Lithium in the Prevention of Suicidal Behavior and All-Cause Mortality in Patients With Mood Disorders: A Systematic Review of Randomized Trials

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Objective: Observational studies suggest that long-term lithium treatment has a strong antisuicidal effect in mood disorders, but it is uncertain whether this association is a genuine therapeutic effect or is due to confounding factors in nonrandomized studies. The authors conducted a systematic review and meta-analysis of randomized trials to investigate the effect of lithium, compared to placebo and other active treatments, on the risk of suicide, deliberate self-harm, and all-cause mortality in patients with mood disorder.

Method: The data source was the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, incorporating results of searches of MEDLINE (1966–June 2002), EMBASE (1980–June 2002), CINAHL (1982–March 2001), PsycLIT (1974–June 2002), PSYNDEX (1977–October 1999), and LILACS (1982–March 2001). The Cochrane Central Register of Controlled Trials (CENTRAL) was searched with the term "lithium" for new records entered into the database from 1999 to 2003. Studies selected included randomized, controlled trials comparing lithium with placebo or all other compounds used in long-term treatment for mood disorders (unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, and rapid cycling, diagnosed according to DSM or ICD criteria). Of 727 references identified in the search, 52 articles were marked as possibly relevant on the basis of the abstract, and 32 randomized, controlled trials were eligible for inclusion in the review. Two independent reviewers extracted the data, and disagreements were resolved by consensus with a third reviewer. Methodological quality was assessed according to the criteria of the Cochrane Collaboration. When the outcomes of interest were not reported, an attempt was made to obtain the required data from the original authors.

Results: In 32 trials, 1,389 patients were randomly assigned to receive lithium and 2,069 to receive other compounds. Patients who received lithium were less likely to die by suicide (data from seven trials; two versus 11 suicides; odds ratio=0.26; 95% confidence interval [CI]=0.09–0.77). The composite measure of suicide plus deliberate self-harm was also lower in patients who received lithium (odds ratio=0.21; 95% CI=0.08–0.50). There were fewer deaths overall in patients who received lithium (data from 11 trials; nine versus 22 deaths; odds ratio=0.42, 95% CI=0.21–0.87).

Conclusions: Lithium is effective in the prevention of suicide, deliberate self-harm, and death from all causes in patients with mood disorders.

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Mood disorders are frequently recurrent and are associated with a lifetime risk of suicide that is about 15 times higher than in the general population (1). There is increasing recognition that strategies for suicide prevention should include improved treatment of mood disorders. Although evidence from randomized trials suggests that drug treatments, including antidepressants and lithium, can substantially reduce the risk of relapse in mood disorders (2, 3), the effects on suicide are uncertain because the low event rate means that individual randomized trials are invariably underpowered to investigate any potential benefit. On the basis of the existing observational and randomized evidence, however, there have been claims that lithium may substantially reduce the risk of suicide in bipolar disorder (4). Proposed mechanisms of action include a lowering of risk secondary to a reduction in risk of depressive relapse, a serotonin-mediated reduction in impulsivity or aggressive behavior, and a nonspecific benefit arising from the long-term monitoring provided during lithium therapy (4). Goodwin and colleagues (5) recently reported a large observational study from a health maintenance organization that found a 2.7-fold increase in the risk of suicide in patients prescribed divalproex, compared to patients prescribed lithium. Goodwin et al. compared active treatments and so partly controlled for some of the limitations of previous studies, including the possibilities that patients who are able to adhere to long-term lithium treatment may be less disturbed and

TABLE 1. Randomized, Controlled Studies Included in a Systematic Reivew of the Effect of Lithium on Suicidal Behavior and All-Cause Mortality in Patients With Mood Disorders

Comparator and Study	Comparisons and Sample Sizes	Inclusion Criteria	Patient and Study Characteristics
Placebo			
Baastrup et al., 1970 (14)	Lithium (0.6–1.5 meq/liter) (N=45) versus placebo (N=39)	Bipolar disorder, recurrent unipolar depression	Only female outpatients who had received lithium openly for at least 1 year were included. Relapse consisted of mania or depression severe enough to necessitate either admission to a mental hospital or regular supervision in the home with administration of supplementary drug therapy.
Coppen et al., 1971 (18)	Lithium (0.8–1.2 meq/liter) (N=28) versus placebo (N=37)	At least one affective illness per year for 3 years, three affective illnesses in the previous 2 years, or two illnesses during the previous year	Treating psychiatrist could prescribe additional treatment other than lithium, if indicated.
Coppen et al., 1981 (21)	Lithium (0.8–1.2 meq/liter) (N=18) versus placebo (N=20)	Hamilton Depression Rating Scale score ≥16	Patients receiving electroconvulsive therapy (ECT) were randomly allocated to receive lithium or placebo while still receiving ECT. Relapse was defined as an increase in morbidity severe enough to warrant admission to a ward or day hospital.
Cundall et al., 1972 (23)	Lithium (0.5–1.2 meq/liter) (N=9) versus placebo (N=9)	Manic-depression diagnosed if the patient ever had mania or hypomania, either spontaneously or as a result of depression treatment	A 1-year trial was followed by a 6-month crossover phase. Lithium was stopped temporarily if ECT was required. Relapses were diagnosed clinically.
Dorus et al., 1989 (24)	Lithium (600–1200 mg/day) (N=89) versus placebo (N=82)	NIMH Diagnostic Interview Schedule and DSM-III criteria	Male veterans hospitalized for alcoholism entered the study after detoxification.
Fieve et al., 1976 (25)	Lithium (0.7–1.2 meq/liter) (N=56) versus placebo (N=59)	Feighner criteria. For unipolar depression, a history of at least two depressive episodes requiring hospitalization at least once during the previous 5 years and complete absence of symptoms of hypomania. For bipolar I disorder, history of at least two episodes of affective disorder in the 2 years before randomization, having been hospitalized for mania, and having had mild to severe depression. For bipolar II disorder, a history of two or more affective episodes in the 2 years before the study, having been hospitalized for depression, and having a history of hypomania that did not require hospitalization. Randomization occurred when the patient remained normothymic and had not been treated with antidepressants for at least 1 month.	—
Hardy et al., 1997 (31)	Lithium (dose not clear) (N=6) versus placebo (N=6)	DSM-III-R criteria for major unipolar depression, Geriatric Depression Rating Scale score <20, Montgomery-Åsberg Depression Rating Scale score <15, standardized Mini-Mental State Examination (MMSE) score >20	Geriatric outpatients with refractory depressive symptoms who failed to show improvement after at least 6 months of maximal doses of antidepressant therapy received lithium augmentation or placebo.
Hullin et al., 1972 (33)	Lithium (up to 1.6 meq/liter) (N=18) versus placebo (N=18)	Admission to a psychiatric hospital with definite manic or depressive illness at least once a year during the previous 5 years	—
Melia, 1970 (37)	Lithium (500–1500 mg/day) (N=9) versus placebo (N=9)	No schizophrenic symptoms when normothymic, no single period of normothymia (freedom from even mild hypomanic or depressive mood swings) longer than 9 months in the 2 years before starting lithium	Before the start of the trial, patients had been taking lithium continuously for at least 9 months in a preliminary open trial.
Prien et al., 1973 (40)	Lithium (median=0.7 meq/liter) (N=101) versus placebo (N=104)	Patients stabilized with maintenance doses of lithium carbonate after remission of acute manic episode and before discharge	Clinical rater and patients were blind to treatment.
Wilkinson et al., 2002 (45)	Lithium (0.3–0.7 mmol/liter) (N=25) versus placebo (N=24)	DSM-IV criteria, Montgomery-Åsberg Depression Rating Scale score <13, MMSE score >23	Only elderly inpatients were included. After recovery and randomization, patients received maintenance antidepressant medication.

