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[Intervention Review]

Lithium versus antidepressants in the long-term treatment of unipolar affective disorder

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ABSTRACT

Background

The main rationale for the use of lithium in the long-term treatment of unipolar affective disorder is its efficacy in treating bipolar affective disorder and resistant depression. However, there is considerable uncertainty about which pharmacological intervention is most effective in the long-term treatment of recurrent unipolar affective disorder.

Objectives

To assess the effects of lithium versus antidepressants for the long-term treatment of recurrent affective disorder.

Search methods

We searched the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Registers (CCDANCTR-Studies and CCDANCTR-References) on 2/9/2005. Reference lists of relevant papers and major textbooks of affective disorder were checked. Experts in the field and pharmaceutical companies were contacted regarding unpublished material.

Selection criteria

Randomised controlled trials comparing lithium against antidepressant medication for the long-term treatment of patients with a diagnosis of affective disorder.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We contacted study authors for additional information. We collected adverse effects information from the trials.

Main results

Eight trials involving 475 people were included. Two of the studies included a mixed group of participants with either bipolar or unipolar disorder. Relapse was defined as admission to hospital and when all kinds of relapses were considered (both depressive and manic), there was a statistically significant difference in favour of lithium (relative risk (RR) fixed effect 0.34, 95% CI 0.14 to 0.82). The results did not exclude the point of no effect, when the random-effects model was used (RR random effects 0.40, 95% CI 0.14 to 1.18). There were no other statistically significant differences between lithium and antidepressants according to all other outcomes considered. Manic or depressive relapse was defined as prescription of non-study medication for mood disorder, manic or depressive relapse (as defined by the study

authors), quality of life, social functioning, occupational functioning, overall drop-out rate, drop-out rate due to side-effects, troublesome side-effects, mortality due to all causes and specifically suicides.

Authors' conclusions

There was adequate efficacy evidence for lithium or antidepressants preventing relapse in unipolar affective disorder, however their relative efficacy was unknown. When considering lithium or antidepressant long-term therapy, patients and clinicians should take into account the patient's clinical history, the side-effects and the individual's likely adherence to the recommended treatment regime. Large-scale, long-term randomised trials in unselected groups of subjects with unipolar affective disorder are needed.

PLAIN LANGUAGE SUMMARY

Lithium versus antidepressants in the long-term treatment of unipolar affective disorder

This systematic review investigated the efficacy and tolerability of lithium compared to antidepressants for the long-term treatment of unipolar affective disorder. Eight randomised studies (reporting on 475 participants) were included in the review. We found no reliable evidence of any robust differences between lithium and antidepressants but nor could we reliably exclude the possibility of clinically significant differences. In this review some studies included a mixed group of participants with either bipolar or unipolar disorder. The review suggests that, while lithium may be of benefit in preventing relapse in unipolar affective disorder, there remains uncertainty about the treatment effect in comparison with antidepressants. Interpretation of this review should consider that the number of participants in the studies was small and the included studies had methodological shortcomings.

BACKGROUND

Unipolar depression is a mood disorder in which sufferers experience one or more episodes of depression in the absence of episodes of elated mood (mania). The disorder is common, with a lifetime prevalence of 17.1% (Kessler 1994). Currently, unipolar depression is the fourth leading cause of world-wide disability (Murray 1997a), but it is predicted that, by 2020, it will be the second leading cause (Murray 1997b). Affective disorder is a major risk factor for suicide, which is of particular concern (Harris 1997).

Most patients with an episode of depression will recover with acute treatment, but often the depression recurs. It has been estimated that over 50% of individuals who have had an initial episode of major depression will have one or more recurrences (Klein 1980; NIMH-NIH 1985). In some cases, two or more episodes of depression can be five years apart and in such cases the choice of long-term treatment is decided by patients and clinicians. However, prophylactic treatment, aimed at preventing or attenuating further episodes of illness, is of vital importance in the management of this disorder.

Current interventions used in prophylactic treatment are those known to be effective in the treatment of acute episodes of depression, which include pharmacotherapy (sometimes with augmentation or combination strategies) and psychotherapy (Geddes 2000). The question of how long to continue antidepressant treatment for has been examined in another review (Geddes 2003). This review will focus on the effectiveness of pharmacological treatments in long-term treatment, comparing the two options most commonly used in practice - lithium or antidepressants.

The main rationale for the use of lithium in the long-term treatment of unipolar affective disorder is its efficacy in treating bipolar affective disorder and resistant depression (Burgess 2001; Bauer 1999). Antidepressants are used in long-term treatment because of their effectiveness in the acute treatment of depression. Although it has been argued that lithium has a superior efficacy over antidepressants in the long-term treatment of unipolar disorder (Greil 1996), in a previous meta-analysis the comparison of lithium with other antidepressants in prophylaxis showed no conclusive advantage for lithium in unipolar illness (Souza 1991). Current practice, in the absence of convincing evidence of superiority of one treatment over another, is to use medication for long-term treatment that has been effective in acute treatment, or to switch to another class of drug if one had previously been ineffective in long-term treatment.

In conclusion, there is considerable uncertainty regarding the relative benefits and risks of the use of drug treatments in the long-term treatment of depression. This review systematically assessed the evidence for the effectiveness of lithium versus antidepressants as long-term treatment for unipolar affective disorder.

