BMJ

BMJ 2013;346:f3646 doi: 10.1136/bmj.f3646 (Published 27 June 2013)

RESEARCH

Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis

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Abstract

Objective To assess whether lithium has a specific preventive effect for suicide and self harm in people with unipolar and bipolar mood disorders.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, CINAHL, PsycINFO, CENTRAL, web based clinical trial registries, major textbooks, authors of important papers and other experts in the discipline, and websites of pharmaceutical companies that manufacture lithium or the comparator drugs (up to January 2013).

Inclusion criteria Randomised controlled trials comparing lithium with placebo or active drugs in long term treatment for mood disorders.

Review methods Two reviewers assessed studies for inclusion and risk of bias and extracted data. The main outcomes were the number of people who completed suicide, engaged in deliberate self harm, and died from any cause.

Results 48 randomised controlled trials (6674 participants, 15 comparisons) were included. Lithium was more effective than placebo in reducing the number of suicides (odds ratio 0.13, 95% confidence interval 0.03 to 0.66) and deaths from any cause (0.38, 0.15 to 0.95). No clear benefits were observed for lithium compared with placebo in preventing deliberate self harm (0.60, 0.27 to 1.32). In unipolar depression, lithium was associated with a reduced risk of suicide (0.36, 0.13 to 0.98) and also the number of total deaths (0.13, 0.02 to 0.76) compared with placebo. When lithium was compared with each active individual treatment a statistically significant difference was found only with carbamazepine for deliberate self harm. Lithium tended to be generally better than the other active comparators, with small statistical variation between the results.

Conclusions Lithium is an effective treatment for reducing the risk of suicide in people with mood disorders. Lithium may exert its antisuicidal effects by reducing relapse of mood disorder, but additional mechanisms should also be considered because there is some evidence that lithium decreases aggression and possibly impulsivity, which might be another mechanism mediating the antisuicidal effect.

Introduction

Mood disorders are a leading cause of global disability, with a lifetime prevalence in the United States of 31.4%.[1-3] The two main subtypes of mood disorder are unipolar (depressive episodes only) and bipolar disorder (mania or hypomania, usually with intermittent depressive episodes).[4] The risk of suicide is between 6% and 10%, 10 times higher than in the non-psychiatric population, and reaching a level of 26% in men admitted to psychiatric hospital with bipolar disorder and a history of deliberate self harm.[5 6]

Medication plays a relatively minor role in most suicide prevention strategies[7 8] although its place may have been underestimated.[9] We previously reported that long term lithium reduced the risk of suicide in mood disorders compared with placebo or other drugs.[10] The low numbers of events and consequent imprecise estimates of the treatment effect left residual uncertainty about the effect of lithium in preventing suicide and the extent to which it occurs in both unipolar and bipolar disorder.[11] Further studies have now been published and here we report updated and extended analyses on the antisuicidal effects of lithium.

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Appendix 1: protocol and search strategy
Appendix 2: references to included studies
Appendix 3: risk of bias
Appendix 4: preplanned sensitivity analyses
Appendix 5: Post hoc sensitivity analyses

Methods

Two researchers (AC, JRG or KH) independently identified all randomised trials (double blind, single blind, or open) comparing lithium with placebo or all other compounds used in the long term treatment for mood disorders (unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, and rapid cycling, diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* or the international classification of diseases criteria). We defined long term treatment as treatment with a minimum duration of at least three months (>12 weeks). We also included combination studies (when drugs of the same class, for instance antipsychotic plus antipsychotic, were combined) and augmentation studies (when drugs belonging to different classes, for instance antipsychotic plus mood stabiliser, were combined). The participants were both males and females, without age limits (children, adolescents, and adults, including elderly people). We allowed both fixed and flexible dose designs. We excluded only studies recruiting participants with a serious concomitant medical illness as an inclusion criterion. Full details on the review methods have been reported in the review protocol, posted on our institutional website before carrying out any analyses (http://cebmh.warne.ox.ac.uk/csr/Lithium%20SR_UPDATE_protocol.pdf; see also appendix 1).

To identify relevant studies we searched Medline, PreMedline, Embase, CINAHL, PsycINFO, LILACS, and the Cochrane Central Register of Controlled Trials from the inception of the databases up to January 2013. We also searched the trial databases of the US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency, the European Medicines Agency, and the Australian Therapeutic Goods Administration for published or unpublished studies. Trial registers were hand searched for published, unpublished, and ongoing randomised controlled trials involving lithium. No language restrictions were applied. Full details on the search strategy are reported in appendix 1. To supplement any incomplete reporting in the original papers or to provide data for old or unpublished studies we contacted all study authors and principal manufacturers. We also checked the websites of the manufacturers for further studies. To assess study quality we used the Cochrane risk of bias tool as a reference guide.[12]

Outcome measures

The main outcomes were suicide events, deliberate self harm events, and all cause mortality. We defined deliberate self harm as a non-fatal outcome in which an individual deliberately initiated behaviour (such as self cutting) or ingested a toxic substance or object with the intention of causing harm to himself or herself, irrespective of motivation.[13] In deliberate self harm the intention to end life may be absent or present to a variable degree.[14] Deliberate self harm is a global health problem[15 16] and is one of the strongest predictors of completed suicide.[17] We did not include suicidal ideation on its own as an outcome.

All cause mortality is free from the variations in both definition and application of the definition that limit the reliability of suicide reports,[10] and also because, given the known toxic effects of lithium,[18] any reduction in suicide might be offset by an increase in deaths from other causes.

Statistical analysis

Where possible we used data from intention to treat analyses; otherwise we used endpoint data for participants who completed the trial. We used Peto's method to calculate odds ratios and 95% confidence intervals because it 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.[18 19] We excluded trials with no events in any treatment arm from the analyses as uninformative. Data were analysed using RevMan 5.1. For trials with more than two arms, we considered each pairwise comparison as if it was a separate trial with two arms.

In the main analyses, we did not combine comparators but did analyses of single head to head comparisons. Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I^2 statistic. This statistic provides an estimate of the percentage of variability due to heterogeneity rather than due to a sampling error.[20] To assess evidence of heterogeneity we used a P value higher or equal to 0.05 from a standard test for heterogeneity.

Sensitivity analyses

We planned two sensitivity analyses: restricting to studies in people with unipolar disorder (studies with at least two third of participants with unipolar depression were eligible) and restricting to studies in which only people aged less than 18 years were recruited.

