmol/l) Divalproex (level 71-125 mcg/ml) Placebo
Outcomes	Time to mood episode Time to manic episode Time to depressive episode Mean change in MRS, DSS, GAS Side-effects
Notes	Primary aim of study was to compare divaproex with lithium and placebo 1/3 of lithium and placebo groups taking lithium in open phase prior to randomisation. Lithium discontinued over 2 weeks Participants discontinued from study if developed a mood episode or serious suicidal ideation.

Risk of bias

Bowden 1995 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Coppen 1971

Methods	Double-blind randomised controlled trial Randomisation not stratified by UP/BP 2 year follow up
Participants	Recurrent affective disorder (65) Inpatients with recurrent affective disorder Minimum of 2 episodes affective disorder in 2 years prior to study
Interventions	Lithium (0.8-1.2 mol/l) Placebo
Outcomes	Time spent in in-patient episode Time spent in out-patient episode Time recieving extra medication ECT treatment Global ratings Interrupted lithium therapy Drop-outs Deaths
Notes	Discontinuation status unknown

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Cundall 1972

Methods	Discontinuation study. Excluded from main analyses
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Cundall 1972 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Glen 1984

Methods	Double-blind randomized controlled trial. 3 years follow-up
Participants	Unipolar disorder 21 Primary depressive illness by diagnosed by RDC criteria No history of mania No physical disability precluding study treatments
Interventions	Lithium (0.6-1.2 mmol/l) Amitriptyline (60-230 mg/ml) Placebo
Outcomes	Relapse Use of anxiolytics Severity of depression Side-effects Biochemistry, cardiac, thyroid and renal function Deviation from protocol Deaths
Notes	Furthur group with more than 1 previous episode depression randomized to lithium or amitriptyline also reported (not included in review)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hardy 1997

Methods	Discontinuation study Excluded from main analyses
Participants	
Interventions	
Outcomes	
Notes	

Hardy 1997 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Hullin 1972

Methods	Discontinuation study Excluded from main analyses
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Laurell 1968

Methods	Double-blind randomised controlled trial Randomisation not stratified by UP/BP 11 month follow-up
Participants	Manic-depressive psychosis (not specified if bipolar or unipolar) (16) Severe affective psychosis excluded
Interventions	Lithium (0.3 g t.i.d) Placebo Amitriptyline (25 mg t.i.d)
Outcomes	Relapse Side-effects
Notes	Study was intended to include 90 participants, but discontinued after 16 had been recruited as investigators (and participants)were convinced of benefit of lithium

Risk of bias		
Item	**Authors' judgement**	**Description**

Laurell 1968 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Melia 1970

Methods	Discontinuation study Excluded from main analyses
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Mendlewicz 1972

Methods	Double-blind randomised controlled trial Randomisation not stratified by UP/BP 4 year follow-up
Participants	Recurrent affective disorder (81) Primary affective disorder diagnosed by Feighner criteria Stable outpatients 2 episodes in 2 years prior to study Sub-groups bipolar I, bipolar II and unipolar disorder Normal functioning between episodes
Interventions	Lithium (0.7 or 0.8 - 1.2 or 1.3 mmol/l) Placebo
Outcomes	Episodes of affective disorder Hospitalization Frequency, severity and length of depressive episodes Hamilton rating scale Months in study Drop-outs
Notes	'Some' subjects receiving open lithium at randomisation

Risk of bias

Mendlewicz 1972 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Prien 1973a

Methods	Single-blind (partly double-blind)randomised controlled trial 2 year follow-up
Participants	Bipolar disorder (205) Inpatients with acute mania 'Large majority' had previous episodes affective disorder Median 3 previous hospitilizations No history cardiovascular, adrenocortical, renal disease, hypothyroidism or brain damage 205 bipolar participants
Interventions	Lithium (0.5 -1.4 mmol/l) Placebo
Outcomes	Relapse - severe (hospital admission), moderate (use of non-study medication) Global affective scale Global assessment affective episodes Inpatient multidimensional psychiatric scale Self report mood scale Katz adjustment scale Side-effects check list Mortality Suicide
Notes	Participants stabilized on lithium prior to randomisation Participants and clinical raters blind, treating physician (who determined admission and withdrawal from study due to poor clinical response) not blind Dosage of study drugs could be increased

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Prien 1973b

Methods	Single-blind (partly double-blind)randomised controlled trial Randomisation not stratified by UP/BP 2 year follow-up

Prien 1973b (*Continued*)