OBJECTIVES

To determine the benefits and risks of lithium versus antidepressants for long-term treatment of unipolar affective disorder. The primary benefit studied was prevention of relapse.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomised controlled trials, published in any language.

Types of participants

All patients suffering from a unipolar affective disorder diagnosed according to explicit criteria, including major depressive disorder and dysthymic disorder, but excluding bipolar affective disorder. When a study, including a mixed group of participants with either bipolar or unipolar disorder, reported on groups with bipolar disorder and unipolar disorder that were randomised separately, we included only the unipolar group in the analysis. When a study, including a mixed group of participants with either bipolar or unipolar disorder, reported on groups with bipolar disorder and unipolar disorder that were not randomised separately, we included all the patients in the analysis, in order to be as comprehensive as possible.

Types of interventions

Studies were included which compared the use of lithium with any antidepressant in long-term treatment. Long-term was defined as any treatment instituted specifically or mainly to prevent further episodes of illness. Antidepressants included all tricyclic antidepressants, (selective) serotonin reuptake inhibitors, noradrenergic reuptake inhibitors, (reversible) monoamine oxidase inhibitors, as well as bupropion, St Johns Wort, flupenthixol and tryptophan. Mood stabilisers, anticonvulsants, antipsychotics, benzodiazepines, or electroconvulsive therapy were not included as antidepressants.

Types of outcome measures

A. Primary outcome measure

Relapse/recurrence of an affective (depressive or manic) episode within defined periods of observation. Ideally, relapse would be defined using precise and consistent criteria. However, in our experience we have found this rarely occurs and definitions of relapse vary from study to study. For this review, relapse was defined as any of the following:

- (a) admission to hospital
- (b) use of additional medication for depression/mania
- (c) relapse however defined by the study authors.

From our preliminary work we know that relapse/recurrence was usually measured using depressive/manic symptom rating scales. Where possible we analysed these as continuous data. These continuous data, however, were often dichotomised at an arbitrary cut point (eg Hamilton Depression Rating Scale score of less than eight) because this facilitates clinical interpretation. Accordingly such data were analysed as dichotomous data.

B. Secondary outcome measures

Benefits

- (a) Quality of life
- (b) Global clinical impression rated by the clinician
- (c) Global clinical impression rated by the patient
- (d) Social functioning

(e) Occupational functioning

Adverse effects

- (a) The overall drop-out rate as a proxy measure of overall acceptability of treatment
- (b) The drop-out rate due to side-effects
- (c) The number of patients reporting at least one adverse event, ie troublesome side-effects
- (d) Change in medication
- (e) Mortality due to all causes and specifically suicides and verdicts of undetermined deaths
- (f) Acts of deliberate self-harm

Search methods for identification of studies

Electronic databases

The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Registers (CCDANCTR-Studies and CCDANCTR-References), incorporating results of group searches of MEDLINE, EMBASE, CINAHL, PsycINFO, PSYINDEX, AMED, CENTRAL and LILACS were searched using the following strategies:

CCDANCTR-Studies (searched on 2/9/2005)

Diagnosis = Depress* or Dysthymi* or "Adjustment Disorder*" or "Mood Disorder*" or "Affective Disorder" or "Affective Symptoms" and
Intervention = Lithium
and
Study Design = RCT

CCDANCTR-References (searched on 2/9/2005)

Keyword = Depress* or Dysthymi* and
Free-text = lithium or camcolit or carbolith or durolith or eskalith or licarbium or liskonum or lit arex or lithane or lithocarb or lithizine or lithonate or lithotabs or manialith or phasal or priadel or quinonorm or quilonum or li-liquid.

The Cochrane Library was also searched using the same terms as for CCDANCTR excluding references that have come from CCDANCTR.

Reference checking

The reference lists of all selected studies were inspected for more published reports and citations of unpublished research. In addition, other relevant papers and major textbooks which cover affective disorder were checked.

Handsearching

Any journals or conference proceedings specifically related to the use of lithium or antidepressants in the long-term treatment of unipolar depression were searched. In particular, the journal *Lithium* (1990-1994) was handsearched.

Personal communications

The authors of significant papers, other experts in the field and pharmaceutical companies marketing antidepressants or lithium were asked of their knowledge of other studies, published as well as unpublished.

Excluded studies

All excluded studies were listed with the reason for exclusion.

Data collection and analysis

Selection of the trials

Two reviewers (AC, KS) independently checked studies generated by the search strategy to ensure they met the previously defined criteria. Any disagreement was resolved by consensus discussion with another member (JG) and non-concurrence was reported.

Quality assessment

Two reviewers independently assessed the methodological quality of the included studies. Quality was assessed according to the Cochrane criteria (Clarke 1997). This pays particular attention to the randomisation procedure, including concealment of allocation and gives studies a rating of A (adequate), B (unclear) or C (inadequate). Those rated C were excluded from the analysis. In addition, other aspects of quality, such as whether the trial was of a double blind design and reporting of withdrawals and dropouts, were described. Where adequate details of randomisation and other characteristics of trials were not provided the authors were contacted in order to obtain further information. If the raters disagreed the final rating was made by consensus, if necessary with the involvement of a third member of the review group.