Results

The electronic searches yielded 1491 potentially relevant studies. On inspection of titles and abstracts, 116 potentially eligible articles were retrieved and full text analysed. We excluded 69 reports that did not meet eligibility criteria and one further unpublished trial was identified from searching websites of trial registers. In total, 48 published trials between 1968 and 2013 were included in the systematic review (fig 1⇓). See appendix 2 for study references.

In addition to placebo, 14 other comparator treatments for lithium were included: amitriptyline, carbamazepine, valproate (including divalproex), fluoxetine, fluvoxamine, imipramine, lamotrigine, mianserin, maprotiline, nortriptyline, olanzapine, phenelzine, quetiapine, and thyroid hormone. Most trials (30 out of 48, 63%) were two arm studies and the rest were three arm or four arm studies where a placebo controlled arm was always present. The reporting of the earlier studies was less rigorous and the designs more heterogeneous than those conducted since the 1990s. In some studies the treating doctor could prescribe additional treatment with lithium or other investigational drugs (or placebo), if indicated. Twelve trials included only participants with unipolar depression and 19 trials included only participants with bipolar disorder; the remaining 17 studies included a mix of participants with bipolar, unipolar, or schizoaffective disorder (table⇓). In 20 of 48 studies (42%) lithium was compared with placebo or one active treatment (amitriptyline, carbamazepine, divalproex, imipramine, lamotrigine, olanzapine, phenelzine, and quetiapine) and reported at least one deliberate self harm event or death. The mean duration of follow-up was 19.1 (SD 7.2) months (range 4-48 months). Overall, 6674 patients were randomised to one of the active agents or placebo and were included in the meta-analysis: 4246 patients contributed to the analysis of suicide or deliberate self harm and 2515 to the analysis of all cause mortality. Comparison between lithium and placebo was most frequently reported (23 studies), with 485 patients assessed for suicide, 1231 for deliberate self harm, and 782 for all cause mortality (25.7%, 36.7%, and 31.1% of the overall analysed sample, respectively). Among the studies included in the meta-analysis, eight were long term randomised controlled trials enriched by selecting patients who responded to an open label

acute phase (see table). Supplementary unpublished information was obtained from the study investigators for 36 (75%) of the included studies. The overall quality of most studies was rated as good, despite the authors of some not reporting full details about randomisation and allocation concealment, and there was only a few randomised controlled trials at low risk of bias in each question based entry (see appendix 3 for risk of bias graph and risk of bias summary figure).

Lithium versus placebo

Lithium was more effective than placebo in reducing the number of suicides (Peto odds ratio 0.13, 95% confidence interval 0.03 to 0.66; fig 2⇓) and deaths from any cause (0.38, 0.15 to 0.95; fig 4). Lithium showed less clear benefits in preventing deliberate self harm than placebo (0.60, 0.27 to 1.32; fig 3⇓). In all the analyses statistical heterogeneity was not detected and I^2 was 0%.

Lithium versus active drugs

The difference in risk of suicides (fig 2) or deaths from any cause between lithium and each active treatment was not statistically significant (fig 4⇓). Lithium was more effective than carbamazepine in reducing the number of deliberate self harm episodes (Peto odds ratio 0.14, 95% confidence interval 0.02 to 0.83; fig 3). Comparative data were sparse but despite this and the heterogeneous range of drugs, lithium was generally better than active comparators, with low statistical heterogeneity between the results.

Sensitivity analyses

Lithium reduced the risk of suicide (0.13, 0.02 to 0.76; fig 5⇓) and all cause mortality (0.36, 0.13 to 0.98; fig 6⇓) compared with placebo in studies of participants with unipolar depression. No statistically significant differences were found for deliberate self harm (see appendix 4). We also carried out a sensitivity analysis, including only the studies of participants with bipolar disorder: the results did not change materially (see appendix 4). It was not possible to carry out the planned sensitivity analysis on children and adolescents because no events of interest were reported in the only two studies included in which participants aged less than 18 years were randomised (Pavuluri et al 2004, Findling et al 2005—see appendix 2 for references to included studies). To conduct a comparison between lithium and drug classes (namely antidepressants, anticonvulsants, and antipsychotics) we carried out a third sensitivity analysis, not prespecified in our review protocol. We found statistically significant results in favour of lithium versus anticonvulsants for deliberate self harm (see appendix 5).

Discussion

This updated synthesis of the evidence for the effectiveness of lithium in preventing suicide and suicidal behaviour identified 16 more randomised trials not included in the previous review, eight of which contributed new data.[10] The number of events was increased by 55% and the total number of participants by 70%. Lithium was associated with a reduced risk of suicide when compared with placebo, and also a reduced risk of deliberate self harm compared with carbamazepine. Our findings are in line with other previous observational studies,[21-24] but they extend the applicability and the strength of the available information. A new finding is that lithium reduces the risk of suicide and total deaths in people with both unipolar and bipolar depressive disorder.

Strengths and limitations of this review

The main limitation of the review is the quantity of the primary evidence. The sample size of most included studies (29 out of 48, 60%) was fewer than 100 participants, with overall few suicide and deliberate self harm events. The low event rate may reflect the fact that usually people judged to be at high risk of suicide are not normally recruited into randomised trials.[25] There was therefore substantial random error and consequent unstable estimates of treatment effect with wide confidence intervals.

Publication bias might be particularly important in a review including studies with small numbers of events and small size of the trials, because only one or two moderately sized trials with neutral or negative results could materially affect the estimates.[26] We systematically contacted study authors and pharmaceutical companies asking for additional unpublished material. Unpublished information was obtained for most of the studies included in the review, which was especially important for deliberate self harm.

Trials included in the present review were clinically heterogeneous in terms of participants, diagnoses, comparators, study durations, and phase of illness. This may indicate a common effect in heterogeneous patient groups, although the small numbers of events and low power limited our ability to detect any interaction between these factors and the treatment effect of lithium.

Lithium seems to reduce the risk of death and suicide by more than 60% compared with placebo. The consistency of the results across trials may indicate that the life preserving effect of lithium is independent of the nature of the comparator. The reduction in the risk in all cause mortality mainly reflects a reduction in risk of suicide, because most of the deaths in the trials were from suicides. However, the analysis of all cause mortality avoids possible ascertainment bias (that is, events in people 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 with lithium.