Participants	bipolar and unipolar disorder (84) Inpatients with acute depression History of at least 1 episode of affective disorder in previous 2 years, plus at least 2 episodes in previous 5 years Exclusion criteria: cardiovascular adrenocortical or renal disease, hypothyroidism, schizophrenia, schizoaffective disorder, organic brain syndrome 78 bipolar and 44 unipolar participants
Interventions	Lithium (0.5 -1.4 mmol/l) Placebo Imipramine- not included in this review
Outcomes	Relapse - severe (hospital admission), moderate (use of non-study medication) Global affective scale Global assessment affective episodes Inpatient multidimensional psychiatric scale Self report mood scale Katz adjustment scale Side-effects check list Mortality Suicide
Notes	Participants stabilised on imipramine and/or lithium prior to randomisation Data analysed separately for first 4 months and 5-24 months. 5-24 month data used for relapse outcomes in this review Treating physician (not blind) responsiable for hospital admission and withdrawal due to poor clinical response

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Prien 1984

Methods	Double-blind randomised controlled trial Seperate unipolar and bipolar studies. Unipolar study only included in review 2 year follow-up
Participants	Unipolar disorder (148) Unipolar study- preliminary phase: episode major depression satisfying RDC Raskin severity of depression and mania scale (RSDM) total depression and mania score > or = 7, Global assessmant scale (GAS) < or = 60 1 previous episode depression in previous 2.5 years To qualify as bipolar, patient must have had at least one manic episode, to qualify as unipolar, patient must have had no manic episode No other psychiatric diagnosis in preceeding 2 years

Prien 1984 (*Continued*)

	No physical illness precluding use of lithium and imipramine Maintenance phase- remained on maintenence medication of lithium and imipramine for two months and achieved GAS score > 60 and RSDM < 7
Interventions	Lithium (0.6 -0.9mmol/l) Lithium + Imipramine Imipramine Placebo
Outcomes	Relapse (RDC for definate major depression or mania and GAS rating < or = 60) GAS RSDM Hamilton rating scale for depression Manic behaviour rating scale Brief psychiatric rating scale Social adjustment self-report questionnaire Life events scale Side-effects
Notes	Participants stabilized on imipramine and lithium following control of acute symptoms and prior to randomisation. 343 participants entered preliminary phase. 150 entered maintenance phase. Reasons for drop-out in preliminary phase included noncompliance, withdrawal of consent, poor clinical response and inability to tolerate study medication Bipolar group (not included in review) randomised to lithium, lithium + imipramine or imipramine)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Quitkin 1978

Methods	Double-blind randomised controlled trial Randomisation stratified by UP/BP 2 year follow-up
Participants	Unipolar and bipolar II disorder (49) Research diagnostic criteri\a (RDC) diagnosis Minimum 2 episodes in previous 7 years Euthymic for 6 months preeceeding study No co-existing medical illness complicating treatment
Interventions	Lithium + Placebo Lithium + Imipramine Imipamine + Placebo Placebo Lithium levels (0.8-1.2 mmol/l)

Quitkin 1978 (*Continued*)

	Imipramine (dose 100-150mg)
Outcomes	Relapse: RDC criteria for major depression , symptoms for 1 week RDC criteria for minor depression, symptoms for 4 weeks RDC criteria for mania RDC criteria for hypomania, symptoms for 1 week Drop- outs
Notes	Open treatment with imipramine 100-150mg for 6 weeks prior to study Dose of imipramine could be increased in case of impending relapse

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Naylor 1974	Primary diagnosis of mental handicap plus selection criteria (frequently occuring affective change or recurrent behavioural changes) casts doubt on validity of diagnosis of affective disorder.

DATA AND ANALYSES

Comparison 1. Lithium v. placebo all mood disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All relapses	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Admission to hospital	2	286	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.14, 0.40]
1.3 Non-study medication	3	351	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.09, 1.20]
1.4 Relapse stated	9	825	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.10, 0.43]
2 Manic relapse	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Admission to hospital	1	81	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.05, 0.94]
2.2 Non-study medication	2	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.22, 0.85]
2.3 Relapse stated	5	484	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.39, 1.08]
3 Depressive relapse	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Admission to hospital	1	81	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.20, 2.23]
3.2 Non-study medication	2	146	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.43]
3.3 Relapse stated	5	484	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.21, 0.86]
6 Suicide	4	375	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.04]
8 Mortality	4	375	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.09, 1.27]
9 Drop-out	6	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.25, 0.48]
10 Drop-out due to treatment failure	4	560	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.21, 0.44]
11 Drop out due to side-effects	2	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.07, 18.91]
12 Side-effects	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 Hypothyroidism	3	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.19 [1.60, 32.32]
12.2 Any reported	4	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [1.57, 3.42]

Comparison 2. Lithium v. placebo - bipolar disorder

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All relapses	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Admission to hospital	1	205	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.13, 0.40]
1.2 Non-study medication	1	205	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.38, 1.97]
1.3 Relapse stated	3	412	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.23, 0.51]
2 Manic relapse	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Admission to hospital	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 Non-study medication	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.3 Relapse stated	2	207	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.42, 1.63]
3 Depressive relapse	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Admission to hospital	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Non-study medication	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.3 Relapse stated	2	207	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.24, 1.09]