Data extraction

Data were extracted by two reviewers (AC, KS) about participant characteristics, intervention details and outcome measures from the included studies. Any disagreements were resolved by consensus discussions with a third member of the review team (JG).

Data analysis

Data were entered into Revman 4.2.8. For binary efficacy outcomes, a pooled relative risk (with 95% confidence intervals) was calculated using a fixed-effects model. Heterogeneity between studies was assessed using the Q statistic (DerSimonian 1986). If significant heterogeneity was identified, sources were investigated. Random-effect models were also used routinely to investigate the sensitivity of results to the choice of statistical method. For continuously distributed outcomes, the weighted mean difference was calculated when standard measures were used across studies and the standardised mean difference when different measures had been used. We used intention-to-treat data when available. If not, end-point data for trial completers were used. Skewed data and non-quantitative data were presented descriptively. Funnel graphs were plotted to assess the possibility of publication bias (the selective publishing of studies showing positive treatment effects). Subgroup and sensitivity analyses were not performed, but could be used in the future.

RESULTS

Description of studies

Thirty-five trials were initially identified as potentially eligible for this systematic review. Twenty-seven of them were excluded because they did not meet the inclusion criteria (diagnosis of bipolar disorder; unclear or mixed; different study design). The remaining eight trials were included in this review. These studies report on 475 participants randomly allocated to lithium or antidepressants.

Two of the studies included a mixed group of participants with either bipolar or unipolar disorder (VA-NIMH 1970 b; Coppen 1976 b). Data in these studies were reported in such a way that the results for the unipolar patients could be separated from those of the bipolar patients. One study reported on groups with bipolar disorder and unipolar disorder that were randomised separately

(Quitkin 1978). Five studies included only unipolar participants (Coppen 1978 b; Glen 1981; Prien 1984; Zanardi 1996 b; MAP 1986 a).

Four of the studies included a third group of participants who were allocated to treatment with placebo (VA-NIMH 1970 b; Quitkin 1978; Glen 1981; Prien 1984) and two of them included a fourth group of participants who were allocated to treatment with lithium plus an antidepressant (imipramine) as a factorial design (Prien 1984; Quitkin 1978). For the purposes of this review the lithium plus imipramine cells were excluded. In four of the studies all the participants were stabilised on lithium treatment for stated lengths of time prior to randomisation (VA-NIMH 1970 b; Coppen 1976 b; Coppen 1978 b; Prien 1984). In the four remaining studies the participants' use of lithium prior to the study was not stated or was unclear.

The studies followed participants from randomisation either until they relapsed or for maximum periods of between 12 months and three years. Three of the studies had a two-year follow-up period and two studies had a three-year follow up period.

The range of lithium levels employed was known for all eight studies and the ranges used were all between 0.5 and 1.4. mmol/l.

Risk of bias in included studies

In accordance with the protocol, the studies were assessed using the Cochrane criteria for quality assessment (Clarke 1997). The ratings given to the studies were as follows: VA-NIMH 1970 b (B), Coppen 1976 b (B), Coppen 1978 b (B), Quitkin 1978 (B), Glen 1981 (A), Prien 1984 (A), Zanardi 1996 b (B), MAP 1986 a (A).

As described in a similar systematic review regarding lithium in the long-term treatment of mood disorders (Geddes 2004a), we did not carry out sensitivity analyses excluding the studies with lower ratings, due to doubts over the validity of the scales used (Juni 1999). However, we did consider that there could be significant methodological problems in the studies which could have the potential to introduce bias into the results of the review.

(1) Randomisation/concealment of allocation

All the studies were described as randomised, but generally no information was given in the published reports regarding the methods used to achieve random allocation. Additional information was sought from the study authors and Cochrane quality ratings were upgraded accordingly.

(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 MAP study (MAP 1986 a). Post-hoc ITT analysis was not possible due to inadequacies in reporting.

(3) Blinding

Five studies out of eight were described as double-blind. In two studies (Zanardi 1996 b and MAP 1986 a) neither providers nor assessors were blind and it was not clear if patients were blind to treatment allocation. One study (VA-NIMH 1970 b) was single blind: the treating physician (who was responsible for hospitalisation and withdrawal of the patients from the study) was aware of the participants' treatment allocation. This could be a source of potential bias.

(4) Numbers of participants

All of the included studies were small, and two were very small - fifteen or fewer patients per arm (Coppen 1976 b; Quitkin 1978). This affected their ability to detect treatment differences, especially if such differences were moderate, or the outcomes were rare (eg suicide). None of the studies presented the use of power calculations to guide sample size.

(5) Selection of participants

The source and selection of participants varied between the studies, and 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: this may have led to heterogeneity between studies results, but can broaden the applicability of the results of the review.

(6) Publication bias

No evidence of major publication bias was found, but the number of studies was too small for it to be excluded unequivocally.

Effects of interventions

A. Primary outcome measure

Relapse

Relapse was defined in various ways in the studies and we therefore categorised it in three ways:

- (i) Admission to hospital
- (ii) Prescription of non-study medication for mood disorder
- (iii) Relapse-however defined by study authors.