Implication for research

Lithium is an effective long term treatment for both bipolar[27 28] and unipolar mood disorders.[29 30] A parsimonious explanation for its antisuicidal effects is that it is mediated by reducing relapse of mood disorder. However, alternative mechanisms should be considered because lithium is not as potent in acute phase therapy as other antidepressants,[30 31] which, in turn, do not seem to have similar antisuicidal efficacy.[32] The antisuicidal effect estimated here is larger than the effect on mood episodes,[27 28] raising the possibility of a specific effect.[33] Possible mechanisms include an effect on aggression or impulsivity, both of which are associated with an increased risk of suicide.[32 34] Lithium may decrease aggression and possibly impulsivity,[35] which might mediate its antisuicidal effect. Similarly, several genes have been found to be associated with suicidal behaviour[36] and abnormalities in the serotonin system in suicide attempters and completers have suggested a biological basis for suicidal behaviour.[37] Understanding the mechanism by which lithium acts to decrease suicidal behaviour could lead to a better understanding of the neurobiology of suicide.

Implications for practice

People treated for an affective disorder have a 30 times greater risk of suicide than the general population, and the evidence that lithium reduces the risk of suicide and possibly deliberate

self harm in people with bipolar disorder and recurrent unipolar depression indicates that lithium should continue to have an important clinical role. Although lithium has several side effects that are of particular concern to clinicians and patients,[13 30] a recent review indicated that the tolerability profile of lithium may be more favourable than is often thought. None the less, lithium therapy is associated with an increased risk of reduced ability to concentrate urine and reduced renal function, hypothyroidism, hyperparathyroidism, and weight gain.[18] Adverse effects are likely to be dose related and the oral dose of lithium and plasma concentrations need monitoring to ensure both optimum efficacy and adequate tolerability.[38] Clinical decision making will need to take a balanced view of the likely benefits and harm of lithium in the individual patient.

We thank the following authors for their help in retrieving or providing additional information on included or excluded studies: Jay Amsterdam, Michael Bauer, Joseph Calabrese, Alec Coppen, David Dunner, Gary Evoniuk, Grace Fischer, Waldemar Greil, Victoria Grochocinski, Erwin Hartong, Nikolaus Kleindienst, Rob Kok, David Kupfer, Erik Lauterback, Rasmus Licht, Lauren Marangell, Bruno Mueller-Oerlinghausen, Andrew Nierenberg, Willem Nolen, Maria Oquendo, Jan-Otto Ottosson, Mani Pavuluri, Fredric Quitkin, Dennis Revicki, Mogens Schou, Mary Beth Serrano, Trisha Suppes, Mauricio Tohen, Eduard Vieta, and David Wilkinson. We also thank Jacqueline Griswold, Michael Brandon Gastineau, Vivian Shelley, and Juan-Carlos Gomez of the Eli Lilly and company for providing additional information on olanzapine. Other pharmaceutical companies were contacted but did not reply. KH and JRG are senior investigators for the National Institute for Health Research.

Contributors: AC, KH, and JRG conceived and designed the review. AC, KH, SS, and JRG identified and acquired reports of trials and extracted data. AC, KH, and JRG contacted authors of trials and pharmaceutical industries for additional information. AC analysed and interpreted the data. KH and JRG provided statistical advice and interpreted the results. AC drafted the report. KH, SS, and JRG critically reviewed the report. All authors saw and approved the final version of the report. No drug manufacturing companies were involved in the design of this study, nor in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the report for publication. Drug companies were only involved in providing unpublished data or unpublished analyses of published data.

Funding: None.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; JRG currently receives research funding from the UK Medical Research Council, UK Economic and Social Research Council, the National Institute for Health Research, and the Stanley Medical Research Institute. He was expert witness for Dr Reddys Laboratories and is chief investigator on the Comparative Evaluation of QUEtiapine-Lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in people with bipolar depression: a 2×2 factorial randomised trial (CEQUEL) to which GlaxoSmithKline have contributed and supplied investigational drugs; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: The technical appendix, statistical code, and dataset are available from the corresponding author at andrea.cipriani@psych.ox.ac.uk

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Accepted: 30 May 2013

Cite this as: *BMJ* 2013;346:f3646

What is already known on this topic

- All psychiatric disorders are associated with an increased risk of suicide, but the risk is highest in mood disorder
- Although drugs play a relatively minor role in most suicide prevention strategies, the role of psychotropics in suicide prevention has been underestimated
- Whether lithium has a specific preventive effect for both suicide and self harm and whether this is found in unipolar depression as well as bipolar disorder remains uncertain

What this study adds

- This updated systematic review reinforces lithium as an effective agent to reduce the risk of suicide in people with mood disorders
- This meta-analysis of randomised evidence found lithium to be protective against suicide in people with unipolar depressive disorder
- Lithium has an enduring role in the treatment of mood disorders, with a possible specific indicated use in people at risk of deliberate self harm or suicide