Comparison 3. Lithium v. placebo - unipolar disorder

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All relapses	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Admission to hospital	0	0	Odds Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Non-study medication	0	0	Odds Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Relapse stated	3	196	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.27]
2 Manic relapse	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Admission to hospital	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 Non-study medication	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.3 Relapse stated	3	196	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.12, 1.75]
3 Depressive relapse	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Admission to hospital	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Non-study medication	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.17, 3.32]
3.3 Relapse stated	3	196	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.26, 0.80]
4 relapse excluding imipramine	3	105	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.32 [0.15, 0.70]

Comparison 4. Lithium v. placebo studies including bipolar patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All relapses	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Admission to hospital	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.16, 0.42]
1.3 Non-study medication	3	351	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.24, 0.70]
1.4 Relapse stated	7	629	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.20, 0.38]

Comparison 5. Lithium v. placebo studies including unipolars

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 All relapses	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Admission to hospital	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.16, 0.42]
2.3 Non-study medication	3	351	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.24, 0.70]
2.4 Relapse stated	7	413	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.18, 0.39]

Comparison 6. Discontinuation studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lithium vs placebo-relapse stated	5	168	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.07, 0.28]

FEEDBACK

discontinuation design

Summary

You state in the Selection Criteria that discontinuation studies (in which all participants had been stable on lithium for some time before being randomised to either continued lithium treatment or placebo substitution) were excluded. However, for example, Prien 1973a seems to me to be clearly of discontinuation design, and you state as a matter of fact in the Characteristics of Included Studies that Participants stabilized on lithium prior to randomisation.

How could this be?

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

We thank Professor Furukawa for his interest in our review: the issue he raises is clearly an important one. A little more detail should clarify things. By discontinuation design we mean those studies which recruited patients who had been stable and free from relapse while taking long- term lithium and then randomised to continue or discontinue. For example, in Baastrup et al (Lancet, 1970, 326-330), the participants had been taking lithium for at least 12 months prior to randomisation. Designs such as these can help inform decisions about continuation or discontinuation in patients who have been well while taking lithium for a year or more. By contrast, in our review * as we explained * we were interested in the efficacy of lithium in patients who were unselected for prior good response to the agent. We believe the Veterans Administration and National Institute of Mental Health Collaborative Study Group (Prien) trial is clearly relevant to this clinical question. In this trial, participants were recruited following an acute episode of mania. After remission, but prior to randomisation, the participants were commenced on lithium and the dose was titrated to give the required blood level. On discharge from hospital, patients were randomly allocated to continue lithium or to discontinue lithium and commence matching placebo. The trial therefore used an open active run-in phase * a design commonly used when use of the investigational drug is clinically complex (as in the case of lithium) and initiation under blind conditions would be problematic. Of course, there is the possibility that sudden withdrawal of the drug at randomisation may have increased the risk of relapse in patients allocated to placebo, but the results were substantially similar when patients who relapsed in the first 3 months of the trial were excluded from the analysis.

Active run-in designs are, to some extent, a compromise to ensure the feasibility of a trial that aims to answer an important clinical question. BALANCE, a trial comparing combination lithium plus valproate with monotherapy with lithium or valproate that we are currently conducting in the UK and USA employs such a design (www.psychiatry.ox.ac.uk/balance) . However, they can also increase the applicability of the results by more accurately reflecting real world clinical practice (Pablos et al., 1998). Long-term lithium therapy is a good example - a patient and clinician would only contemplate long term therapy if the drug was tolerated in the short-term. The Prien study provided timely evidence for lithium at a time of great controversy, was methodologically innovative and was a landmark trial in psychiatry.

Pablos, M. A., Barr, R. G., & Shea, S. (1998). Run-in periods in randomized trials: implications for the application of results in clinical practice. JAMA 279, 222-225.

John Geddes
Professor of Epidemiological Psychiatry
Department of Psychiatry
University of Oxford
Warneford Hospital Tel: +44 1865 226480
OXFORD OX3 7JX Fax: +44 1865 793101
URL: www.cebmh.com

Contributors

Toshi Furukawa
psychiatrist
furukawa@med.nagoya-cu.ac.jp
20/02/2004 10:47:27

WHAT'S NEW

Last assessed as up-to-date: 18 March 2001.

2 November 2008	Amended	Converted to new review format.

HISTORY

Review first published: Issue 2, 2001

19 March 2001	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

Kay Jamison has given lectures sponsored by Solvay Pharmaceuticals, a manufacturer of lithium. Guy Goodwin has on two occasions acted as an advisor to Solvay Pharmaceuticals.

JG has received research funding and support from Sanofi-Aventis and GlaxoSmithKline and is currently in discussion with several other companies that manufacture SSRIs about collaboration on planned independent trials and systematic reviews.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- South East region NHSE Research and Development, UK.

NOTES

This review is currently being updated. We hope to publish the update in Issue 2, 2009.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimanic Agents [*therapeutic use]; Bipolar Disorder [drug therapy]; Lithium [*therapeutic use]; Mood Disorders [*drug therapy]; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Humans