(1.1) All relapses (see figure 01.01)

(i) Admission to hospital (see figure 01.01.01)

Only three studies reported data on this outcome (Coppen 1976 b; Coppen 1978 b; MAP 1986 a), including a total of 142 participants. Even if there was no significant heterogeneity between the results of these studies (chi squared 2.22, df = 2, P = 0.33), there was a statistically significant difference in favour of lithium (relative risk (RR) fixed effect 0.34, 95% confidence interval (CI) 0.14 to 0.82), but the results did not exclude the point of no effect when the random-effects model was used (RR random effects 0.40, 95% CI 0.14 to 1.18).

(ii) Prescription of non-study medication for mood disorder (see figure 01.01.02)

Only three studies reported data on this outcome (MAP 1986 a; Coppen 1978 b; Glen 1981), a total of 249 participants were included. There was no statistically significant difference between comparators (RR fixed effect 0.81, 95% CI 0.62 to 1.05; chi squared 6.73, df = 2, P = 0.03).

(iii) Relapse however defined (see figure 01.01.03)

Seven studies reported data on this outcome (Glen 1981; VA-NIMH 1970 b; Coppen 1976 b; Quitkin 1978; Prien 1984; Zanardi 1996 b; MAP 1986 a), which included a total of 434 participants. There was no statistically significant difference between comparisons (RR fixed effect 1.00, 95% CI 0.81 to 1.24; chi squared 11.42, df = 6, P = 0.08).

(1.2) Manic relapse (see figure 01.03)

(i) Admission to hospital (see figure 01.03.01)

No data available.

(ii) Prescription of non-study medication for mood disorder (see figure 01.03.02)

No data available.

(iii) Relapse however defined (see figure 01.03.03)

Six studies reported data on this outcome (MAP 1986 a; VA-NIMH 1970 b; Quitkin 1978; Glen 1981; Prien 1984; Zanardi 1996 b), which included a total of 404 participants. There was no statistically significant difference between comparisons (RR fixed effect 0.46, 95% CI 0.17 to 1.25; chi squared 2.68, df = 5, P = 0.75).

(1.3) Depressive relapse (see figure 01.02)

(i) Admission to hospital (see figure 01.02.01)

No data available.

(ii) Prescription of non-study medication for mood disorder (see figure 01.02.02)

No data available.

(iii) Relapse however defined (see figure 01.02.03)

Six studies reported data on this outcome (VA-NIMH 1970 b; Quitkin 1978; Glen 1981; Prien 1984; Zanardi 1996 b; MAP 1986 a), which included a total of 404 participants. There was no statistically significant difference between comparisons (RR fixed effect 1.13, 95% CI 0.90 to 1.42; chi squared 8.68, df = 5, P = 0.12).

B. Secondary outcome measures

Benefits

General health, quality of life, social and occupational functioning
We had planned to compare the general health and social functioning of participants receiving long-term lithium treatment with those receiving antidepressants. Few studies included such outcome measures, and where they did, the actual data collecting 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 showed no differences between treatments.

(i) Clinical global impression of clinician

Three studies included some kind of global assessment made by clinicians. Details of these global ratings are given below.

VA-NIMH 1970 b

The treating physician (non-blind) completed the Global Affective Scale (GAS) every four weeks. This scale rated affective symptoms on a seven point scale. In this study (bipolars and unipolars), 42% episode-free completers in the lithium group and 38% in the imipramine group had prolonged periods of mild or moderately severe symptoms (the remaining patients were either asymptomatic or showed mild symptoms on only one or two visits). Social workers carried out a global assessment of affective episodes every six months following home visits and interviews with the participant and their family: there were no statistically significant differences in terms of number severity of episodes between lithium carbonate and imipramine. This study also used the Inpatient Multidimensional Psychiatric Scale and the Katz Adjustment Scale, but no results were reported.

Prien 1984

A 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 otherwise not reported. Several other rating scales for affective symptoms were also used but the results were not reported.

MAP 1986 a

The GAS was completed by a psychiatrist at each clinic visit. GAS scores were not otherwise reported. Several other rating scales for affective symptoms (Clinical Global Impressions Scale, Brief Psychiatric Rating Scale, Bech-Rafaelsen Melancholia Scale, Bech-Rafaelsen Mania Scale, AMDP-system) 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.

VA-NIMH 1970 b

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.

MAP 1986 a

Patient rated side-effects and satisfaction with treatment on a 100-mm Visual Analogue Scale (VAS). The 100-mm VAS after 2.5 years indicated no significant differences in terms of disturbing side-effects (Li. vs. Ami: 77 +/- 23 vs. 80 +/- 22: P = 0.609) and satisfaction with treatment in general (Li. vs. Ami: 83 +/- 13 vs. 86 +/- 14: P = 0.536). In addition, the patients completed the Adjective Mood Scale (Bf-S) and self-ratings regarding Premorbid Personality (PP-I) and the health belief models (KK-S). These results were not reported.

(iii) Employment during the study period

None of the studies made reference to participants' employment.

Adverse effects

(i) Number of patients reporting at least one adverse event - troublesome side-effects (see figure 01.06.02)

Only one study reported on troublesome side-effects (Prien 1984): there was no statistically significant difference between lithium and antidepressants (RR fixed effects 0.45, 95% CI 0.14 to 1.48; 1 study, 76 participants).