Table

Table 1| Characteristics of studies included in the systematic review

Study*, region	Diagnosis	Follow-up (weeks)	Enrichment design	Age (setting)	Comparisons			
					Name	No of particpants	Blood level/dose	Other drugs
Amsterdam 2010, United States	Bipolar II disorder	50	Yes	≥18 years (outpatients)	Lithium, fluoxetine, placebo	26, 28, 27	0.5-01.5 mEq/L, 10-40 mg/d, —	Short term benzodiazepines or trazodone
Baastrup 1970, Europe	Bipolar disorder, recurrent unipolar depression	22	Yes	≥18 years (outpatients)	Lithium, placebo	45, 39	0.6-1.5 mEq/L, —	Unclear
Bauer 2000, Europe	Major depressive disorder	20	Yes	≥18 years (outpatients)	Lithium, placebo	14, 15	0.5-1.0 mEq/L, —	Unclear
Bowden 2000, United States	Bipolar disorder	52	No	18 to 75 years (outpatients)	Lithium, divalproex, placebo	91, 187, 94	0.8-1.2 mEq/L, 71-125 mg/L, —	Rescue medication only
Bowden 2003, Canada, Europe, United States	Bipolar I disorder	76	Yes	≥18 years (unclear)	Lithium, lamotrigine, placebo	46, 59, 70	0.8-1.1 mEq/L, 100-400 mg/d, —	Rescue medication only
Calabrese 2003, Canada, Europe, United States	Bipolar I disorder	78	Yes	≥18 years (outpatients)	Lithium, lamotrigine, lamotrigine, lamotrigine, placebo	121, 50, 124, 47, 121	0.8-1.1 mEq/L, 50 mg/d, 200 mg/d, 400 mg/d, —	Rescue medication only
Calabrese 2005, United States	Bipolar I or II disorder, rapid cycling	88	No	≥18 years (outpatients)	Lithium, divalproex	32, 28	0.92 mEq/L (mean dose), 77 mg/L (mean dose)	Lorazepam or alprazolam
Coppen 1971, Europe	Bipolar disorder, unipolar depression	112	No	Unclear (inpatients and outpatients)	Lithium, placebo	28, 37	0.8-1.2 mEq/L, —	Any other therapy allowed
Coppen 1976, Europe	Bipolar disorder, recurrent unipolar depression	52	Yes	≥18 years (outpatients)	Lithium, maprotiline	21, 18	0.8-1.2 mEq/L, 150 mg/d	Electroconvulsive therapy or supportive psychotherapy
Coppen 1978, Europe	Unipolar depression	78	No	≥18 years (outpatients)	Lithium, mianserin	20, 21	0.8-1.2 mEq/L, 60-90 mg/d	Rescue medication and supportive psychotherapy
Coppen 1981, Europe	Unipolar depression	52	No	33 to 73 years (outpatients)	Lithium placebo	18, 20	0.8-1.2 mEq/L, —	Nitrazepam or triazolam
Coxhead 1992, Europe	Bipolar disorder	52	No	18 to 65 years (outpatients)	Lithium, carbamazepine	16, 15	0.6-1.0 mEq/L, 38-51 mmol/L	Only temazepam
Cundall 1972, Europe	Bipolar disorder, recurrent unipolar depression	52	Yes	≥18 years (outpatients)	Lithium, placebo	9, 9	0.5-1.2 mEq/L, —	Unclear
Dorus 1989, United States	Unipolar depression, alcoholism	52	No	Unclear (outpatients)	Lithium, placebo	89, 82	600–1200 mg/d, —	Psychotherapy
Fieve 1976, United States	Bipolar disorder, unipolar depression	208	No	≥18 years (outpatients)	Lithium, placebo	38, 43	0.7-1.2 mEq/L, —	Unclear
Findling 2005, United States	Bipolar I or II disorder	76	No	5 to 17 years (outpatients)	Lithium, divalproex	30, 30	0.6-1.2 mEq/L, 50-100 mg/L	Adjunctive antidepressants or antipsychotics
Franchini 1994, Europe	Unipolar depression	104	No	18 to 65 years (outpatients)	Lithium, fluvoxamine	32, 32	0.5-0.9 mEq/L, 200 mg/d	Unclear
Geddes 2010, Europe, United States	Bipolar disorder	104	No	≥18 years (inpatients and outpatients)	Lithium, divalproex	110, 110	0.4-1.0 mEq/L, 750-1250 mg/d	Non-investigational co-therapies could be continued
Glen 1984, Europe	Unipolar depression	128	No	25 to 65 years (unclear)	Lithium, amitriptyline	57, 50	Up to 1.2 mEq/L, 75-100 mg/d	Rescue medication only

(continued)

Study*, region	Diagnosis	Follow-up (weeks)	Enrichment design	Age (setting)	Comparisons			Other drugs
					Name	No of particpants	Blood level/dose	
Greil 1996, Europe	Unipolar depression	128	No	18 to 65 years (outpatients)	Lithium, amitriptyline	40, 41	0.4-0.8 mEq/L, 75-100 mg/d	Additional medication, if needed
Greil 1997a, Europe	Bipolar disorder	128	No	18 to 65 years (outpatients)	Lithium, carbamazepine	87, 88	0.4-0.8 mEq/L, 4-12 mg/L	Additional medication, if needed
Greil 1997b, Europe	Schizoaffective disorder	128	No	18 to 65 years (outpatients)	Lithium, carbamazepine	52, 58	0.58 mEq/L (mean dose), 6.4 mg/L (mean dose)	Additional medication, if needed
Hardy 1997, Canada	Unipolar depression	104	Yes	≥ 65 years (outpatients)	Lithium, placebo	6, 6	Dose unclear	Antidepressants
Hartong 2003, Europe	Bipolar disorder	104	No	≥ 18 years (outpatients)	Lithium, carbamazepine	44, 50	0.6-1.0 mEq/L, 6-10 mg/L	Benzodiazepines
Hullin 1972, Europe	Bipolar disorder, unipolar depression, schizoaffective disorder	26	Yes	Unclear (outpatients)	Lithium, placebo	18, 18	Up to 1.6 mEq/L, —	Unclear
Kane 1982†, United States	Bipolar disorder, unipolar depression	104	No	18 to 65 years (outpatients)	Lithium, imipramine, placebo	11, 11, 13	0.8-1.2 mEq/L, 100-150 mg/d, —	Unclear
Kok 2007, Europe	Major depressive disorder	104	No	≥60 years (inpatients)	Lithium, phenelzine	15, 14	0.6-1.2 mEq/L, 15-60 mg/d	Benzodiazepines or antipsychotics
Laurell 1968, Europe	Bipolar disorder, unipolar depression	39	No	Unclear	Lithium, amitriptyline, placebo	4, 6, 6	900 mg/d, 75 mg/d, —	Unclear
Lauterbach 2008, Europe	Depressive disorders	52	No	≥18 years (inpatients)	Lithium, placebo	84, 83	0.6-0.8 mEq/L, —	After recruitment individuals continued to be treated according to their doctor's choice
Licht 2010, Europe	Bipolar I disorder	52	No	≥18 years (inpatients)	Lithium, lamotrigine	78, 77	0.5-1.0 mEq/L, 100-400 mg/d	Benzodiazepines allowed throughout the, study
Lusznat 1988, Europe	Bipolar disorder, schizoaffective disorder	52	No	17 to 64 years (inpatients)	Lithium, carbamazepine	27, 27	0.6-1.4 mEq/L, 6-12 mg/L	Benzodiazepines, antidepressants, or antipsychotics, if necessary
Melia 1970, Europe	Recurrent affective disorder	104	Yes	23 to 72 years (outpatients)	Lithium, placebo	9, 9	500-1500 mg/d, —	Rescue medication only
Nierenberg 2006, United States	Major depressive disorder	14	No	18 to 75 years (outpatients)	Lithium, triiodothyronine	69, 73	Up to 900 mg/d, up to 50 µg/d	Anxiolytics,, hypnotics, or trazodone were permitted
Nierenberg 2009, United States	Bipolar I or II disorder	26	No	≥18 years (outpatients)	Lithium, no treatment	284 (experimental)	300–600 mg/d (or more)	Unclear
Oquendo 2011, United States	Bipolar disorder	78	No	18 to 75 years (outpatients)	Lithium, divalproex	49, 49	0.6-1.0 mEq/L, 45-125 mg/L	Antidepressant or antipsychotics as rescue medication
Pavuluri 2004, United States	Bipolar disorder	26	No	5 to 18 years (outpatients)	Lithium, divalproex	17, 20	0.6-1.0 mEq/L, 50-120 mg/L	Risperidone as add-on
Placidi 1986, Europe, United States	Unipolar depression, bipolar disorder,schizoaffective disorder	156	No	≥18 years (inpatients and outpatients)	Lithium, carbamazepine	41, 42	300-1200 mg/d, 400-1600 mg/d	Rescue medication only
Prien 1973a*, United States	Unipolar depression, bipolar disorder	104	Yes	18 to 60 years (outpatients)	Lithium, imipramine, placebo	45, 39, 38	0.8 mEq/L (mean dose), 125 mg/d (mean dose), —	Unclear
Prien 1973b, United States	Bipolar disorder	104	Yes	18 to 60 years (outpatients)	Lithium, placebo	101, 104	0.7 mEq/L (mean dose), —	Unclear