Study Quality[a]				Reported Outcomes		
Allocation Concealed	Blinding	Follow-Up	Diagnosis	Deaths	Suicides	Deliberate Self-Harm[b]
Yes	Patient, rater	22 weeks	Bipolar disorder, recurrent unipolar depression	Yes	Yes	No
Not clear	Patient, rater	112 weeks	Unipolar depression, bipolar disorder	Yes	Yes[c]	Yes[c]
Not clear	Patient, rater	52 weeks	Unipolar depression	No	Yes[c]	Yes[c]
Not clear	Not stated	52 weeks	Bipolar disorder, recurrent unipolar depression	No	No	No
Not clear	Not stated	52 weeks	Unipolar depression, alcoholism	Yes	No	No
Not clear	Not stated	208 weeks	Unipolar and bipolar disorder	No	Yes[c]	Yes[c]
Not clear	Not stated	104 weeks	Refractory unipolar depression	Yes	Yes	No
Not clear	Not specified	26 weeks	Bipolar disorder, recurrent unipolar depression, schizoaffective disorder	No	No	No
Yes	Patient, clinician	104 weeks	Recurrent affective depression	No	No	No
No	Patient, rater	104 weeks	Bipolar disorder	Yes	Yes	No
Not clear	Not stated	104 weeks	Unipolar depression	Yes[c]	Yes[c]	Yes[c]

(continued)

TABLE 1. Randomized, Controlled Studies Included in a Systematic Reivew of the Effect of Lithium on Suicidal Behavior and All-Cause Mortality in Patients With Mood Disorders *(continued)*

Comparator and Study	Comparisons and Sample Sizes	Inclusion Criteria	Patient and Study Characteristics
Amitriptyline			
Glen et al., 1984 (27)	Lithium (up to 1.2 meq/liter) (N=69) versus amitriptyline (N=58) versus placebo (N=9)	Diagnosis of primary depressive illness, no history of mania	After recovery from index episode, two groups of patients were randomly allocated to treatments. Group 1 had a history of more than one episode of depression and group 2 had a history of just one episode within the 5 years before the index episode.
Greil et al., 1996 (28)	Lithium (0.4–0.8 mmol/liter) (N=40) versus amitriptyline (75–100 mg/day) (N=41)	Research Diagnostic Criteria (RDC) and DSM-III-R criteria	Patients were recruited while hospitalized and were treated as outpatients during the maintenance phase. Randomization occurred when patients were stable (Global Assessment Scale [GAS] score >70) for at least 2 weeks within 6 months after discharge. In a second stage of recruitment, randomization was also allowed during acute-phase treatment.
Laurell and Ottosson, 1968 (35)	Lithium (900 mg/day) (N=4) versus amitriptyline (75 mg/day) (N=6) versus placebo (N=6)		Only female outpatients who had received lithium openly for at least 1 year were included. Relapse consisted of mania or depression severe enough to necessitate either admission to a mental hospital or regular supervision in the home with administration of supplementary drug therapy.
Carbamazepine			
Coxhead et al., 1992 (22)	Lithium (0.5–1.0 mmol/liter) (N=16) versus carbamazepine (38–51 µmol/liter) (N=15)	DSM-III criteria	—
Greil et al., 1997 (29)	Lithium (0.4–0.8 mmol/liter) (N=87) versus carbamazepine (4–12 mg/liter) (N=88)	RDC and DSM-III-R criteria	Patients were recruited while hospitalized and were treated as outpatients during the maintenance phase. Randomization occurred when patients were stable (GAS score >70) for at least 2 weeks within 6 months after discharge. In a second stage of recruitment, randomization was also allowed during acute-phase treatment.
Greil et al., 1997 (30)	Lithium (mean=0.58 mmol/liter, SD=0.12) (N=52) versus carbamazepine (mean=6.4 mg/liter, SD=1.5) (N=58)	RDC and DSM-III-R criteria	Patients were recruited while hospitalized and were treated as outpatients during the maintenance phase. Randomization occurred when patients were stable (GAS score >70) for at least 2 weeks within 6 months after discharge. In a second stage of recruitment, randomization was also allowed during acute-phase treatment.
Hartong et al., 2003 (32)	Lithium (0.6–1.0 mmol/liter) (N=23) versus carbamazepine (6–10 mg/liter) (N=30)	DSM-III-R bipolar disorder with at least two episodes during the previous 3 years	Patients recovered from their last episode were recruited and randomly assigned to study medication either at the start of the prophylactic treatment phase or during an acute episode of hypomania or depression.
Lusznat et al., 1988 (36)	Lithium (0.6–1.4 meq/liter) (N=27) versus carbamazepine (0.6–1.2 mg/100 ml) (N=27)	Mania or hypomania and a Bech-Rafaelson Mania Scale score ≥10	Study included a 6-week acute trial and a 12-month follow-up trial.
Placidi et al., 1986 (38)	Lithium (300–1200 mg/day) (N=41) versus carbamazepine (400–1600 mg/day) (N=42)	At least two DSM-III major affective, schizoaffective, or schizophreniform episodes in the past 3 years	Both inpatients and outpatients were included. Relapse was defined as a Clinical Global Impression (CGI) severity scale score ≥5.
Simhandl et al., 1993 (43)	Lithium (0.6–0.8 mmol/liter) (N=26) versus carbamazepine (15–25 µmol/liter) (N=30) versus carbamazepine (28–40 µmol/liter) (N=28)	DSM-III-R criteria, at least one episode within the last 2 years before the index episode	—
Watkins et al., 1987 (44)	Lithium (0.4–0.9 mmol/liter) (N=18) versus carbamazepine (5–12 mg/liter) (N=19)	DSM-III mania or major depressive episode, at least one well-defined, recorded previous episode and a known time of recovery not "covered" by prophylactic drugs (monoamine oxidase inhibitors, tricyclics)	—

Study Quality[a]				Reported Outcomes		
Allocation Concealed	Blinding	Follow-Up	Diagnosis	Deaths	Suicides	Deliberate Self-Harm[b]
Not clear	Patient, rater	128 weeks	Unipolar depression	Yes	Yes	No
Not clear	Open	128 weeks	Recurrent unipolar depression	Yes[c]	Yes[c]	Yes[c]
Not clear	Not specified	39 weeks	Bipolar disorder, recurrent unipolar depression	Yes[c]	Yes[c]	Yes[c]
Not clear	Patient, rater	52 weeks	Bipolar disorder	No	No	No
Not clear	Open	128 weeks	Bipolar disorder	Yes[c]	Yes[c]	Yes[c]
Not clear	Open	128 weeks	Schizoaffective disorder	Yes[c]	Yes[c]	Yes[c]
Not clear	Not specified	104 weeks	Bipolar disorder	Yes[c]	Yes[c]	Yes[c]
Not clear	Patient, rater	52 weeks	Bipolar disorder, schizoaffective disorder	No	No	No
Not clear	Not specified	156 weeks	Unipolar depression, bipolar disorder, schizoaffective disorder	No	No	No
Not clear	Not stated	104 weeks	Unipolar depression, bipolar disorder	No	No	No
Not clear	Not stated	Average time in trial: 20 months (lithium); 16 months (carbamazepine)	Unipolar depression, bipolar disorder	No	No	No

(continued)

TABLE 1. Randomized, Controlled Studies Included in a Systematic Review of the Effect of Lithium on Suicidal Behavior and All-Cause Mortality in Patients With Mood Disorders *(continued)*

Comparator and Study	Comparisons and Sample Sizes	Inclusion Criteria	Patient and Study Characteristics
Divalproex			
Bowden et al., 2000 (15)	Lithium (0.8–1.2 meq/liter) (N=91) versus divalproex (71–125 mg/ml) (N=187) versus placebo (N=94)	DSM-III-R criteria, at least one other manic episode in the previous 3 years. Randomization criteria: Mania Rating Scale score ≤11, Depressive Syndrome Scale score ≤13, GAS score >60	Initial open phase of ≤3 months was followed by a maintenance phase. Patients could be enrolled in the open phase while manic, partly recovered from a manic episode, or euthymic after the episode but not while depressed.
Fluvoxamine			
Franchini et al., 1994 (26)	Lithium (0.5–0.9 meq/liter) (N=32) versus fluvoxamine (0.2–0.4 meq/liter) (N=32)	DSM-III-R criteria	Inpatients who recovered from an index depressive episode were included. Recovery was defined as euthymia for at least 8 consecutive weeks and absence of depressive symptoms (Hamilton Depression Rating Scale score ≤18 and Montgomery-Åsberg Depression Rating Scale score ≤20).
Imipramine			
Kane et al., 1982 (34)	Lithium (0.8–1.2 meq/liter) (N=11) versus imipramine (100–150 mg/day) (N=11) versus lithium plus imipramine combination (N=14) versus placebo (N=13)	Two episodes of RDC depression or mania in the previous 7 years, euthymic for 6 months before study entry	All participants were outpatients. Patients with unipolar depression and patients with bipolar II disorder were included in separate randomized trials.
Prien et al., 1973 (39)	Lithium (median=0.8 meq/liter) (N=45) versus imipramine (median=125 mg/day) (N=38) versus placebo (N=39)	At least one affective episode requiring hospitalization during the preceding 2 years and two episodes requiring hospitalization during the preceding 5 years	Patients with schizoaffective disorder were excluded. During hospitalization antidepressants and ECT were administered.
Prien et al., 1984 (41)	Lithium (0.45–1.1 meq/liter) (N=79) versus imipramine (75–150 mg/day) (N=75) versus lithium plus imipramine combination (N=74) versus placebo (N=34)	RDC major unipolar depression, major bipolar depression or mania; Raskin Severity of Depression and Mania scale score ≥7, GAS score ≤60; at least one major depressive or manic episode during the 2.5 years before the current episode	In preliminary phase, patients whose acute symptoms were controlled received stable maintenance doses for 2 consecutive months. Maintenance phase lasted 2 years.
Lamotrigine			
Bowden et al., 2003 (16)	Lithium (0.8–1.1 meq/liter) (N=46) versus lamotrigine (100–400 mg/day) (N=59) versus placebo (N=70)	Current DSM-IV manic or hypomanic symptoms, manic or hypomanic symptoms within 60 days of screening visit, manic or hypomanic symptoms at enrollment and at least one additional manic or hypomanic episode and one depressed episode within 3 years of enrollment	Study consisted of a 2-week screening phase, an 8–16-week open-label phase, and a 76-week double-blind phase for patients who responded to lamotrigine.
Calabrese et al., 2003 (17)	Lithium (0.8–1.1 meq/liter) (N=121) versus lamotrigine (200–400 mg/day) (N=121) versus placebo (N=121)	At least one episode of mania, hypomania, or depression in the past 3 years; no alcohol or drug abuse within past month. Randomization criteria: CGI severity scale score ≤3 for 4 consecutive weeks, adequate medication-free period, and lithium tapering over a period >3 weeks	Outpatients with current or recent (within 60 days) DSM-IV depression were included in a 2-week screening phase, an 8–16-week open-label phase, and a 76-week double-blind trial.
Mianserin			
Coppen et al., 1978 (20)	Lithium (0.8–1.2 mol/liter) (N=20) versus mianserin (60–90 mg/day) (N=21)	Lithium clinic patients with at least three previous episodes	After 1 year in the trial, patients receiving mianserin had a dose increase to 90 mg/day and received this dose for 6 more months. More serious depressive illness was treated by ECT.
Maprotiline			
Coppen et al., 1976 (19)	Lithium (0.8–1.2 meq/liter) (N=21) versus maprotiline (150 mg/day) (N=18)	Attendence at a lithium clinic for at least 1 year, at least three previous episodes of affective disorder	In case of relapse, assessor could prescribe ECT or supportive psychotherapy as additional treatment.

Study Quality[a]				Reported Outcomes		
Allocation Concealed	Blinding	Follow-Up	Diagnosis	Deaths	Suicides	Deliberate Self-Harm[b]
Not clear	Not stated	52 weeks	Bipolar disorder	No	No	No
Not clear	Patient, rater	104 weeks	Unipolar depression	Yes[c]	Yes[c]	Yes[c]
Not clear	Open	104 weeks	Bipolar disorder, recurrent unipolar depression	No	No	No
No	Patient, rater	104 weeks	Unipolar depression, bipolar disorder	Yes	Yes	No
No	Patient, rater	104 weeks	Unipolar depression, bipolar disorder	No	Yes[c]	Yes[c]
Not clear	Not stated	76 weeks	Bipolar disorder	Yes	Yes	Yes
Not clear	Not stated	76 weeks	Bipolar disorder	Yes[c]	Yes[c]	Yes[c]
Not clear	Patient, rater	78 weeks	Recurrent unipolar depression	No	Yes[c]	Yes[c]
Not clear	Patient, rater	52 weeks	Unipolar depression, bipolar disorder	No	Yes[c]	Yes[c]

(continued)

TABLE 1. Randomized, Controlled Studies Included in a Systematic Review of the Effect of Lithium on Suicidal Behavior and All-Cause Mortality in Patients With Mood Disorders *(continued)*

Comparator and Study	Comparisons and Sample Sizes	Inclusion Criteria	Patient and Study Characteristics
Nortriptyline			
Sackeim et al., 2001 (42)	Nortriptyline (75–125 ng/ml) plus lithium (0.5–0.9 meq/liter) (N=28) versus nortriptyline (75–125 ng/ml) (N=27) versus placebo (N=29)	RDC major depressive disorder, pretreatment 24-item Hamilton depression scale score ≥21	In a study of continuation pharmacotherapy to prevent post-ECT relapse, patients who received at least five ECT treatments in an open ECT phase or fewer treatments if they responded (defined as a 60% reduction in Hamilton depression scale score and a maximum score of 10 within 2 days of ECT discontinuation and reassessment 4–8 days after ECT) were assigned to receive medication or placebo for 24 weeks.

[a] All studies except Placidi et al. (38) included intent-to-treat analyses.
[b] Includes attempted suicide.
[c] Figures confirmed by original authors.

that nonspecific effects of the close follow-up associated with lithium therapy may reduce the risk of suicide. Nonrandomized studies such as the study of Goodwin et al., however, cannot exclude fully the possibility of confounding by indication, i.e., the decision to prescribe lithium or divalproex may be influenced by other patient factors that, in turn, are associated with suicide risk (6–8).

Lithium is a drug with recognized toxicity, and suicide is just one of a number of possible causes of death in patients receiving long-term lithium treatment. It is important, therefore, to consider all-cause mortality, because of the possibility that any possible antisuicidal effect of lithium is offset by increased deaths from other causes.

To obtain an unbiased assessment of the potential antisuicidal effect—and the effects on all-cause mortality—of lithium, we conducted a systematic review and meta-analysis of the evidence from randomized trials of lithium in patients with mood disorders.

Method

Inclusion Criteria

We included randomized, controlled trials comparing lithium with placebo or all other compounds used in long-term treatment for mood disorders (unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, and rapid cycling, diagnosed according to DSM and ICD criteria). We included only long-term treatment (prophylaxis) trials. We arbitrarily defined long-term treatment as treatment with a minimum duration of 3 months.

Search Strategy

We based our search strategy on the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, incorporating results of group searches of MEDLINE (1966–June 2002), EMBASE (1980–June 2002), CINAHL (1982–March 2001), PsycLIT (1974–June 2002), PSYNDEX (1977–October 1999), and LILACS (1982–March 2001). We used the search term "lithium" and restricted the search from 1999 to 2003. The Cochrane Central Register of Controlled Trials (CENTRAL) was searched with the term "lithium" for new records entered into the database from 1999 to 2003.

To supplement the results from the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register and CENTRAL database, MEDLINE (1999–2003), EMBASE (1999–2003), PsycINFO (1999–2003), and CINAHL (1999–2003) were searched by a librarian using a modified Cochrane randomized, controlled trial filter and the following terms: (lithium or lithium carbonate or calith or camcolit* or carbolit* or ceglution or duralith or durolith or eskalith or hypnorex or hynorex or hyponrex or lentolith or licab or licarb or licarbium or lidin or lilipin or li?liquid or li-liquid or lilitin or limas or liskonum or litarex or lithan or lithane or litheum or lithicarb or lithionate or lithizine or lithobid or lithocarb or lithocap or lithonate or lithosun or lithotabs or litheril or litilent or manialit* or maniprex or phanate or phasal or plenur or priadel or quilonium or quilonorm or quilonum or teralithe or theralite) AND (mood disorders or affective disorders, psychotic or bipolar disorder or cyclothymic disorder or depressive disorder or depression, involutional or dysthymic disorder or seasonal affective disorder or affective disorders or depression, reactive or dysthymic disorder or seasonal affective disorder or affective disorders, psychotic or bipolar disorder or affective disorders or bipolar disorder or cyclothymic personality or major depression or dysthymic disorder or endogenous depression or involutional depression or reactive depression or recurrent depression or treatment resistant depression or seasonal affective disorder or schizoaffective disorder or affective neurosis or depression or dysthymia or involutional depression or manic depressive psychosis or bipolar depression or schizoaffective psychosis or depress* or bipolar or schizoaffective).

In addition, other relevant articles and major textbooks that cover mood disorders were checked. The authors of significant papers, other experts in the field, and pharmaceutical companies that manufacture lithium or the comparator drugs were contacted to identify other relevant published or unpublished randomized, controlled trials.

Outcomes

The primary outcomes were suicide, deliberate self-harm (including attempted suicide), and death from all causes in patients randomly assigned to receive lithium or another compound. All-cause mortality was specified as an outcome for several reasons. First, it is free from the variations in both definition and application of the definition that limit the reliability of suicide reports, and it includes deaths from suicide that have not been correctly classified. Second, given the known toxic effects of lithium, any reduction in suicide may be offset by an increase in deaths from other causes, and this possibility would be apparent in the comparison of all-cause mortality rates. Last, all-cause mortality includes suicide plus all other deaths, and the number of deaths from all causes must be at least as large as the number of suicides.

If lithium has a specific action in preventing suicide, one would expect it to also reduce attempted suicide and deliberate self-

Study Quality[a]				Reported Outcomes		
Allocation Concealed	Blinding	Follow-Up	Diagnosis	Deaths	Suicides	Deliberate Self-Harm[b]
Yes	Treatment team, outcome assessor, data analysts	24 weeks	Unipolar depression	Yes	Yes	No

harm. As suicide occurs too infrequently to be used as a primary outcome in individual clinical trials, use of a composite outcome of suicide plus attempted suicide/self-harm is likely to increase the event rate and, thus, power of the study (9). For example, a composite outcome of negative events, including suicide and deliberate self-harm, was used as the primary outcome in the recent International Suicide Prevention Trial, which found evidence in favor of clozapine, compared to olanzapine, in patients with schizophrenia and schizoaffective disorder (10). We therefore planned, a priori, to investigate a composite of suicide plus episodes of deliberate self-harm.

Data Extraction and Quality Assessment

Two reviewers (A.C. and J.R.G.) independently extracted data; disagreements were resolved by discussion and consensus with a third member of the team (K.H.). For each trial we identified inclusion and exclusion criteria, duration of follow-up, diagnosis, doses, and main outcome measures. We assessed the methodological quality of studies according to the criteria of the Cochrane Reviewers' Handbook (11). Crossover studies were included, but only the first phase of such trials (before crossover) was considered. For trials in which our outcomes of interest were not reported, we attempted to obtain the required data from the original authors.

Data Analysis

Data from intention-to-treat analyses were used where possible; otherwise endpoint data for trial completers were used. Deaths and self-harm are comparatively rare in clinical trials, and data were sparse. Several trials had no such events in one or more arms. Meta-analysis of sparse data can be problematic, because some methods add continuity corrections to trial arms with zero events, and these corrections may exert a substantial effect on the overall results (12). Peto's method was used to calculate odds ratios and 95% confidence intervals (CIs) because this method does not apply continuity corrections and has been shown to be the most reliable method when applied to data on sparse events from studies without extreme imbalances (12). Trials with no events in any treatment arm were excluded from the analyses because they are uninformative (12). Sensitivity analyses using other meta-analytic methods were done to assess the robustness of the results. Statistical heterogeneity, in which variation between the results of the individual trials is greater than can be explained by chance alone, was investigated with chi-square tests. Data were analyzed by using the metan routine in Stata (13).

For trials with more than two arms, we considered each pairwise comparison as if it were separate two-arm trials. For example, if a trial compared lithium with another active drug and with placebo, we included the lithium versus placebo arm and the lithium versus active drug arm as separate trials. This approach included the single lithium group twice in the meta-analysis. We therefore investigated the effect of this double counting by sensitivity analyses that excluded each of the two trials from the pooled analysis.

Results

Included Trials

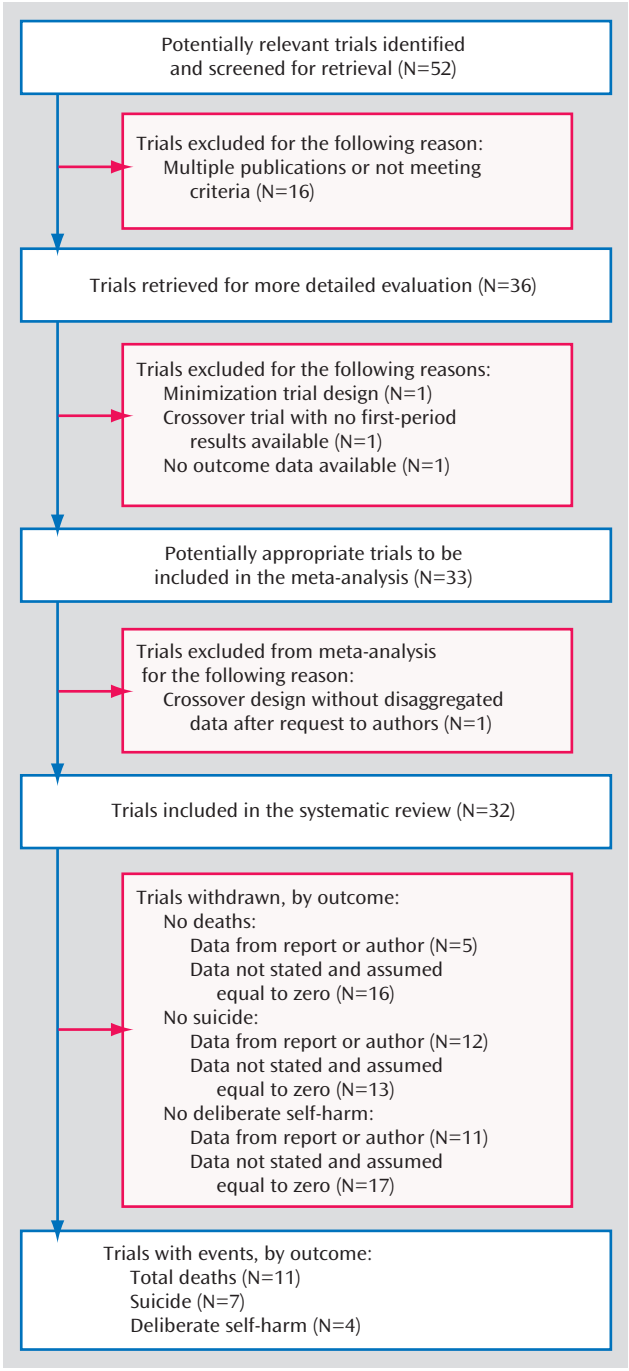
A total of 727 references were identified in the search; 52 references were marked as possibly relevant on the basis of the content of the abstract. After reading the papers and excluding duplicates, we included 32 randomized, controlled trials in the study (14–45) (summarized in Table 1; see Figure 1 for flowchart). These trials comprised 19 comparisons of lithium to placebo (14–18, 21, 23–25, 27, 31, 33–35, 37, 39–41, 45), three to amitriptyline (27, 28, 35), nine to carbamazepine (22, 28–30, 32, 36, 38, 43, 44), one to divalproex (15), one to fluvoxamine (26), three to imipramine (alone or in combination with lithium) (34, 39, 41), two to lamotrigine (16, 17), one to mianserin (20), one to maprotiline (19), and one to nortriptyline (alone or in combination) (42). There was therefore considerable clinical heterogeneity between the trials. In total, 1,389 patients were randomly assigned to receive lithium, and 2,069 were assigned to receive other compounds. The results reported here were unaffected in the sensitivity analyses that excluded trials contributing more than one comparison with lithium.

The low rates of the outcome events meant that statistical tests of heterogeneity were underpowered to detect even substantial qualitative heterogeneity. Formal statistical investigation of any heterogeneity by meta-regression was therefore not possible and was limited to sensitivity analysis and visual examination of the forest plots.

Suicide and Deliberate Self-Harm

Seven trials reported the occurrence of suicides (Figure 2) (17, 27–30, 39, 40). Two trials were informative for lithium versus placebo (39, 40), two for lithium versus ami-

FIGURE 1. Flow Diagram Showing Selection of Studies Included in a Meta-Analysis of the Effect of Lithium on Suicidal Behavior and All-Cause Mortality in Patients With Mood Disorders



triptyline (27, 28), two for lithium versus carbamazepine (29, 30), and one for lithium versus lamotrigine (17). Patients allocated to receive lithium were less likely to die by suicide (two suicides among lithium-treated patients versus 11 suicides among patient who received comparators) (Peto odds ratio=0.26, 95% CI=0.09–0.77, p=0.01) (χ^2=1.57, df=6, p=0.95, chi-square test for heterogeneity). Despite the heterogeneous comparators, there was no evidence of statistically significant variation between the results of the individual trials. Numerically fewer suicides occurred in the lithium group in all the trials except one, in which one suicide occurred in both the lithium and comparator (carbamazepine) groups (30).

Only seven deliberate self-harm events were reported (none among the lithium-treated patients, five among the carbamazepine-treated patients, one among the lamotrigine-treated patients, and one among the patients who received placebo). The difference between groups, however, was not statistically significant because of the low event rate. When suicide and deliberate self-harm events were considered together as a composite outcome (Figure 3), fewer patients who received lithium experienced this negative outcome (Peto odds ratio=0.21, 95% CI=0.08–0.50, p=0.0005) (χ^2=0.44, df=8, p=1.00, chi-square test for heterogeneity). All the trials reported fewer instances of this composite event in the lithium-treated group.

Although there was no statistically significant heterogeneity, post hoc analyses were conducted in subgroups of particular interest. No significant differences were found between the results from the placebo-controlled trials and the active comparison trials. There was no evidence of any difference between trials that included patients with unipolar depression and trials that included patients with bipolar disorder.

Mortality From All Causes

Eleven trials comprising 12 comparisons (17, 18, 24, 27–31, 39, 40, 45) contributed data that could be used in the pooled analysis of all-cause mortality. In the majority of trials there were no deaths (Figure 4). Six of the 12 trials were informative for lithium versus placebo (18, 24, 31, 39, 40, 45), three for lithium versus tricyclic antidepressants (27, 28, 39), two for lithium versus carbamazepine (29, 30), and one for lithium versus lamotrigine (17). There were fewer deaths overall among the patients who received lithium (nine versus 22, Peto odds ratio=0.42, 95% CI=0.21–0.87, p=0.02) (χ^2=4.98, df=11, p=0.93, chi-square test for heterogeneity).

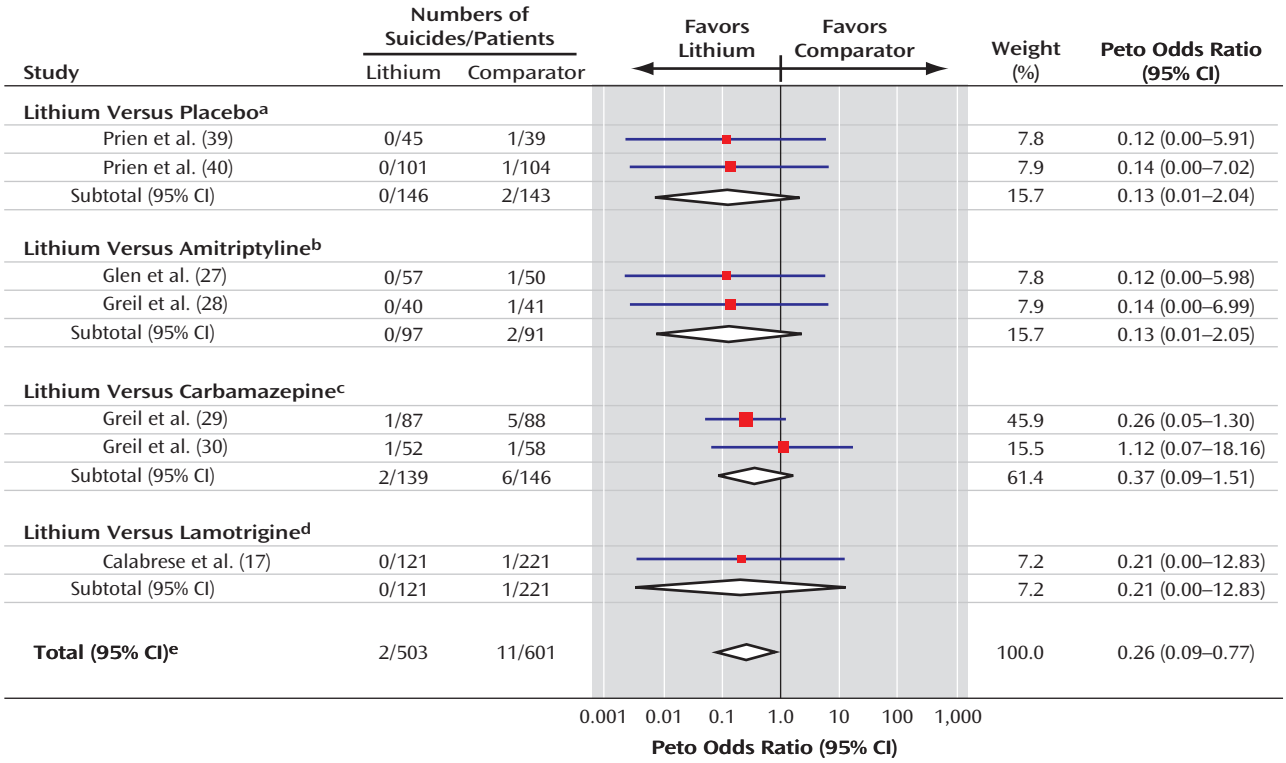
Therefore, despite the heterogeneous comparators, little statistical variation was found between the results of the individual trials. Numerically fewer deaths occurred in the lithium group in all trials, except three. In two of these trials (30, 45), the number of deaths was the same in both groups; in the other small trial (31), one death occurred in the lithium-treated group, and none occurred in the placebo group.

Again, post hoc analyses found no differences between the results from trials with placebo comparator and those with an active drug comparator or between the results from trials that included patients with unipolar depression and those that included patients with bipolar disorder.

Discussion

In this review and meta-analysis, we synthesized the available randomized evidence of the effect of lithium on

FIGURE 2. Forest Plot Showing Meta-Analysis of Suicides in Randomized Trials Comparing Lithium With Placebo or Active Comparators



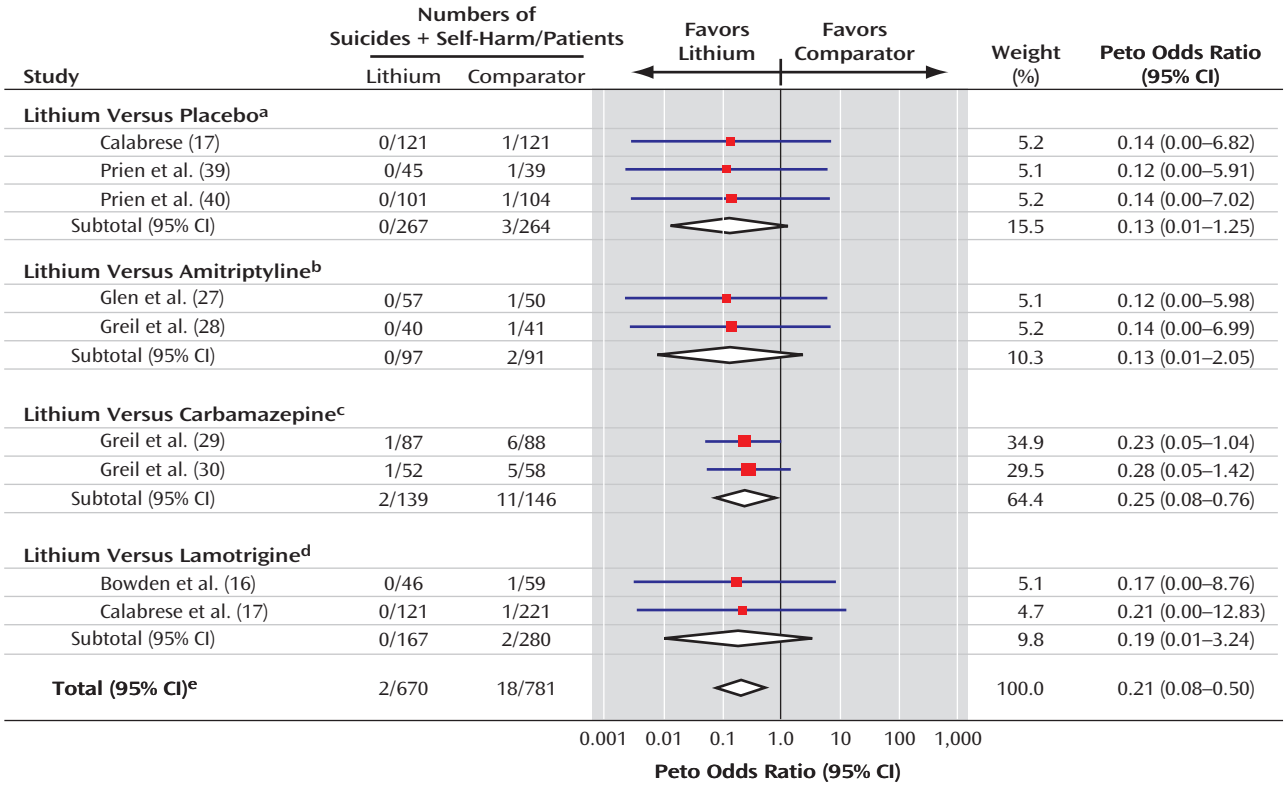
[a] Test for heterogeneity: χ^2<0.001, df=1, p=0.95; test for overall effect: z=1.46, p=0.15.
[b] Test for heterogeneity: χ^2<0.001, df=1, p=0.95; test for overall effect: z=1.45, p=0.15.
[c] Test for heterogeneity: χ^2=0.80, df=1, p=0.37; test for overall effect: z=1.38, p=0.17.
[d] Test for overall effect: z=0.74, p=0.46.
[e] Test for heterogeneity: χ^2=1.57, df=6, p=0.95; test for overall effect: z=2.43, p=0.01.

suicide, deliberate self-harm, and all-cause mortality. This work extends the findings of previous reviews because 1) it includes only randomized trials and 2) further data on deaths and causes of death were obtained from the original authors. The effect of lithium on the prevention of symptomatic relapse was not assessed, and the present findings should be considered alongside this evidence, which we reviewed previously for bipolar disorder (3). As with all quantitative reviews, the current study is subject to a number of limitations. Publication bias—caused by the tendency for trials with negative or neutral findings not to be published—can seriously limit the reliability of meta-analyses (46). It is possible that trials that failed to demonstrate an advantage for lithium over a comparator are less likely to be published. We consider this possibility particularly unlikely in recent industry-sponsored trials that have included lithium as a comparator, because any design bias in such trials could reasonably be expected to favor the investigational drug (47). However, because of the small numbers of events and small size of the trials, only one or two moderately sized trials with neutral or negative results could materially affect the estimates.

Overall, few deaths from suicide occurred in the trials included in this meta-analysis, which perhaps reflects the fact that patients judged to be at high risk of suicide are not normally recruited to randomized trials. The low numbers of events led to substantial random error and, consequently, unstable estimates of the treatment effect with wide confidence intervals. Thus, the results must be interpreted with caution because the true effect of lithium may be either smaller or greater than we estimated. However, the evidence seems unequivocal that patients treated with lithium were much less likely to die from suicide or from any cause than patients given an alternative to lithium, whether the alternative was placebo or another compound. Lithium appears to reduce the risk of death and suicide by approximately 60% and the risk of a composite of suicide and deliberate self-harm by about 70%. This substantial effect is comparable to that reported in the recent observational study by Goodwin et al. (5), although it is less than that estimated from previous nonrandomized studies (4). To our knowledge, this study provides the first demonstration with evidence from randomized trials that any treatment can reduce suicide, specifically, and mortality, in general, in psychiatric disorders.

The trials were clinically heterogeneous in terms of patients, diagnoses, and comparators, and the small numbers of events limited the power of the analysis to detect

FIGURE 3. Forest Plot Showing Meta-Analysis of Suicides Plus Deliberate Self-Harm in Randomized Trials Comparing Lithium With Placebo or Active Comparators



[a] Test for heterogeneity: χ^2<0.001, df=2, p=1.00; test for overall effect: z=1.77, p=0.08.
[b] Test for heterogeneity: χ^2<0.001, df=1, p=0.95; test for overall effect: z=1.45, p=0.15.
[c] Test for heterogeneity: χ^2=0.03, df=1, p=0.87; test for overall effect: z=2.45, p=0.01.
[d] Test for heterogeneity: χ^2=0.01, df=1, p=0.94; test for overall effect: z=1.15, p=0.25.
[e] Test for heterogeneity: χ^2=0.44, df=8, p=1.00; test for overall effect: z=3.48, p=0.0005.

any interaction between these factors and the treatment effect of lithium. Despite these limitations, the consistency of the results across trials may indicate that the life-preserving effect of lithium is independent of that of the comparator.

Long-term evidence for other agents in the prevention of relapse in bipolar disorder is very limited (48), and so the results of the current analysis may reflect a general superior efficacy of lithium for the treatment of mood disorder or may reflect a specific antisuicidal property. The consistency of the findings across comparators suggests that lithium prevents suicide rather than that any other drug increases the risk of suicide.

The reduction in the risk of all-cause mortality mainly reflects reduction in risk of suicide, because most of the deaths in the trials were suicides. However, the analysis of all-cause mortality avoids possible ascertainment bias (i.e., events in patients who take lithium may be more or less likely to be classified as suicides) and increases power (because more events are included, and there is less random error). The comparability in the relative risk reduction of both suicide and all-cause mortality also indicates that there was no increase in fatal events due to lithium. The composite of suicide plus deliberate self-harm also showed a similar effect and may be a more feasible primary outcome in future trials. That there were fewer cases of deliberate self-harm than of suicide overall may indicate that data on deliberate self-harm were not recorded systematically in these trials. Given the pattern for suicidal behavior in the general population (49), the number of patients with deliberate self-harm might be expected to be greater than the number of patients who die by suicide, although this pattern may not be present in the patient population represented in these trials. Clearly, however, if these events are underrecorded, this failure should be rectified in future trials.

In conclusion, this meta-analysis of randomized trials indicates that lithium reduces the risk of suicide in patients with mood disorders. Lithium remains the treatment with the most substantial evidence base for the prevention of relapse in bipolar disorder and should be a first-line therapy for patients with that disorder, including those at risk of suicidal behavior.

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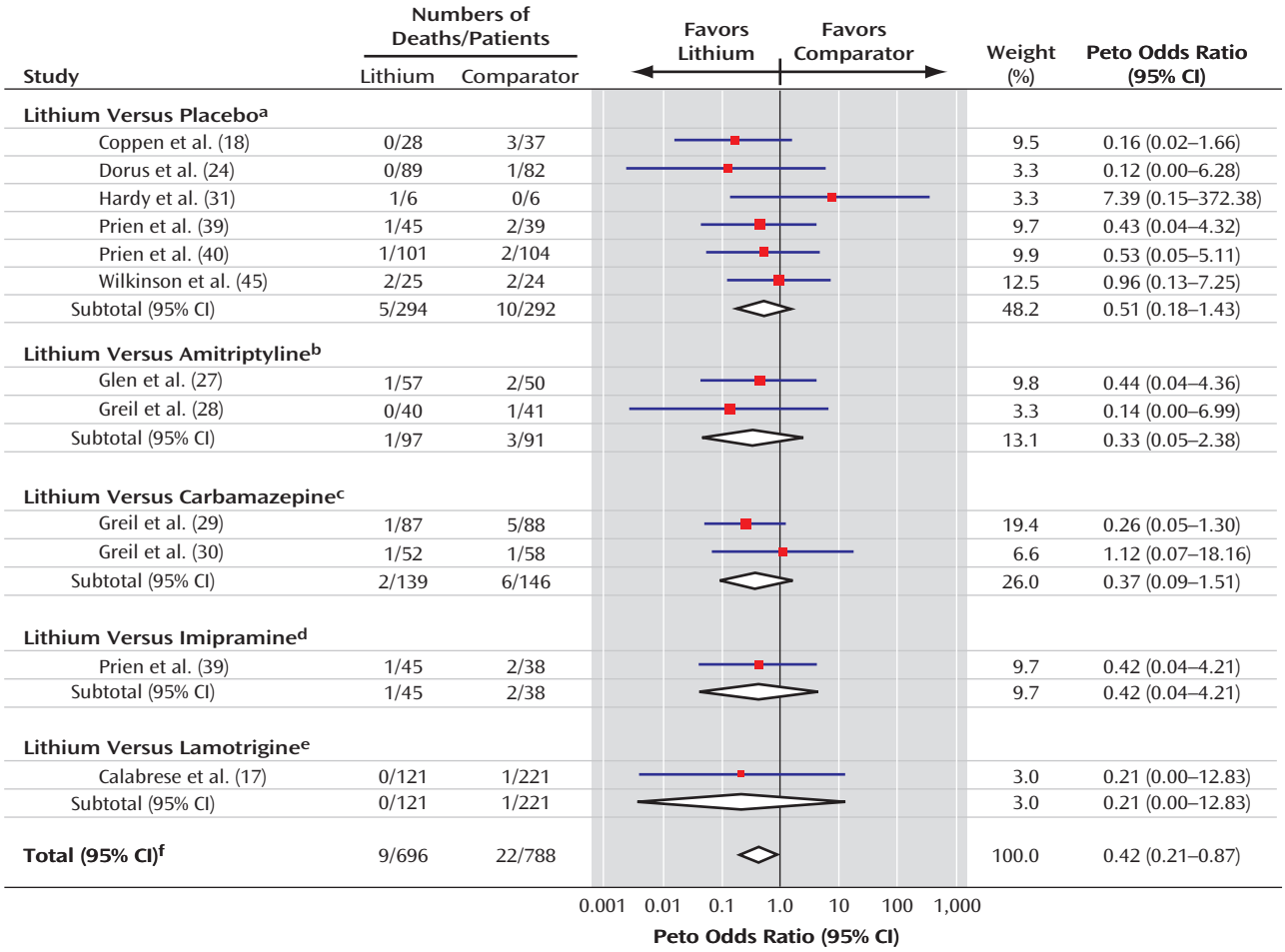
FIGURE 4. Forest Plot Showing Meta-Analysis of Deaths From All Causes in Randomized Trials Comparing Lithium With Placebo or Active Comparators



[a] Test for heterogeneity: χ^2=3.60, df=5, p=0.61; test for overall effect: z=1.28, p=0.20.
[b] Test for heterogeneity: χ^2=0.25, df=1, p=0.62; test for overall effect: z=1.10, p=0.27.
[c] Test for heterogeneity: χ^2=0.80, df=1, p=0.37; test for overall effect: z=1.38, p=0.17.
[d] Test for overall effect: z=0.74, p=0.46.
[e] Test for overall effect: z=0.74, p=0.46.
[f] Test for heterogeneity: χ^2=4.98, df=11, p=0.93; test for overall effect: z=2.35, p=0.02.

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