(ii) Mortality due to all causes and specifically suicides and verdicts of undetermined deaths (see figure 01.07 and 01.08)

Four studies reported mortality (VA-NIMH 1970 b; Zanardi 1996 b; MAP 1986 a; Glen 1981), but one of them did not report the outcome according to bipolar and unipolar patients, so it was not possible to use these data in the meta-analysis (VA-NIMH 1970 b). Overall, mortality rates were low. Three out of 131 participants on antidepressants died during the trial compared with one out of 141 on lithium (RR fixed effects 0.39, 95% CI 0.06 to 2.60; chi squared 0.01 df = 1, P = 0.92; 3 studies, 272 participants) (see figure 01.07). The only one non-suicide death in participants on antidepressants was reported as due to 'myocardial infarction'. The only death in the

lithium group was recorded as due to 'cerebrovascular accident'. No participants taking lithium committed suicide compared with two on antidepressants (amitriptyline in both trials) (RR fixed effects 0.31, 95% CI 0.03 to 2.92; chi squared 0.01 df = 1, P = 0.93; 8 studies, 475 participants) (see figure 01.08).

(iii) Overall drop-out rate as a proxy measure of overall acceptability of treatment (see figure 01.04)

Drop-out rates were reported in six studies (MAP 1986 a; VA-NIMH 1970 b; Coppen 1976 b; Coppen 1978 b; Glen 1981; Zanardi 1996 b). Rates were estimated from various time-points into the studies, so these data could be of limited use. Some 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 was unstated or unclear. Thus, it could be 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 reasons were adverse events and treatment failure.

Analysis of drop-out rates showed no statistically significant differences between lithium and antidepressants (RR fixed effects 0.67, 95% CI 0.43 to 1.06; chi squared 2.92, df = 3, P = 0.40; six studies, 345 participants) (see figure 01.04). This result was consistent across the studies. Attempts to examine drop-out rates on an intention-to-treat basis were not possible due to inadequate reporting.

(iv) Drop-out rate due to side-effects (see figure 01.05).

There was no statistically significant difference in terms of number of patients who failed to complete treatment between lithium and antidepressants (RR fixed effects 1.04, 95% CI 0.31 to 3.52; chi squared 3.08 df = 2, P = 0.21; 4 studies, 262 participants).

(v) Number of patients reporting at least one adverse event - any reported (see figure 01.06.01)

Three studies made some reference to side-effects (Prien 1984; Glen 1981; VA-NIMH 1970 b), but one of them did not report the outcome according to bipolar and unipolar patients, so it was not possible to use these data in the meta-analysis (VA-NIMH 1970 b). There was no statistically significant difference in terms of number of patients who reported on any adverse event between lithium and antidepressants (RR fixed effects 0.93, 95% CI 0.52 to 1.68; chi squared 0.11 df = 1, P = 0.74; 2 studies, 203 participants).

(vi) No data were reported on suicide attempts, deliberate self-harm or suicidal ideation. Additional information has been sought from the study authors.

DISCUSSION

This systematic review of eight randomised controlled trials compared lithium with antidepressants in the long-term treatment of unipolar affective disorder. The results showed that there remains uncertainty over the value of lithium in the long-term treatment of unipolar disorder in comparison with antidepressants. The number of participants in the studies was small (475 participants; the large majority of which had a diagnosis of unipolar disorder) and the included studies had various

methodological shortcomings: This point should be considered when interpreting the results.

The only statistically significant result referred to the outcome relapse defined as admission to hospital; however, this result became statistically non-significant when a random-effects model was used. This tendency in favour of lithium could be interpreted as a possible advantage for lithium in severe depression or severe recurrence, even if elsewhere a lithium prophylactic potential was hypothesised only for milder depressive recurrences (Prien 1984). However, in the present systematic review the number of participants for this outcome was very small (142 participants) and it is difficult to draw clinically significant conclusions from these data (for instance, the number of dropouts exceeded the number of admissions and the differential dropouts from treatment arms rendered the interpretation of the finding very difficult). Overall, this review suggests that whilst lithium may be of benefit in preventing relapse in unipolar affective disorder, there remains uncertainty about quantification of this value in comparison with antidepressants.

Both lithium and antidepressants are currently used as long-term treatment for unipolar affective disorders. In a systematic review which included trials with 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) (Burgess 2001). As authors highlighted in their paper, analysis of mixed groups of patients with mood disorder may be of limited clinical use, as there is growing evidence that different disorders respond differently to treatments: clinicians considering lithium prophylaxis for an individual generally have some diagnostic indication as to whether their patient suffers from bipolar or unipolar disorder. On the other hand, a recent systematic review found that long-term treatment with antidepressants in patients suffering from unipolar affective disorder reduced the odds of depressive relapse by around two-thirds, which is approximately equivalent to a halving of the absolute and relative risk (Geddes 2003). Although there was some statistical heterogeneity between trials, the treatment effect was reasonably similar across different classes of antidepressant and the risk of relapse seemed similar across heterogeneous groups of patients, including those who had recently responded to treatment of an acute episode of illness and those who had been successfully taking long-term treatment for several months or even years. Another systematic review investigated whether antidepressants are effective for bipolar depression and found no coherent basis for doubting that conventional antidepressants have efficacy in bipolar depression on the basis of the existing evidence (Gijsman 2004c). In addition, the size of the antidepressant effect was comparable to that in unipolar depression, suggesting that antidepressants may be of comparable efficacy in unipolar and bipolar depression (Geddes 2004a).