(continued)

Study*, region	Diagnosis	Follow-up (weeks)	Enrichment design	Age (setting)	Comparisons			Other drugs
					Name	No of particpants	Blood level/dose	
Prien 1984*, United States	Unipolar depression, bipolar disorder	104	Yes	21 to 60 years (in and outpatients)	Lithium, imipramine, placebo	79, 75, 34	0.6-0.9 mEq/L, 75–150 mg/d, -	Unclear
Revicki 2005, United States	Bipolar disorder	52	No	≥18 years (outpatients)	Lithium, divalproex	109, 112	900-1200 mg/d, 15-20 mg/kg/d	Rescue medication only
Sackeim 2001, United States	Major depression	24	No	≥18 years (unclear)	Lithium, nortriptyline, placebo	28, 27, 29	0.5-0.9 mEq/L, 75-125 ng/mL, —	Unlcear
Simhandl 1993, Europe	Unipolar depression, bipolar disorder	104	No	18 to 75 years (outpatients)	Lithium, carbamazepine, carbamazepine	26, 30, 28	0.6-0.8 mEq/L, 15-25 mmol/L, 28-40 mmol/L	Rescue medication only
Suppes 2008, United States	Bipolar II disorder	16	No	18 to 65 years (outpatients)	Lithium, lamotrigine	54, 48	0.8-1.2 mEq/L, 200-400 mg/d	Short term benzodiazepines
Tohen 2005, Africa, Australia, Canada, Europe, United States	Bipolar I disorder	52	Yes	≥18 years (in and outpatients)	Lithium, olanzapine	214, 217	0.6-1.2 mEq/L, 5-20 mg/d	Benzodiazepines or antipsychotics were allowed
Watkins 1987, Europe	Unipolar depression, bipolar disorder	52	No	≥65 years (outpatients)	Lithium, carbamazepine	18, 19	0.4-0.9 mEq/L, 5-12 mg/L	Antimanic or antidepressant drugs
Weisler 2011, Asia, Europe, United States	Bipolar I disorder	104	Yes	≥18 years (outpatients)	Lithium, quetiapine, placebo	418, 404, 404	0.6-1.2 mEq/L, 300-800 mg/d, —	Benzodiazpines, hypnotics, or anticholoinrgics were permitted
Wilkinson 2002, Europe	Unipolar depression	104	No	≥65 years (outpatients)	Lithium, placebo	25, 24	0.3-0.7 mEq/L, —	Antidepressants

*See appendix 2 for references of included studies.

†Lithium plus imipramine arm also in study, which used same dose regimens as monotherapy arms.

Figures

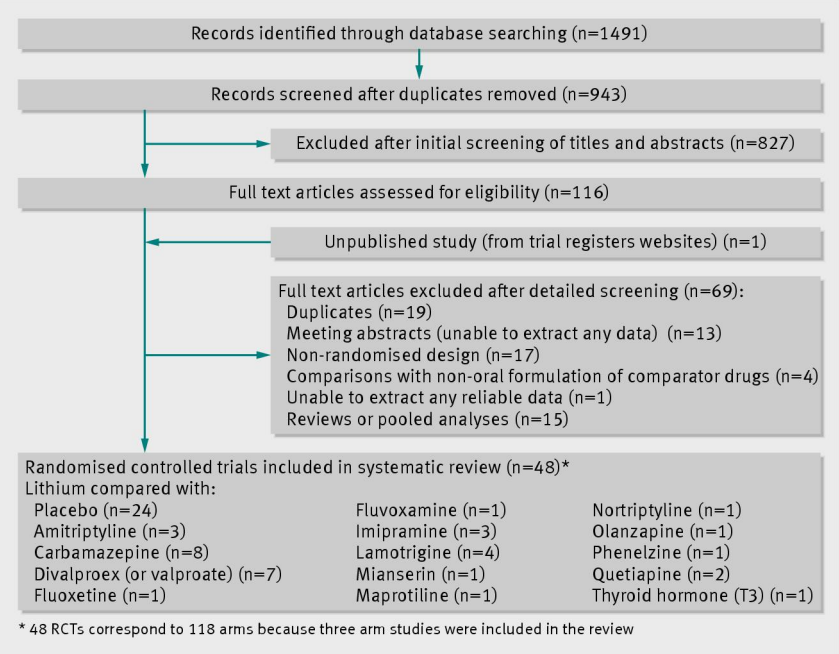


Fig 1 Included and excluded studies

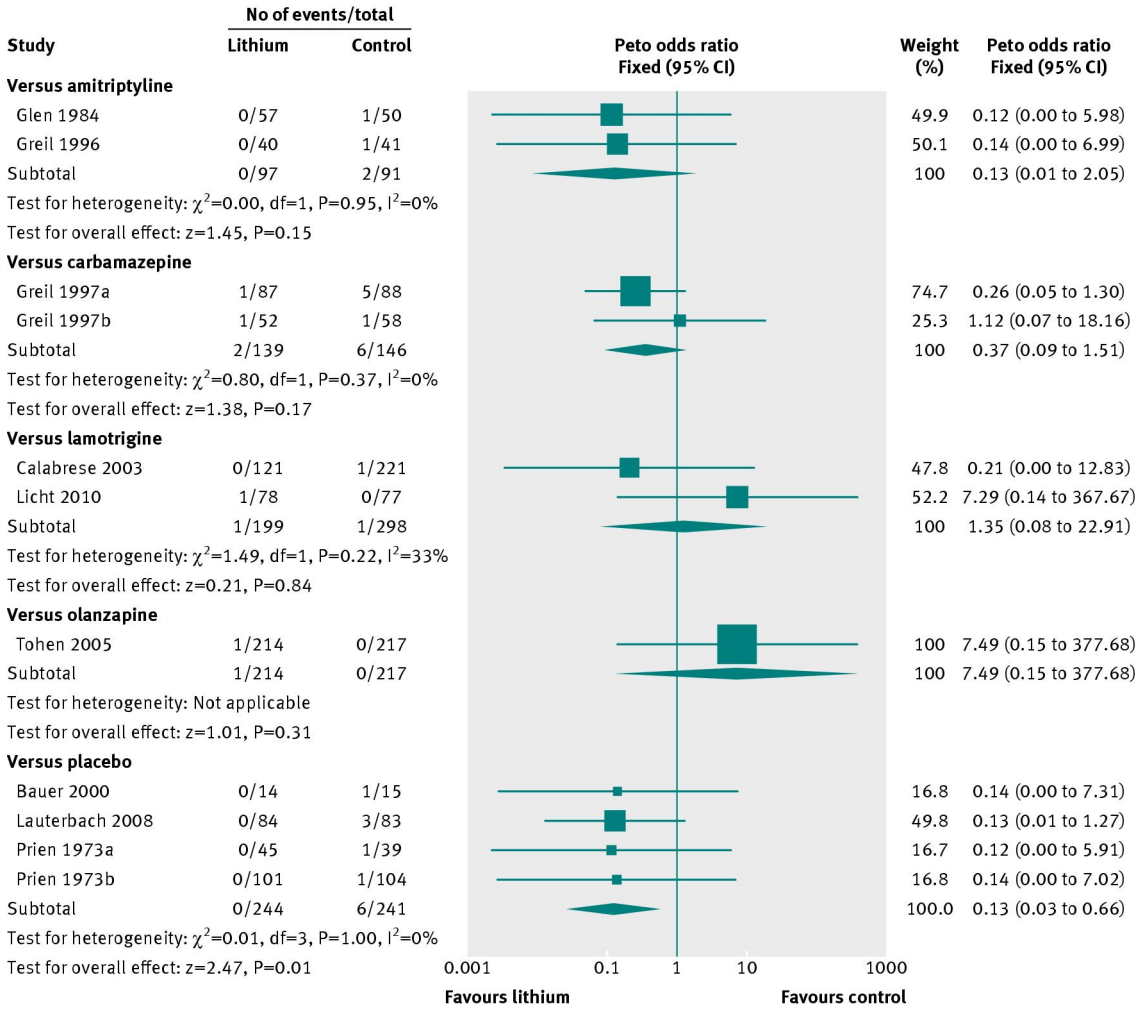


Fig 2 Forest plot showing meta-analysis of suicides in randomised trials comparing lithium with placebo or with active comparators

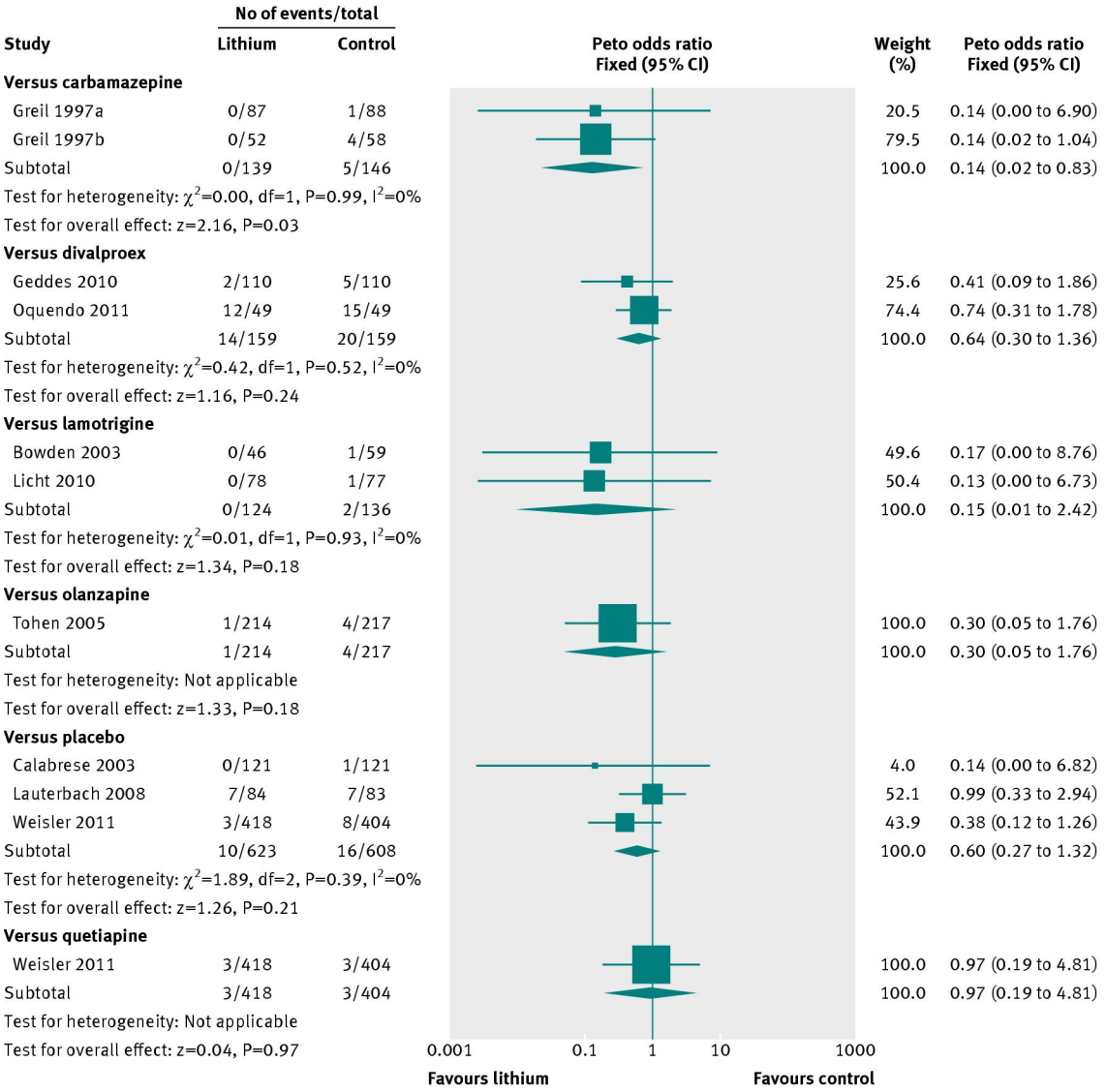
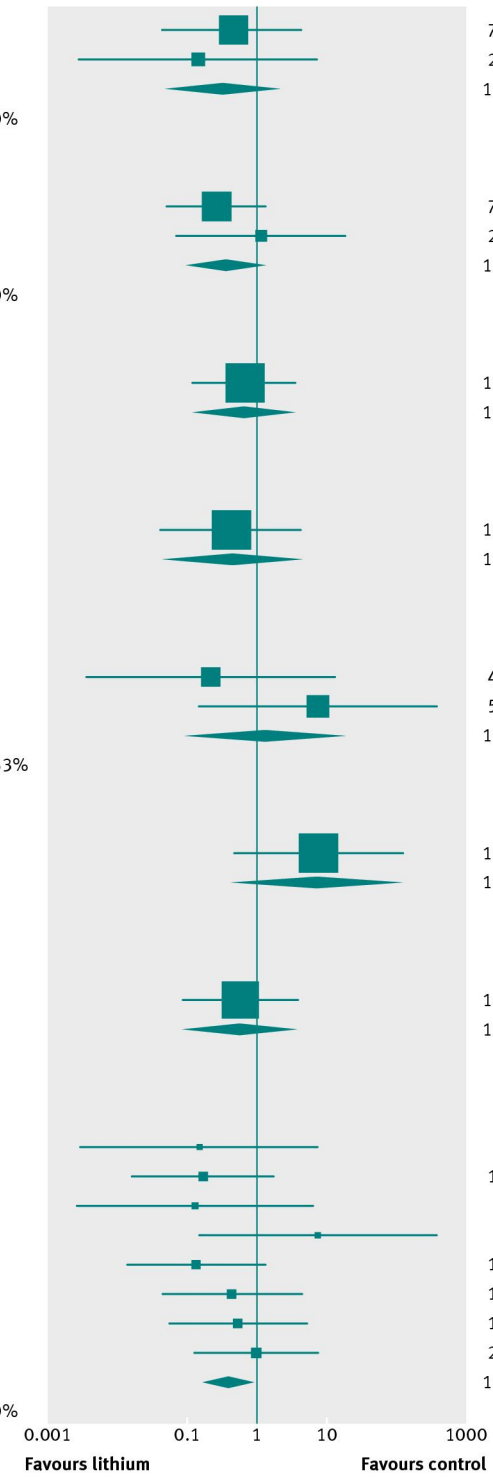


Fig 3 Forest plot showing meta-analysis of deliberate self harm in randomised trials comparing lithium with placebo or with active comparators



Study	No of events/total: Lithium	No of events/total: Control	Peto odds ratio Fixed (95% CI)	Weight (%)	Peto odds ratio Fixed (95% CI)
Versus amitriptyline					
Glen 1984	1/57	2/50		74.6	0.44 (0.04 to 4.36)
Greil 1996	0/40	1/41		25.4	0.14 (0.00 to 6.99)
Subtotal	1/97	3/91		100.0	0.33 (0.05 to 2.38)
Test for heterogeneity: χ^2=0.25, df=1, P=0.62, I^2=0%					
Test for overall effect: z=1.10, P=0.27					
Versus carbamazepine					
Greil 1997a	1/87	5/88		74.7	0.26 (0.05 to 1.30)
Greil 1997b	1/52	1/58		25.3	1.12 (0.07 to 18.16)
Subtotal	2/139	6/146		100.0	0.37 (0.09 to 1.51)
Test for heterogeneity: χ^2=0.80, df=1, P=0.37, I^2=0%					
Test for overall effect: z=1.38, P=0.17					
Versus divalproex					
Geddes 2010	2/110	3/110		100.0	0.67 (0.11 to 3.90)
Subtotal	2/110	3/110		100.0	0.67 (0.11 to 3.90)
Test for heterogeneity: Not applicable					
Test for overall effect: z=0.45, P=0.65					
Versus imipramine					
Prien 1973a	1/45	2/38		100.0	0.42 (0.04 to 4.21)
Subtotal	1/45	2/38		100.0	0.42 (0.04 to 4.21)
Test for heterogeneity: Not applicable					
Test for overall effect: z=0.74, P=0.46					
Versus lamotrigine					
Calabrese 2003	0/121	1/221		47.8	0.21 (0.00 to 12.83)
Licht 2010	1/78	0/77		52.2	7.29 (0.14 to 367.67)
Subtotal	1/199	1/298		100.0	1.35 (0.08 to 22.91)
Test for heterogeneity: χ^2=1.49, df=1, P=0.22, I^2=33%					
Test for overall effect: z=0.21, P=0.84					
Versus olanzapine					
Tohen 2005	2/214	0/217		100.0	7.53 (0.47 to 120.76)
Subtotal	2/214	0/217		100.0	7.53 (0.47 to 120.76)
Test for heterogeneity: Not applicable					
Test for overall effect: z=1.43, P=0.15					
Versus phenelzine					
Kok 2007	2/15	3/14		100.0	0.58 (0.09 to 3.85)
Subtotal	2/15	3/14		100.0	0.58 (0.09 to 3.85)
Test for heterogeneity: Not applicable					
Test for overall effect: z=0.57, P=0.57					
Versus placebo					
Bauer 2000	0/14	1/15		5.4	0.14 (0.00 to 7.31)
Coppen 1971	0/28	3/37		15.5	0.16 (0.02 to 1.66)
Dorus 1989	0/89	1/82		5.4	0.12 (0.00 to 6.28)
Hardy 1997	1/6	0/6		5.4	7.39 (0.15 to 372.38)
Lauterbach 2008	0/84	3/83		16.1	0.13 (0.01 to 1.27)
Prien 1973a	1/45	2/39		15.8	0.43 (0.04 to 4.32)
Prien 1973b	1/101	2/104		16.1	0.53 (0.05 to 5.11)
Wilkinson 2002	2/25	2/24		20.3	0.96 (0.13 to 7.25)
Subtotal	5/392	14/390		100.0	0.38 (0.15 to 0.95)
Test for heterogeneity: χ^2=4.99, df=7, P=0.66, I^2=0%					
Test for overall effect: z=2.06, P=0.04					

Fig 4 Forest plot showing meta-analysis of deaths from all causes in randomised trials comparing lithium with placebo or with active comparators

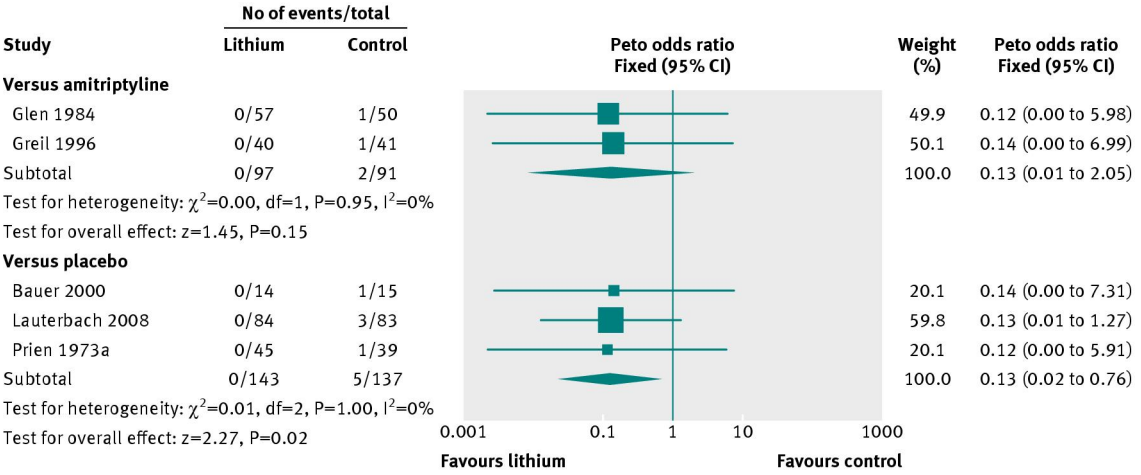


Fig 5 Forest plot showing meta-analysis of suicides in randomised trials comparing lithium with placebo or with active comparators only in people with unipolar disorder

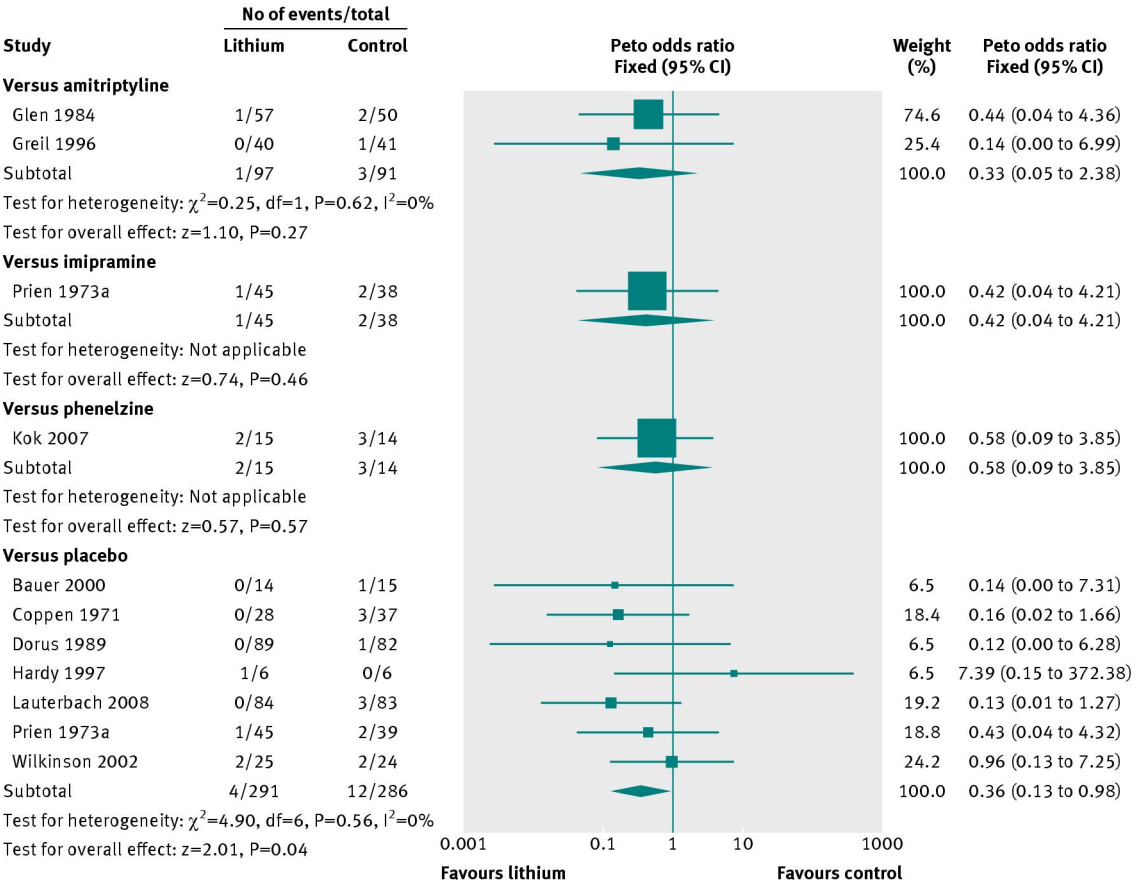


Fig 6 Forest plot showing meta-analysis of deaths from all causes in randomised trials comparing lithium with placebo or with active comparators only in people with unipolar disorder