In the current review, the modest number of participants meant that sub-group analyses (for example, comparing participants with longer or shorter histories of mood disorder) have not been possible. There was heterogeneity in the estimates of effect in preventing relapse between the studies. It is possible that the heterogeneity between the studies could 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 (Quitkin 1978; Prien 1984) were of a factorial design. The studies included in this review employed lithium levels ranging between 0.5 and 1.4 mmol/l but this review did not investigate relative efficacy of higher or lower lithium levels.

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. In addition to being a considerable clinical problem, non-adherence is a potentially significant source of bias in research studies. 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.

The review showed overall adverse effect rates were not significantly different between lithium and antidepressants: little information had been reported on the incidence of specific adverse effects, or on 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.

Two studies included in this review reported on suicides. In another five studies authors replied that no suicides occurred. In the remaining study, suicide was not reported, but it can be inferred reliably that, if suicides had occurred in these studies they would have been reported. 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 (Burgess 2001). There is randomised evidence that lithium reduces the risk of suicide in patients with mood disorders (Cipriani 2005): this recent systematic review investigated the effect of lithium in comparison to placebo and other active treatments on the risk of suicide, deliberate self-harm and all-cause mortality in patients with mood disorder, and found that patients allocated to lithium were less likely to die by suicide (seven trials; Odds Ratio 0.26; 95% CI 0.09 to 0.77; $P = 0.01$). In this study, the consistency of the results across trials may indicate that the life-preserving effect of lithium is independent of the comparator and the consistency of the findings across comparators suggests that it is lithium that prevents suicide rather than any other drug increasing the risk of suicide. Alternative explanations for the low rates found have been proposed: a more general effect of the regular specialised medical care that these patients received, and also the possibility

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.

Further information has been sought from the authors on deliberate self-harm or suicidal ideation and, if received, will be included in future versions of this review.

AUTHORS' CONCLUSIONS

Implications for practice

In unipolar disorder, the evidence for the efficacy of lithium is less robust than in bipolar disorder. However, it may vary between patient subgroups and lithium and antidepressants should both continue to be considered for long-term treatment in mood disorders. There is adequate evidence of their efficacy in preventing relapse in unipolar affective disorder, but their relative efficacy is unknown. When considering lithium or antidepressant long-term therapy, patients and clinicians should take into account the patient's clinical history, the side-effects and the individual's likely adherence to the recommended treatment regime. Cost analysis is also needed. 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

Large-scale long-term randomised trials comparing lithium with other long-term treatments in unselected groups of subjects with unipolar affective disorder are needed. Meaningful measures of relapse, such as relapse requiring hospital admission or intensive home treatment or institution of additional treatment for an episode of mood disorder should be included as primary outcomes. Adverse effects, simple replicable measures of general health and social functioning, and patients' own views of treatment should be recorded too. Outcomes relating to death, suicide and other suicidal attitudes should be assessed 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. Research on effectiveness outcomes of long-term treatment (concordance with treatment, factors affecting concordance, ie effect of lithium clinics, differences in levels of patient education, monitoring and support) should be routinely implemented.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Coppen 1976 b

Methods	Double-blind randomised controlled trial. 1 year follow up.
Participants	Unipolar (n=30) and bipolar disorder. Attending lithium clinic for at least 1 year before study. At least 3 previous episodes of affective disorder.
Interventions	Lithium (0.8-1.2 mEq/l) Maprotiline 150mg/d
Outcomes	Assessment of affective morbidity (4 point scale).

Lithium versus antidepressants in the long-term treatment of unipolar affective disorder (Review)

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Coppen 1976 b (Continued)

Beck depression Inventory.
Weight.
Side effects.
Duration of inpatient and outpatient episodes.

Notes Study began with unipolar and bipolar. Later, bipolar excluded because 2 bipolar subjects developed manic episodes during study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Coppen 1978 b

Methods Double-blind randomised controlled trial.
18 month follow up.

Participants Unipolar (n=41).
Attending lithium clinic.
3 or more previous episodes of affective disorder.

Interventions Lithium (0.8-1.2 mEq/l).
Mianserin (60 mg/d, increased to 90 mg/d after 1 year. Levels achieved: 36.7 +/-4.3 ng/ml)

Outcomes Rated at 1 year.
Assessment of affective morbidity (4 point scale).
Side effects.
Duration of inpatient and outpatient episodes.
ECT treatments.

Notes 3 subjects had not received lithium previously. It appears that these 3 were randomised to receive lithium during the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Glen 1981

Methods 2 separate double-blind randomized controlled trials.
3 years follow-up.
Group 1 had more than 1 previous episode of depression in past 5 years. Group 2 had only 1 previous episode.

Participants Unipolar disorder (group 1 n=103, group 2 n=19).
Primary depressive illness diagnosed by RDC criteria
No history of mania
No physical disability precluding study treatments
Age < 65.

Glen 1981 (Continued)

Interventions	Lithium (0.6-1.2 mmol/l) Amitriptyline (60-230 mg/ml) Placebo (for group 2 only; not included in this review).	
Outcomes	Relapse Use of anxiolytics Severity of depression Side-effects Biochemistry, cardiac, thyroid and renal function Deviation from protocol Deaths	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

MAP 1986 a

Methods	Randomized trial. Providers of medication and assessors were not blind to treatment allocation. Unclear if patients blind. Follow-up 2 1/2 years. Separate arms of study for bipolar and schizoaffective disorder (not included in this review).	
Participants	Unipolar depression (n=86). Inclusion criteria: ICD-9 unipolar depressive episode, at least 1 previous episode in 5 years preceding index episode, age 18-65, no alcohol/drug misuse, no physical contraindication to drug treatments, no preventative treatment for 2 months prior to onset of current episode.	
Interventions	Lithium (aimed for 0.6 -0.8mmol/l, achieved mean 0.59 +/- 0.12). Amitriptyline (75-100mg, 88.5 +/- 60.5ng/ml).	
Outcomes	Relapse: admission to hospital, recurrence according to RDC criteria, additional psychotropic medication, severe side effects. Also measured: Clinical global impression scale, Global assessment scale, Brief Psychiatric Rating Scale, Bech-Rafaelson Melancholia Scale and Mania Scale, AMPD system.	
Notes	512 subjects were eligible for the study, but only 86 participated. Reasons for non-participation: could not be stabilized before randomization, unwilling to participate, external reasons (language, legal reasons), not specified.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Prien 1984

Methods	Double-blind randomised controlled trial Separate unipolar and bipolar studies. Unipolar study only included in review	
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Lithium versus antidepressants in the long-term treatment of unipolar affective disorder (Review)

Prien 1984 (Continued)

2 year follow-up

Participants	<p>Unipolar disorder (n=148)</p> <p>Unipolar study- preliminary phase: episode major depression satisfying RDC criteria, Raskin severity of depression and mania scale (RSDM) total score ≥ 7, Global assessment scale (GAS) ≤ 60</p> <p>1 or more previous episodes of depression in previous 2.5 years</p> <p>To qualify as bipolar, patient must have had at least one manic episode, to qualify as unipolar, patient must have had no manic episode</p> <p>No other psychiatric diagnosis in preceeding 2 years</p> <p>No physical illness precluding use of lithium and imipramine</p> <p>Age 21-60</p> <p>Maintenance phase-</p> <p>remained on maintenance medication of lithium and imipramine for two months and achieved GAS score ≥ 60 and RSDM ≤ 7</p>
Interventions	<p>Lithium (aimed for 0.6 -0.9mmol/l, achieved 0.43-1.15, mean 0.66)</p> <p>.Lithium + Imipramine Imipramine (aimed for 150 mg/d, achieved mean of 137 mg/d)</p> <p>Placebo(not included in this review)</p>
Outcomes	<p>Relapse (RDC for definite major depression or mania and GAS rating ≤ 60)</p> <p>GAS</p> <p>RSDM</p> <p>Hamilton rating scale for depression</p> <p>Manic behaviour rating scale</p> <p>Brief psychiatric rating scale</p> <p>Social adjustment self-report questionnaire</p> <p>Life events scale</p> <p>Side-effects</p>
Notes	<p>Participants stabilized on imipramine and lithium following control of acute symptoms and prior to randomisation. 343 participants entered preliminary phase. 148 entered maintenance phase. Reasons for drop-out in preliminary phase included noncompliance, withdrawal of consent, poor clinical response and inability to tolerate study medication</p> <p>Bipolar group (not included in review) randomised to lithium, lithium + imipramine or imipramine</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Quitkin 1978

Methods	<p>Double-blind randomised controlled trial</p> <p>Randomisation stratified by UP/BP</p> <p>2 year follow-up</p>
Participants	<p>Unipolar (n=27) and bipolar II disorder (n=22)</p> <p>Research diagnostic criteria (RDC) diagnosis</p> <p>Minimum 2 episodes in previous 7 years</p> <p>Euthymic for 6 months before study</p> <p>No co-existing medical illness complicating treatment</p> <p>Age < 65.</p>
Interventions	<p>Lithium (0.8-1.2 mmol/l)</p> <p>Lithium + Imipramine</p> <p>Imipramine (100-150 mg/d)</p>

Lithium versus antidepressants in the long-term treatment of unipolar affective disorder (Review)

Quitkin 1978 (Continued)

Placebo (not included in this review).

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 Dropouts
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

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

VA-NIMH 1970 b

Methods	Single-blind (partly double-blind) randomised controlled trial Randomisation not stratified by UP/BP 2 year follow-up
Participants	Bipolar and unipolar disorder 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 Age <60 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 (not included in this review) Imipramine (50-200mg/day, median 125mg)
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 out-comes in this review Treating physician (not blind) responsible for hospital admission and withdrawal due to poor clinical response

Risk of bias

Bias	Authors' judgement	Support for judgement
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VA-NIMH 1970 b *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear
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Zanardi 1996 b

Methods	Randomized trial. Neither providers nor assessors were blind. Not clear if patients were blind to treatment allocation. 3 year follow up.
Participants	Unipolar (n=64). DSM-III-R criteria for recurrent depression with current depressive episode.
Interventions	Lithium (600-900mg/d, levels achieved=0.5-0.9 mmol/L). Flvoxamine (200mg/d, levels achieved=70-200mM/L)
Outcomes	Relapse = major depressive episode according to DSM-III-R criteria. Side effects. HAM-D score. MADRS. Hopkins Symptom Check List.
Notes	Recruited as inpatients, and treated with antidepressants (flvoxamine, amitriptyline, imipramine, clomipramine) according to psychiatrists choice before randomisation to study treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Additional data for Greil 1996 study from personal communication to SB.

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

Study	Reason for exclusion
Abou-Salah 1983	Acute treatment trial, plus a trial of lithium vs placebo.
Ahlfors 1981	Open trial. Mixed bipolar and unipolar reported together. Comparison of flupenthixol vs lithium.
Baastrup 1970	Compares lithium vs placebo. Discontinuation study, not maintenance.
Bauer 2000	Compares lithium vs placebo.
Blackwell 1971	Letter. No original data included.
Coppen 1971	Compares lithium vs placebo.
Coppen 1973	Review. No original data reported.
DiMascio 1974	First study compares lithium vs chlorpromazine in acute mania, followed by comparison of lithium vs placebo. Second study investigates combination of lithium and amitriptyline in treatment of depression.
Fieve 1968	Not randomised

Study	Reason for exclusion
Gram 1972	Compares lithium vs placebo.
Hardy 1997	Discontinuation study, not maintenance.
Hoencamp 1994	Acute treatment study.
Joffe 1992 b	Acute treatment study.
Linder 1989	Acute treatment study.
Lingjaerde 1973	Compares lithium + antidepressant vs antidepressant alone.
Lingjaerde 1974	Compares lithium + antidepressant vs lithium alone.
Linnoila 1984	No maintenance trial.
Melia 1970	Compares lithium vs placebo. Discontinuation study rather than maintenance.
Mendels 1972	Acute treatment study.
Murphy 1975 d	Acute treatment study.
Nahuneck 1971	Acute treatment study (maximum 50 days).
Noyes 1974	Not RCT.
Peselow 1990	Only 10% of sample were randomised (to lithium vs placebo). Comparison of lithium vs antidepressants not RCT.
Prien 1973 (b)	Compares lithium vs placebo.
Schou 1972	Review. No original data reported.
Schou 1979	Review. No original data reported.
Shapiro 1989	Bipolar disorder only.
Shelley 1974	Compares lithium vs placebo.
Stallone 1973	Compares lithium vs placebo.
STOP-PD 2004	Acute treatment study (12 weeks). No lithium arm.
Szuba 1994	Acute treatment study.
Watanabe 1975	Acute treatment study (maximum 5 weeks).
Wilkinson 2002	Compares lithium vs placebo.
Worrall 1979 a	Acute treatment study.

DATA AND ANALYSES

Comparison 1. Lithium vs antidepressants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All relapses	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Admission to hospital	3	152	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.14, 0.82]
1.2 Non-study medication	3	249	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.05]
1.3 Relapse however defined	7	434	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.81, 1.24]
2 Depressive relapse	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Admission to hospital	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Non-study medication	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Relapse however defined	6	404	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.42]
3 Manic relapse	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Admission to hospital	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Non-study medication	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Relapse however defined	6	404	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.17, 1.25]
4 Overall dropout rate	6	345	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.43, 1.06]
5 Dropout rate due to side effects	4	262	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.31, 3.52]
6 Side effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Any reported	2	203	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.22]
6.2 Troublesome	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.20, 1.40]
7 Mortality	3	272	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.06, 2.60]
8 Suicide	8	475	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.03, 2.92]

Analysis 1.1. Comparison 1 Lithium vs antidepressants, Outcome 1 All relapses.

Analysis 1.2. Comparison 1 Lithium vs antidepressants, Outcome 2 Depressive relapse.

Analysis 1.3. Comparison 1 Lithium vs antidepressants, Outcome 3 Manic relapse.

Analysis 1.4. Comparison 1 Lithium vs antidepressants, Outcome 4 Overall dropout rate.

Analysis 1.5. Comparison 1 Lithium vs antidepressants, Outcome 5 Dropout rate due to side effects.

Analysis 1.6. Comparison 1 Lithium vs antidepressants, Outcome 6 Side effects.

Analysis 1.7. Comparison 1 Lithium vs antidepressants, Outcome 7 Mortality.

Analysis 1.8. Comparison 1 Lithium vs antidepressants, Outcome 8 Suicide.

WHAT'S NEW

Date	Event	Description
2 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 4, 2006

Date	Event	Description
22 August 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AC, KS and SB collected the data; AC and JG ran the analysis; AC, KS and JG drafted the paper; SB, SC and GG revised the manuscript.

DECLARATIONS OF INTEREST

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Antimanic Agents [*therapeutic use]; Depressive Disorder [*drug therapy] [psychology]; Lithium Compounds [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans