Review article for Bipolar Disorders

Lithium and suicide in mood disorders:

updated meta-review of the scientific literature

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ABSTRACT

Objectives: Suicide and suicidal behaviour is increased in mood disorders, particularly bipolar disorders. Observational studies and small randomised controlled studies (RCTs) support the idea that taking lithium is associated with a reduction in these rates. This paper aims to review the best evidence for the effect of lithium on rates of suicide and self harm.

Methods: We searched systematically for systematic reviews and meta-analyses of RCTs of lithium and suicide and self harm.

Results: A large number of reviews were identified, but only 16 publications were systematic reviews. Of these three systematic reviews of lithium and suicide rates and one of lithium and self harm confined only to RCTs were identified. Despite some methodological concerns, the evidence to date is overwhelmingly in favour of lithium as an antisuicidal agent, even balanced against any potential disadvantages of its use in regular clinical practice.

Conclusions: The results are discussed in the context of the difficulties in conducting studies in this area and the supporting evidence that observational studies and non-randomised studies can provide. Given this evidence, however, the use of lithium is still under-represented in clinical practice and should be incorporated more assertively into current guidelines.

Key words: lithium, suicide, self harm, systematic review, meta-analysis, randomised controlled trial, bipolar disorder, unipolar depression, mood disorders.

INTRODUCTION

Mood disorders are associated with a marked increase in the risk of suicide and suicidal behaviour.[1] Lifetime risk of suicide in those with mood disorders in general is up to ten times higher than the non-psychiatric population,[2] with the risk in bipolar disorder estimated as between 15 and 30 times that of the general population.[3,4] Although it could be argued that these figures may be an overestimate of the true rates,[5] rates of self harm are also higher in those with mood disorders, particularly bipolar disorder,[2] with 25 to 50% of patients attempting suicide.[6] As a history of self harm is the most significant predictor of subsequent suicide,[7] it is also an important aspect of suicidal behaviour.

Despite these findings, the role that medication in general might play in the treatment and prevention of suicide has not been well studied.[7] Medication (including lithium) plays a relatively minor role in most suicide prevention strategies,[8-10] or is mentioned only briefly.[11] However, there is robust evidence that lithium reduces the risk of relapse in patients with mood disorders[12] and is superior to other mood stabilisers,[13] so there is good reason to suggest that lithium might be effective in reducing not only mood episodes, but suicidal behaviour as well.

Since the 1970s, a series of (both observational and randomised) studies have suggested that lithium does indeed reduce the risk of suicide.[14] For example, Goodwin et al, in a large observational study of 20,638 patients with bipolar disorder, investigated data collected by a health maintenance organisation in the USA and compared rates of suicide attempt and suicide death in those taking lithium compared with those taking valproate. They showed a greater antisuicidal effect in those taking lithium. The risk of suicide was 2.7 times higher (95% confidence interval [CI], 1.1-6.3; P = .03) during treatment with valproate than during treatment with lithium. Corresponding hazard ratios for nonfatal attempts were 1.7 (95% CI, 1.2-2.3; P = .002) for attempts resulting in hospitalisation and 1.8 (95% CI, 1.4-2.2; P<.001) for attempts diagnosed in the emergency department[15]. Similar results have been found in other observational studies,[16-19] with a beneficial effect of lithium on suicide rates when compared to anticonvulsants such as valproate, gabapentin and carbamazepine and also to antidepressants. These studies included large numbers of patients, however, as for all observational

studies, they could be criticised as prone to bias (especially those based on lithium clinic samples). Any beneficial effect might reflect better compliance with medication in a dedicated clinic setting, or reflect selective prescribing of lithium to patients thought to be at lower risk of suicide. Furthermore, deaths by other causes are often not considered in these reports. Theoretically, given the potential physical effects of lithium on thyroid and renal function it is possible that a benefit of lithium in preventing suicide might be offset by increased risk of death from physical disorders. More rigorous research methods are thus needed to provide more reliable data about lithium's preventative effect on suicide.

Given these issues with observational data, the best quality evidence to support or refute the hypothesis that lithium reduces suicidal ideation should come from randomised controlled trials (RCTs). There have been a considerable number of RCTs investigating the effect of lithium in mood disorders, starting in the early 1970s. The earlier studies were generally small, with variable methodology and incomplete reporting of factors affecting bias. More recent studies have used much stricter methodology and reporting in order to reduce the risk of bias.[20-23] However, each individual study has been relatively small, has focussed primarily on efficacy and has reported suicidal behaviour as a rare incidental finding, rather than a primary outcome. These individual RCTs are unlikely to have sufficient power to assess any association of suicidal behaviour with lithium treatment. Pooling data through the use of meta-analysis allows for issues such as low event rates to be addressed. Thus, data from high quality systematic reviews and meta-analyses of RCTs investigating lithium and suicide or self harm should give the most reliable evidence to date.

The aim of this paper was to review the current literature on the effect of lithium on suicide in patients with mood disorders, by searching for systematic reviews of RCTs. Suicidality is a complex phenomenon, and suicide completers, attempters, and ideators are likely to be heterogenous yet partially overlapping populations who may have different risk factors and characteristics, so we broadened our search to cover many aspects of suicidal thoughts and behaviour and its relationship to lithium treatment.

METHODS

To identify relevant evidence for the impact of lithium treatment on rates of suicide or self-harm in patients with mood disorders we searched PubMed, PsycINFO, and the Cochrane Library for systematic reviews and meta-analyses of RCTs published between 1980 and June 2017. No age or language restrictions were applied and the following key words were used: *lithium, suicide, self-harm, suicide attempt, non-suicidal self-injury, depression, bipolar, mood disorder*. In case of multiple publications on the same topic, only the most recent or most comprehensive review was considered. The reference lists of reports identified were used to find additional publications.

RESULTS

Initial searching of the databases retrieved 1008 references, which were narrowed, by an initial screen of the title, followed by screening of the abstract, and later of the full paper where necessary (Figure 1). Sixteen systematic reviews were identified, which included data from RCTs (Table 1). These systematic reviews cover a number of questions. Some focus on suicide, some on self harm and some on both. In addition, some specifically address the issue of lithium in suicidal behaviour, whereas others investigate the overall effect of lithium on outcome, with suicidal behaviour measured as one of several outcome measures. Some of them pooled a combination of randomised and observational studies, and therefore were subject to selection bias. In addition there was significant heterogeneity in the studies included in each review in terms of participants, diagnoses, comparators, study durations, and phase of illness. The reviews identified were used as evidence to answer clinically relevant questions, namely: does lithium have an effect on rates of suicide (and rates of all-cause mortality), on rates of self-harm, or on suicidal ideation?

1. Lithium and suicide

Three systematic reviews were identified which combined data solely from RCTs in a robust methodology to investigate specifically the effect of lithium on rates of suicide.[25,26,93] Two[25,26] were published by the same group of authors (Cipriani and colleagues) initially in 2005, with an updated review published in 2013. Both of these reviews used a similar methodology and combined results from RCTs lasting at least three months in patients with mood disorders, in which there was comparison of lithium versus placebo, or versus any active drugs. A third review was also identified, published in 2017[93], which investigated all types of strategy for suicide prevention (including lithium) with broader inclusion criteria for relevance and quality.

In the initial review[25] Cipriani and colleagues found 32 RCTs with 1,377 patients randomised to lithium, and 2,052 to other compounds and reported a reduction of suicide (Odds Ratio [OR] 0.26, 95% Confidence Interval [CI] 0.09-0.77), a reduction of suicide and self harm combined data (OR 0.21, 95% CI 0.08-0.50) and reduced overall risk of death from any cause (OR 0.42, 95% CI 0.21-0.87) in those on lithium compared to other medications. Cipriani and colleagues updated their search and review in 2013 to incorporate new data.[26] Forty-eight RCTs were now included (published between 1968 and 2013) and included data from 6,674 randomised patients. This allowed for the synthesis of 16 more RCTs than were reported in the 2005 review, eight of which contributed new data, almost doubling the 2005 population (94.6% increase in the overall sample size). The authors confirmed the previous results but the much larger sample size allowed them to investigate the potential anti-suicidal effect of lithium on different populations of patients with specific mood disorders. When compared to placebo, lithium in mood disorders significantly reduced the risk of suicide (OR 0.13, 95% CI 0.03-0.66) and the risk of deaths from any cause (0.38, 0.15 to 0.95). Lithium showed less clear benefits in preventing deliberate self harm than placebo (0.60, 0.27 to 1.32). In contrast to the earlier review, lithium was not found to be more effective at reducing suicide or all-cause mortality when compared with other pharmacological treatments. However, lithium was significantly more effective than carbamazepine in reducing self-harming behaviour (OR 0.14, 95%CI 0.02-0.83). Conducting a

sensitivity analysis to include only the studies comparing lithium with placebo or with active comparators only in people with unipolar depression, the OR was still in favour of lithium (0.13, 95% CI 0.02-0.76). Overall, lithium seems to reduce the risk of death and suicide by more than 60% compared with placebo. The analysis of all cause mortality avoids possible ascertainment bias (i.e. that events in people who take lithium may be more or less likely to be classified as suicides) and increases the power of the analysis (because more events are included). 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. This was an important finding: the reduction in deaths by suicide is not offset by an increase in deaths from other causes.

However, a recent meta-analysis of both RCTs and pooled analyses published in 2017[93] came to a somewhat different conclusion. The authors investigated all strategies for suicide prevention, and in their analysis of the effect of lithium included only 6 studies. They included a new study (by Girlanda and colleagues[94]) which had been published after the 2013 review by Cipriani[26] and also included a study with no suicidal events in either the lithium or placebo groups[95]. Their overall conclusion was that although 4 of the 6 studies they included suggested a benefit for lithium (with overall numbers of 1 suicide out of 313 patients in the lithium group vs 6/306 in the control group) the result was not statistically significant. The decision to include the study by Girlanda[94] altered the overall results of the review, but the study itself had significant methodological challenges. It was a pragmatic trial to explore whether adding lithium to usual care could reduce suicide rates in high-risk patients in the clinic setting. To meet this pragmatic aim, it was a randomised, assessor-blind study of lithium in a very specific group of high-risk subjects with treatment resistant depression and a history of an episode of self harm in the past 12 months. However, the study was underpowered (needing 200 for a statistically significant effect but recruiting only 56) due to the well documented difficulty of recruiting into trials such as these (see discussion below). The study was not double-blind and there was no placebo arm (lithium was added or not to ‘usual care’). Although one patient died by suicide

in the lithium group and none in the usual care group, the very small numbers of events and the underpowering of the study make it difficult to draw any conclusions from this data. Whilst the authors of the 2017 systematic review [93] point out that the strength of their review is that they did not exclude any studies based on quality or relevance, it could be argued that the significant methodological challenges with the study by Girlanda[94] (which are recognised and thoroughly discussed by the authors) should exclude it from a systematic review of trials in this area.

The two reviews by Cipriani and colleagues[25, 26] help to overcome some of the issues associated with research in this field and offer clear evidence of an association between lithium treatment and reduced suicidality. However, even with this gold standard of randomised evidence synthesised systematically, there are a number of issues that need to be addressed. Firstly, as with any systematic review or meta-analysis the conclusions that can be drawn are limited by the quality of the primary studies that contribute to the review. In this case, most of the primary studies were small, and their quality (especially for the older ones) was variably reported, if performed. In addition, the primary studies were heterogeneous in terms of population (unipolar depression or bipolar disorder or mixed), study duration, comparator medications and use of adjunctive medication, and the results were not always presented in their separate groups. Thus, for example, whilst Cipriani and colleagues[26] specified a minimum treatment period of 3 months in their review, the range varied, with a mean follow-up of 19.1 (SD 7.2) months and a range of 4-48 months. There were not sufficient numbers to assess whether the anti-suicidal effect of lithium continues over months, years and even decades, which are all questions relevant to the patient and clinician. Whilst to some extent the clinical heterogeneity is reassuring in that this mimics clinical practice and implies that the benefit of lithium is consistent across different patient groups, it has the disadvantage that small numbers of events and low power limit the reviewers' ability to detect any interaction between these factors and the treatment effect of lithium. In both meta-analyses, the number of events and power were often too small to explore any interaction between these factors and the treatment effect of lithium.

In general, the low baseline rate of suicide (a relatively rare event) makes it difficult to show a difference between lithium and placebo or alternative treatment in an RCT. The studies are relatively small and have insufficient power to show a difference between treatment groups. This low baseline rate of suicidal behaviour in general may be even lower in trials than general clinical populations as suicidal patients are often excluded from participating in trials in the first place.[27] Even combining studies in a systematic review and meta-analysis may not provide sufficient statistical power to show a difference in a relatively rare event. Thus for example, a number of systematic reviews of the effects of lithium in maintenance treatment were identified where suicide was assessed as one of several outcomes.[12,84,85] However, the numbers of suicides in the lithium treated group and the comparator group were in single figures, which prevented any meaningful conclusion. In addition, any publication bias will have a relatively large effect: one or two unpublished trials demonstrating negative or neutral results may have a large influence on effect sizes in a review of studies with such low event rates[25, 26, 28]. This is a situation where observational data (whilst potentially more prone to bias as discussed above) may be usefully used to support findings of systematic reviews of RCTs. Studies such as Goodwin[15] (n=20,638, discussed above) and Hayes[29] (n=14,396, discussed below) include numbers far greater than could ever be recruited into an RCT treatment trial. As such, these observational studies are important sources of evidence, to support or refute the findings of the systematic reviews.

Another difficulty is that the outcomes of interest (suicide, self harm, suicidal thoughts) are often not reported or recorded, and the evidence discussed comes mainly from incidental findings, where suicide was not an outcome measure in the trial's design[30]. However, specific RCTs to investigate the effects of lithium treatment on suicidality are limited: ethically it would be hard to justify a placebo treatment arm in participants experiencing suicidal ideation, and suicidal ideations or actions are often exclusion criteria for large scale clinical trials. Gathering robust research evidence from placebo controlled RCTs specifically designed to investigate the effects of lithium on suicidality has therefore been more challenging than in other treatment areas. For instance, despite the high incidence of suicide and self-harming behaviour among adolescents, there are to date no RCTs directly

investigating the effect of lithium, or indeed any pharmaceutical agents on suicide in younger populations[31, 32]. There are however now a number of RCTs investigating suicide in adults, whose design have overcome these issues by comparing lithium to other mood-stabilisers, anti-depressants or anti-psychotic treatments, so that all options for the participant consist of some treatment; for example antidepressant alone versus antidepressant plus lithium[33]. However, the issues of recruitment and retention over the long term in such a RCT still result in relatively small numbers of participants. For example, the researchers in the BALANCE trial, comparing lithium, divalproex and the combination in the prevention of relapse in bipolar disorder, recruited participants across 41 centres. Initially, they had planned a recruitment target of 1068 participants followed over 2 years starting in 2000. Having modified their target number, they reported in 2010 on the results of 330 participants[23]. Whilst this is a large and significant treatment trial, rates of self harm were in single figures in each treatment group, and there were no suicides.

Finally, there is the issue that recorded verdicts of suicide may not represent the true rate. These usually rely on a coroner's verdict, which are subject to bias, and may be recorded as an open verdict in cases where the evidence is unclear. In addition, there is bias in that those who are on lithium may be more or less likely to be classified as death by suicide. One way of addressing this is also to look at all cause mortality. If numbers of deaths by suicide have been reduced in those on lithium (as suggested by Cipriani[26] 2013), one might expect a corresponding increase in deaths attributed to other causes. However this was looked for and not found, reassuring us that the reduction in suicide on lithium is a real effect.

2. Lithium and self harm

One Cochrane review of RCTs was identified, which focussed on all pharmacological treatments in prevention of self harm, but contained a sub-group analysis of the effects of lithium.[34] This review, along with two other related reviews, updated a single Cochrane review originally published in 1999.[35] Another Cochrane review by the same group identified all interventions in children and young people

in the prevention of self-harm, but no trials of pharmacological agents were identified that could be included.[32]

In total, the review by Hawton and colleagues included seven RCTs with a total of 546 patients.[34] Interestingly, the reviewers did not find any new trials when they searched for this update, compared to their original search in 1999. This may be because the difficulties in conducting RCTs in this group in general are particularly pronounced when considering drug treatment. In addition, they used strict criteria for inclusion; participants needed to have a history of self harm in the six months preceding trial entry. This excluded a number of studies which included participants with a more distant history of self harm (for example Oquendo et al[36]) or studies which included a mixed group where a history of self harm was present in some, but not all members of the group. Focussing on the effect of lithium, only one RCT (n=167) was identified by the systematic review as meeting criteria for inclusion.[37] This trial investigated the effectiveness of lithium compared to placebo in individuals who had made suicide attempts (defined as self harm acts with explicit or implicit evidence that the individual intended to die) in the context of a depressive spectrum disorder. No significant treatment effects on repetition of self-harm for lithium (OR 0.99, 95% CI 0.33 to 2.95), or on the secondary outcomes of depression score, hopelessness, suicidal ideation or suicide were found. Interestingly, the original authors did report that the lithium treated group had fewer suicides (0/84 versus 3/83) and that this difference was statistically significant. Taking the event proportion in the placebo group as a comparison standard (3/83 = 3.6%), they concluded that probability of no event in the lithium group was lower than 5%. Adjusting their analysis for differing person-years of exposure in the two groups they concluded that the 95%CI of the placebo incidence rate of suicides of IR = 0.065 (range 0.013-0.190) did not cover the zero IR of the lithium group (p = 0.049). However, the reanalysis in the systematic review[34] (0/84 versus 3/83; OR 0.14, CI 0.01 to 2.68; k = 1; N = 167) did not support this claim for statistical significance and concluded there was no difference between the groups in suicide rates, whilst accepting that this may be secondary to the small number of event rates .

The study by Oquendo[36] was excluded by the Hawton et al. review because not all patients had reported self-harm in the previous six-month period. This was a long-term RCT of add-on lithium (mean duration 495 days) or valproate (mean duration 550 days) among 98 patients with depression or bipolar disorder with a history of suicide attempt. No suicide deaths occurred during the study and there were no significant differences between rates of suicide attempts between the two groups, but again numbers were small and the study is unlikely to have had sufficient power to show a difference. It is also noteworthy that Cipriani and colleagues analysed the effects of lithium on self harm in mood disorders and reported that the effect of lithium in preventing self harm when compared to placebo was less clear than its effects on suicide (OR 0.60, 95% CI 0.27 to 1.32).[26] Lithium was however more effective than carbamazepine in reducing the number of self harm episodes (OR 0.14, CI 0.02 to 0.83). These findings from RCTs are in contrast to the observational data, which suggest that lithium may indeed reduce self-harm when compared to other anticonvulsants. [15,24] In the specific population of patients with bipolar disorder, a recent large population-based electronic health records study investigated rates of self harm in 6671 individuals on different mood stabilising treatment.[29] The rate of self harm in people prescribed maintenance mood stabilizer medication for bipolar disorder was 340 (95% CI 313-370) per 10,000 person years at risk (PYAR). In unadjusted analysis, self-harm rates were reduced in people taking lithium compared with those taking valproate, olanzapine, or quetiapine. The rate of unintentional injury was 616 (95% CI 579-656) per 10,000 PYAR and rates were lower in people taking lithium compared with those taking valproate or quetiapine, but not olanzapine in both unadjusted and adjusted analyses). This is important because, as well as an increased risk of suicide, individuals with bipolar disorder have a risk of death from accidental injury which is 6 times that of the general population.[38] The rate of suicide deaths in the cohort was 14 (95% CI, 9-21) per 10,000 PYAR, but the numbers were too low to show differences by individual drugs. These results support the idea that lithium is associated with lower rates of self-harm, but as with all observational studies, the results can show an association, not a direction of causality. It might be argued that lithium is more likely to be prescribed in those who are perceived to be at reduced risk of self harm, thus

producing an association with a lower rate. Indeed the baseline characteristics of the lithium treated group seem to support this; the members of this group were, on average older, were less likely to have a history of prior self harm and were less likely to be anxious and depressed. The authors addressed this issue by correcting the results using a propensity score (an indicator of combined risk of self harm) and the benefit of lithium over other drugs in reducing self harm remained. It has also been argued that the findings may be confounded by the secondary benefits of being on lithium (such as repeated blood tests, more clinic attendances). However, in a large naturalistic longitudinal study of non-fatal self harm in individuals with bipolar disorder which replicated the protective effects of lithium, no difference was observed in the number of physician contacts in patients on lithium compared to those on other medications.[29] The Veterans Administration in the United States, is currently undertaking a large randomized trial of lithium for suicide prevention, expecting to randomize 1,862 veterans with depression (from both bipolar disorder and major depressive disorder) to either adjunctive lithium or placebo, and to follow them for up to a year (https://clinicaltrials.gov/ct2/show/NCT01928446).

3. Lithium and suicidal ideation

Suicidal ideation and thoughts of hopelessness should be another important area of study with respect to lithium. However, the data is disappointingly sparse. Just as for suicidal acts, subjects with suicidal ideation are usually actively excluded from treatment trials, so even secondary data on the prevalence of suicidal ideation in treatment trials is likely to vastly underestimate the phenomenon. In addition, just as mortality data is often not reported, suicidal ideation may not have been assessed or reported in the treatment trials.

One study has specifically investigated the effect of lithium on both suicidal behaviour and thoughts, by investigating lithium as an augmenting agent to antidepressants.[39] A subgroup of the patients assigned to lithium and citalopram achieved therapeutic lithium levels and had significantly higher remission rates on the Sheehan Suicidality Tracking scale (a measure of suicidal behaviour and

thoughts) compared to patients assigned to placebo and citalopram. Other trials involving lithium have focussed on suicidal acts and/or self harm, and do not report thoughts or ideation. There are no systematic reviews of RCTs which involve the role of lithium in suicidal ideation. A new study has been proposed to address this issue (clinicaltrials.gov identifier NCT02039479).[40] This will be a multi-centre placebo controlled RCT of patients with unipolar or bipolar disorder suffering from a major depressive episode with suicidal thoughts and/or behaviour comparing lithium versus placebo as an adjunct to treatment as usual and prospectively measuring suicidal thoughts and actions using measures such as the S-STS and the Columbia-Suicide Severity Rating Scale (C-SSRS). This study is likely to take some years to complete, but the results are awaited with interest.

DISCUSSION

Taken together, the randomised evidence, supported by observational data, suggests lithium therapy should be the treatment of choice for people with bipolar disorder, particularly those who are at risk of suicide,[41] and that it may also have role in protecting those with depressive disorders against fatal suicidal acts.[33]

There have been several hypotheses that have been proposed to explain this effect. The simplest is that lithium mediates its effect directly by reducing relapse of mood disorder. In addition it is also possible that lithium mediates its effect by reducing the prominent inter-episodic sub-syndromal mood symptoms and mood instability which persist between clinically significant mood episodes and are an important component of the clinical picture.[42, 43] There is good evidence that lithium reduces risk of relapse in patients with mood disorders.[12] It is not unreasonable to assume that given that most suicidal attempts occur in periods of mood instability and not in euthymia, if mood can be improved and euthymia prolonged, a reduction in suicide attempts will be seen. However, against this hypothesis is the fact that other antidepressants and mood stabilisers do not seem to have the same antisuicidal effect, despite their effectiveness in treating mood episodes. In addition, the effect of lithium on suicide seems to be larger than its effect on mood, and the effect on suicidal behaviour has

been observed even when mood stabilisation has not occurred.[44] Some researchers have suggested that lithium may have specific effects against suicide that are independent of mood-stabilizing actions. Thus, for example a study of patients with mood disorder with a history of at least one suicide attempt reported that suicide attempts were reduced in all participants, regardless of their improvement in affective symptoms.[45]

The International Group for the Study of Lithium Treated Patients studied a large cohort of patients with affective disorders on and off lithium and showed that lithium reduced all cause mortality to that seen in the general population.[46,47]. Other groups reported similar findings,[48,49] suggesting that lithium not only can have a suicide preventative effect, but also potentially some ability of reduce rates of mortality from other causes. Given the significantly high rates of suicide and all cause mortality in patients with affective disorders, this is an encouraging finding. The indications of an independent anti-suicidal action also have clinical implications for those withdrawing from lithium treatment due to insufficient mood-stabilising effects, as despite observing a lack of improvement in affective symptoms, lithium may be providing a protective effect against suicidal behaviour. This suggests a possible clinical justification for maintaining lithium treatment in patients at risk of suicide, who have had a lack of response to lithium treatment, rather than switching to a new treatment entirely.[50] Conversely, it is worth noting that there is evidence of a temporary increase in suicide risk up to 20-fold at the point of discontinuation from long-term lithium treatment particularly if lithium is stopped abruptly.[51,52] This has direct clinical implications: discontinuing lithium must always be completed with caution, particularly if suicidality is deemed to be a risk.[53]

The beneficial effect of lithium on suicidal behaviour could be mediated by a reduction of aggression or impulsivity, both of which associated with increased suicide risk[24] and are common traits in bipolar disorder. The anti-aggressive properties of lithium are well reported,[53] as are reductions in impulsivity.[54] This hypothesis may also offer an explanation for the lack of anti-suicidal effects of other treatments for mood disorders, particularly given that most suicide attempts occur in depressive states.[51] The lack of anti-suicidal effects of these other drugs may be due to a lack of effect[33] or even

worsening[56] on symptoms associated with suicide such as agitation, restless, irritability and anger. Lithium treatment is associated with a reduction of these symptoms, and may therefore reduce suicidal behaviour through this mechanism.[30] A specific biological mechanism can mediate this effect. Kalkman and colleagues, for example, has proposed evidence of a role of glutamine synthetase in lithium's effects on suicide.[57] Brain glutamine synthetase function is suppressed in patient groups in which suicide rates are highest, such as mood disorder, epilepsy and diabetes, and reduced glutamine synthetase activity has been reported in cases of completed suicide in both depressed and non-depressed individuals. Lithium is a glycogen synthase kinase 3 (GSK3) inhibitor and in animals can increase the expression of glutamine synthetase and brain glutamine levels.[57]

Alternatively, lithium may improve decision-making in patients with bipolar disorder. Adida studied euthymic patients diagnosed with bipolar disorder, and showed that patients treated with lithium ($p=0.007$) and healthy controls ($p=0.001$) were significantly more likely to select cards from the 'safe decks' than patients who were not treated with lithium.[58] Impaired decision-making is associated with an increased risk of suicidal acts, and this study supports the idea that lithium may mediate its benefit on suicidality by improved decision-making. Practically, taking lithium tends to increase access to clinical care and the increased monitoring may help to reduce suicidal acts, by recognising and treating early warning signs such as dysphoria and agitation or suicidal ideation.[59] Clozapine is the only other drug shown to have significant anti-suicidal effects and it shares the opportunity for increased clinical care through a need for physical monitoring of side effects.[33] However, a large scale study comparing clozapine to olanzapine has shown a consistent finding of anti-suicidal properties of clozapine whilst controlling for contact-time with clinicians.[60] It may be more likely that the similar positive effect of clozapine and lithium on suicidal behaviour is related to their pronounced effects on serotonin. Dysfunction in the serotonergic system has been associated with suicidal behaviour[61] and it has been suggested that the change in serotonergic functioning as a result of treatment with these drugs may be the mechanism of reduction of suicidal acts.[62] However, the link is likely to be more complex, as other drugs such as serotonergic antidepressants do not appear to have the specific antisuicidal effect

shown by lithium and clozapine, which appears to be independent of the effect that they have on core symptoms of mood and/or psychosis.

CONCLUSIONS

The anti-suicidal actions of lithium have been consistently reported over the past 40 years, in both observational studies and RCTs. Whilst each design has possible weaknesses as already discussed, the combined evidence is overwhelmingly in favour of the antisuicidal action of lithium. Lithium is the only medication in bipolar disorder thus far to have been shown to have a specific antisuicidal effect over and above its action on mood episodes.

In the previous special issue of this journal focussing on lithium, the conclusion was very similar to that we have come to today. Grof[63] concluded that there was clear evidence of an antisuicidal effect of lithium, but commented that this had not translated into guidelines or clinical practice. Whilst more recent guidelines have incorporated these recommendations in acute and maintenance treatment of affective disorders[1, 64-66] the clinical use of lithium is still underrepresented and there has been an observed decline in the prescription of lithium in favour of new drugs.[53]

It is possible that this relative underuse of lithium may be related to its lack of publicity in comparison to other commercially marketed drugs,[53] or it may be related to the perceived difficulties in prescribing and monitoring associated with lithium treatment. The association of lithium with a number of adverse effects, including effects on renal function, hypothyroidism and hypercalcaemia[67] and the required routine monitoring of serum levels required for effective treatment[68] may be perceived as a deterrent by both clinicians and patients. In fact, more recent evidence suggests that many of the side effects are less common than originally thought,[67,69] are often treatable and are comparable to those side effects experienced by patients taking other psychotropic medications.[68] Moreover, we know that some patients are more prone to experiencing adverse events such as renal problems than others, for example women under 60 years old and those with frequently high lithium serum levels.[68] Clinicians can take protective measures to reduce the risk of their patients experiencing such side effects, by for

instance by closely monitoring serum levels to avoid sustained periods where lithium levels are high.[41] New innovations such as the lithiumeter [87] allow the management of lithium levels to be more streamlined and to help patients to adhere carefully to self and clinician-guided monitoring. The lithiumeter is a quantitative schematic of lithium's indications and risks balanced against plasma lithium concentrations, outlining ideal monitoring practices and schedules. It guides clinical decision-making through the phases of initiation, optimisation and the avoidance of acute and chronic toxicity. This guidance should improve patient and clinician satisfaction, and give better long-term outcomes, which in turn would encourage more confident prescribing of lithium. There have also been innovations with regard to the more subtle side effects that are commonly reported with lithium. Whilst it is difficult to separate the neurocognitive impairments caused by acute mood states with those caused by lithium treatment, recent narrative reviews suggest that whilst lithium impairs neurocognition across some domains, it seems to preserve others. To study these effects in greater detail, clinicians and researchers need to be able to measure the components of neurocognitive function that change with lithium treatment. One such measure is the 'Lithium Battery'[88], which is available in clinical and research versions, and can be used as a tool to note and manage neurocognitive concerns as part of routine clinical and research practice.

With respect to side effects, it is also worth noting the evidence for the effects of lithium on non-suicide mortality.[70] This is important; the antisuicidal effect of lithium also seems to be accompanied by a reduction in non-suicide related deaths as well.

Clinicians are also understandably concerned about the relatively high toxicity of lithium in overdose.[71] The clinical use of lithium with the hope of reducing suicidal risk may seem paradoxical, in that lithium has a very limited therapeutic index or margin of safety and can be lethal in overdose. Balancing this against the known antisuicidal effects of lithium presents a dilemma for both clinicians and patients when making therapeutic decisions about prophylaxis, especially in patients with known risk factors for suicide. However, it appears that patients rarely use lithium as a means to complete suicide,[72,73] and lithium has been found to be associated with a reduction in the lethality of suicidal acts.[24] The

fatality risk of lithium overdoses is only moderate, and very similar to those of modern antidepressants and second-generation antipsychotics.[74] The clinician needs to balance this risk against the known benefits of lithium in reducing the substantial risk of suicide in bipolar patients.

Another reason for mistrust of lithium may be the lack of understanding regarding the exact mechanisms by which it produces its effects. Despite the widespread use of lithium in bipolar disorder for over 50 years, we still know little about its exact mechanism of action or about the early predictors of therapeutic response. Whilst this is also true of other medications used in psychiatry, questions such as which patients will show a complete or partial response, whether that response will recur on reinitiating after a break, and whether lithium has an effect in the early days of treatment are not clear. At present, such investigations require lengthy clinical trials, which are expensive, and therefore risky.[75,76] These issues have prompted interest in trying to identify early or intermediate outcomes that could be used reliably in early-phase trials to provide initial evidence of efficacy. The absence of validated targets and the consequent difficulties of conducting clinical development programmes contribute to the dearth of therapeutic innovation in this field. An example of such an experimental medicine study in the field of bipolar disorder is the OxLith study,[77] an innovative placebo controlled RCT which is exploring the nature and significance of mood instability in bipolar disorder in the early weeks of lithium treatment. Chronic mood instability, which persists between clinically significant mood episodes, is an important component of the clinical picture.[43] It is a risk factor for the emergence of bipolar disorder[78] and is often a disabling feature once the disorder is established.[79] In addition, reactivity of mood to external events is greater in bipolar disorder compared with other mood disorders.[80] Using a mood monitoring system such as True Colours (https://oxfordhealth.truecolours.nhs.uk/www/en/)[78] mood instability can be recorded longitudinally. One possibility is that persistent mood instability is a risk factor for clinically significant mood episodes and that better mood stabilisation may improve outcomes, including suicidal behaviour. If so, measuring a change in mood stability in response to lithium over a short period such as a few weeks could predict long-term therapeutic efficacy. Experimental medicine studies such as

these, if they were able to identify early markers of response and change could enable large scale RCTs with sufficient power to show changes in relatively rare, but clinically central issues in bipolar disorder such as suicidal thoughts and acts. Until these innovative trials are completed, the evidence to date suggests that lithium's long-term mood stabilising properties, together with its protective effect against suicide mean that for many, it remains the best treatment choice for bipolar disorder.[41] However, despite the abundance of research, the mechanism by which lithium confers its protective effect remains unclear. Further research is needed into the underlying neurobiological mechanisms by which lithium prevents suicide.

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REFERENCES

1. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, Hopwood M, Lyndon B, Mulder R, Murray G, Porter R, Singh AB. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015 Dec;49(12):1087-206
2. Latalova K, Kamaradova D, Prasko J. Suicide in bipolar disorder: a review. Psychiatr Danub. 2014;26(2):0-114.
3. Tondo L, Lepri B, Baldessarini RJ. Suicidal risks among 2826 Sardinian major affective disorder patients. Acta Psychiatr Scand. 2007;116(6):419-28.
4. Pompili M, Gonda X, Serafini G, Innamorati M, Sher L, Amore M, Rihmer Z, Girardi P. Epidemiology of suicide in bipolar disorders: a systematic review of the literature. Bipolar Disord. 2013;15(5):457-90.
5. Saunders KE, Hawton K. Clinical assessment and crisis intervention for the suicidal bipolar disorder patient. Bipolar Disord. 2013;15(5):575-83.
6. Valtonen H, Suominen K, Partonen T, Ostamo A, Lönnqvist J. Time patterns of attempted suicide. J Affect Disord. 2006;90(2):201-7.
7. Saunders KE, Hawton K. The role of psychopharmacology in suicide prevention. Epidemiol Psychiatr Sci. 2009;18(3):172-8.
8. World Health Organization. Preventing suicide: A global imperative: World Health Organization. 2014.
9. Department of Health. Preventing suicide in England: A cross-government outcomes strategy to save lives. London: Her Majesty's Government/Department of Health, 2012.
10. National Institute for Health and Clinical Excellence. Self-harm: Longer-term management. National Institute for Health and Clinical Excellence; 2011. (https://www.nice.org.uk/guidance/cg133)
11. Office of the Surgeon General (US, National Action Alliance for Suicide Prevention (US. 2012 National strategy for suicide prevention: goals and objectives for action: a report of the US Surgeon General and of the National Action Alliance for Suicide Prevention.
12. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, Coghill DR, Fazel S, Geddes JR, Grunze H, Holmes EA, Howes O, Hudson S, Hunt N, Jones I, Macmillan IC, McAllister-Williams H, Miklowitz DR, Morriss R, Munafò M, Paton C, Saharkian BJ, Saunders K, Sinclair J, Taylor D, Vieta E, Young AH. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016 Jun;30(6):495-553.
13. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, Salanti G, Motomura K, Shimano-Katsuki S, Leucht S, Cipriani A. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9.
14. Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: Update and new findings. J Clin Psychiatry. 2003;64(Suppl5):44-52.
15. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA. 2003;290(11):1467-73.
16. Collins JC, McFarland BH. Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. J Affect Disord. 2008;107(1):23-8.
17. Søndergård L, Lopez AG, Andersen PK, Kessing LV. Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. Bipolar disord. 2008;10(1):87-94.

18. Isometsä E, Sund R, Pirkola S. Post-discharge suicides of inpatients with bipolar disorder in Finland. Bipolar disord. 2014;16(8):867-74.
19. Toffol E, Hätönen T, Tanskanen A, Lönnqvist J, Wahlbeck K, Joffe G, Tiihonen J, Haukka J, Partonen T. Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: A nationwide registry-based prospective cohort study. J Affect Disord. 2015;183:159-65.
20. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, Pope HG, Chou JC, Keck PE, Rhodes LJ, Swann AC. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch. Gen. Psychiatry. 2000;57(5):481-9.
21. Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N, DeVeaugh-Geiss J. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry. 2003;64(9):1013-24.
22. Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, Montgomery P, Earl N, Smoot TM, DeVeaugh-Geiss J. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch. Gen. Psychiatry. 2003;60(4):392-400.
23. BALANCE investigators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010;375(9712):385-95.
24. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord. 2006;8(5p2):625-39.
25. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry. 2005;162(10):1805-19.
26. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. 2013;346:f3646.
27. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. Am J Psychiatry. 2006;163(1):41-7.
28. Egger M, Smith GD. Bias in location and selection of studies. Br Med J 1998;316(7124):61.
29. Hayes JF, Pitman A, Marston L, Walters K, Geddes JR, King M, Osborn DP. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: a UK population-based electronic health records study. JAMA Psychiatry. 2016;73(6):630-7.
30. Tondo L, Baldessarini RJ. Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients. Epidemiol Psichiatr Soc. 2009;18(03):179-83.
31. Ougrin D, Tranah T, Stahl D, Moran P, Asarnow JR. Therapeutic interventions for suicide attempts and self-harm in adolescents: systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2015;54(2):97-107.
32. Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Townsend E, van Heeringen K, Hazell P. Interventions for self-harm in children and adolescents. Cochrane Database Syst Rev 2015, Issue 12. Art. No.: CD012013.
33. Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry. 2007;68(3):380-3.

34. Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Hazell P, Townsend E, van Heeringen K. Pharmacological interventions for self-harm in adults. Cochrane Database Syst Rev 2015, Issue 7. Art. No.: CD011777.
35. Hawton KKE, Townsend E, Arensman E, Gunnell D, Hazell P, House A, Van Heeringen K. Psychosocial and pharmacological treatments for deliberate self harm. Cochrane Database Syst Rev 1999, Issue 4.
36. Oquendo MA, Galfalvy HC, Currier D, Grunebaum MF, Sher L, Sullivan GM, Burke AK, Harkavy-Friedman J, Sublette ME, Parsey RV, Mann JJ. Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. Am J Psychiatry. 2011;168(10):1050-6.
37. Lauterbach E, Felber W, Müller-Oerlinghausen B, Ahrens B, Bronisch T, Meyer T, Kilb B, Lewitzka U, Hawellek B, Quante A, Richter K. Adjunctive lithium treatment in the prevention of suicidal behaviour in depressive disorders: a randomised, placebo-controlled, 1-year trial. Acta Psychiatr Scand. 2008;118(6):469-79.
38. Hoang U, Stewart R, Goldacre MJ. Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006. Br Med J. 2011;343:d5422.
39. Khan A, Khan SR, Hobus J, Faucett J, Mehra V, Giller EL, Rudolph RL. Differential pattern of response in mood symptoms and suicide risk measures in severely ill depressed patients assigned to citalopram with placebo or citalopram combined with lithium: role of lithium levels. J Psychiatr Res. 2011;45(11):1489-96.
40. Lewitzka U, Jabs B, Fülle M, Holthoff V, Juckel G, Uhl I, Kittel-Schneider S, Reif A, Reif-Leonhard C, Gruber O, Djawid B. Does lithium reduce acute suicidal ideation and behavior? A protocol for a randomized, placebo-controlled multicenter trial of lithium plus Treatment As Usual (TAU) in patients with suicidal major depressive episode. BMC Psychiatry. 2015;15(1):117.
41. Malhi GS. Lithium therapy in bipolar disorder: a balancing act?. Lancet. 2015;386(9992):415-6.
42. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry. 2002;59(6):530-7.
43. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch. Gen. Psychiatry. 2003;60(3):261-9.
44. Müller-Oerlinghausen B, Müser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord. 1992;25(4):261-9.
45. Ahrens B, Müller-Oerlinghausen B. Does lithium exert an independent antisuicidal effect?. Pharmacopsychiatry. 2001;34(04):132-6.
46. Müller-Oerlinghausen B, Wolf T, Ahrens B, Schou M, Grof E, Grof P, Lenz G, Simhandl C, Thau K, Wolf R. Mortality during initial and during later lithium treatment. Acta Psychiatr Scand. 1994;90(4):295-7.
47. Müller-Oerlinghausen B, Wolf T, Ahrens B, Glaenz T, Schou M, Grof E, Grof P, Lenz G, Simhandl C, Thau K, Vestergaard P. Mortality of patients who dropped out from regular lithium prophylaxis: a collaborative study by the International Grow for the Study of Lithium-Treated Patients (IGSLI). Acta Psychiatr Scand. 1996;94(5):344-7.
48. Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. Long-term lithium and mortality. Lancet. 1990;335(8701):1347.
49. Wolf T, Müller-Oerlinghausen B, Ahrens B, Grof P, Schou M, Felber W, Grof E, Lenz G, Nilsson A, Simhandl C, Thau K. How to interpret findings on mortality of long-term lithium treated manic-

depressive patients?! Critique of different methodological approaches. J Affect Disord. 1996;39(2):127-32.
50. Rihmer Z, Gonda X. Pharmacological prevention of suicide in patients with major mood disorders. Neurosci Biobehav Rev. 2013;37(10):2398-403.
51. Tondo L, Baldessarini RJ, Hennen J, Floris G, Silvetti F, Tohen M. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. J Clin Psychiatry. 1998;59(8):405-14.
52. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry. 1998;60:77-84.
53. Young AH. Lithium and suicide. Lancet Psychiatry. 2014;1(6):483-4.
54. Müller-Oerlinghausen B, Lewitzka U. Lithium reduces pathological aggression and suicidality: a mini-review. Neuropsychobiology. 2010;62(1):43-9.
55. Kovacsics CE, Gottesman II, Gould TD. Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. Annu. Rev. Pharmacol. Toxicol.. 2009;49:175-98.
56. Baldessarini RJ, Pompili M, Tondo L, Tsapakis E, Soldani F, Faedda GL, Hennen J. Antidepressants and suicidal behavior: are we hurting or helping. Clin Neuropsychiatry. 2005;2(1):75.
57. Kalkman HO. Circumstantial evidence for a role of glutamine-synthetase in suicide. Med. Hypotheses. 2011;76(6):905-7.
58. Adida M, Jollant F, Clark L, Guillaume S, Goodwin GM, Azorin JM, Courtet P. Lithium might be associated with better decision-making performance in euthymic bipolar patients. Eur Neuropsychopharmacol. 2015;25(6):788-97.
59. Tondo L, Albert MJ, Baldessarini RJ. Suicide rates in relation to health care access in the United States: an ecological study. J Clin Psychiatry. 2006;67(4):517-23.
60. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R. Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). Arch. Gen. Psychiatry. 2003;60(1):82-91.
61. Lee BH, Kim YK. Potential peripheral biological predictors of suicidal behavior in major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2011;35(4):842-7.
62. Mann JJ. A current perspective of suicide and attempted suicide. Ann. Intern. Med. 2002;136(4):302-11.
63. Grof P, Müller-Oerlinghausen B. A critical appraisal of lithium's efficacy and effectiveness: the last 60 years. Bipolar Disord. 2009;11(s2):10-9.
64. Pfennig A, Bauer M. S3 guidelines on bipolar disorders are contemporary and important instruments for clinical practice. Nervenarzt. 2013;84(7):874-5.
65. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J. Biol. Psychiatry. 2013;14(3):154-219.
66. Kendall T, Morriss R, Mayo-Wilson E, Marcus E; Guideline Development Group of the National Institute for Health and Care Excellence. Assessment and management of bipolar disorder: summary of updated NICE guidance. BMJ 2014;349:g5673..
67. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379(9817):721-8.
68. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. Lancet. 2015;386(9992):461-8.
69. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based cohort study. PLoS Med. 2016;13(8):e1002058

70. Smith EG, Austin KL, Kim HM, Eisen SV, Kilbourne AM, Miller DR, Zivin K, Hannemann C, Sauer BC, Valenstein M. Mortality associated with lithium and valproate treatment of US Veterans Health Administration patients with mental disorders. Br J Psychiatry. 2015: 207: 55–63
71. Hansen HE, Amdisen A. Lithium intoxication. (Report of 23 cases and review of 100 cases from the literature). Q J Med 1978; 47(2): 123–144.
72. Vestergaard P, Aagaard J. Five-year mortality in lithium-treated manic-depressive patients. J Affect Disord. 1991;21(1):33-8.
73. Waddington D, McKenzie IP. Overdose rates in lithium-treated versus antidepressant-treated outpatients. Acta Psychiatr Scand. 1994;90(1):50-2.
74. Watson WA, Litovitz TL, Klein-Schwartz W, Rodgers GC Jr, Youniss J, Reid N, Rouse WG, Rembert RS, Borys D. 2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS). Am J Emerg Med 2004; 22: 386–392.
75. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013;381(9878):1672-82.
76. Malhi GS, Geddes JR. Carving bipolarity using a lithium sword. Br J Psychiatry. 2014;205(5):337–9.
77. Saunders KE, Cipriani A, Rendell J, Attenburrow MJ, Nelissen N, Bilderbeck AC, Vasudevan SR, Churchill G, Goodwin GM, Nobre AC, Harmer CJ. Oxford Lithium Trial (OxLith) of the early affective, cognitive, neural and biochemical effects of lithium carbonate in bipolar disorder: study protocol for a randomised controlled trial. Trials. 2016;17(1):116.
78. Bonsall MB, Wallace-Hadrill SM, Geddes JR, Goodwin GM, Holmes EA. Nonlinear time-series approaches in characterizing mood stability and mood instability in bipolar disorder. In: Proc. R. Soc. B 2012 (Vol. 279, No. 1730, pp. 916-924). The Royal Society.
79. Bopp JM, Miklowitz DJ, Goodwin GM, Stevens W, Rendell JM, Geddes JR. The longitudinal course of bipolar disorder as revealed through weekly text messaging: a feasibility study. Bipolar disord. 2010;12(3):327-34.
80. Benazzi F. Characteristics of bipolar II patients with interpersonal rejection sensitivity. Psychiatry Clin. Neurosci.. 2000;54(4):499-501.
81. Baldessarini RJ, Tondo L, Hennen J. Treating the suicidal patient with bi-polar disorder: reducing suicide risk with lithium. Ann N Y Acad Sci 2001;932:24-43.
82. Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. Acta Psychiatr Scand 2001;104(3):163-172.
83. Tondo L, Pompili M, Forte A, Baldessarini RJ. Suicide attempts in bipolar disorders: comprehensive review of 101 reports. Acta Psychiatr Scand 2016;133(3):174-86.
84. Burgess SS, Geddes J, Hawton KK, Taylor MJ, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. The Cochrane Library. 2001.
85. Cipriani A, Smith KA, Burgess SS, Carney SM, Goodwin G, Geddes J. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. The Cochrane Library. 2006.
86. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
87. Malhi GS, Gershon S, Outhred T. Lithiumeter: Version 2.0. Bipolar Disord. 2016;18(8):631-41.
88. Malhi GS, McAulay C, Gershon S, Gessler D, Fritz K, Das P, Outhred T. The Lithium Battery: assessing the neurocognitive profile of lithium in bipolar disorder. Bipolar Disord. 2016;18(2):102-15.
89. Yerevanian BI, Choi YM. Impact of psychotropic drugs on suicide and suicidal behaviors. Bipolar disord. 2013;15(5):594-621.

90. Zalsman G, Hawton K, Wasserman D, van Heeringen K, Arensman E, Sarchiapone M, Carli V, Höschl C, Barzilay R, Balazs J, Purebl G. Suicide prevention strategies revisited: 10-year systematic review. The Lancet Psychiatry. 2016;3(7):646-59.
91. Baldessarini RJ, Tondo L. Suicidal risks during treatment of bipolar disorder patients with lithium versus anticonvulsants. Pharmacopsychiatry. 2009;42(02):72-5.
92. Rosenthal R. Writing meta-analytic reviews. Psychol Bull. 1995;118:183–192.
93. Riblet NB, Shiner B, Young-Xu Y, Watts BV. Strategies to prevent death by suicide: meta-analysis of randomised controlled trials. Br J Psychiatry. 2017;210:396-402.
94. Girlanda F, Cipriani A, Agrimi E, Appino MG, Barichello A, Beneduce R, Bighelli I, Bisoffi G, Bisogno A, Bortolaso P, Boso M. Effectiveness of lithium in subjects with treatment-resistant depression and suicide risk: results and lessons of an underpowered randomised clinical trial. BMC research notes. 2014;7(1):731.
95. Khan A, Khan SR, Hobus J, Faucett J, Mehra V, Giller EL, Rudolph RL. Differential pattern of response in mood symptoms and suicide risk measures in severely ill depressed patients assigned to citalopram with placebo or citalopram combined with lithium: role of lithium levels. J Psychiatr Res. 2011;45(11):1489-96.

Table 1. Characteristics of systematic reviews and meta-analyses investigating lithium and suicide or self harm. Narrative reviews have not been included.

Study ID	Year of search	Aim	Total studies included	Type of studies included	Inclusion criteria	Quality of evidence
Baldessarini 2001[81]	2000	To assess the risk of suicide or self harm in patients with affective disorders on long-term lithium	33	Randomised and observational	Mixed group of mood disorders (bipolar disorder, major depression and schizoaffective disorder).	Reported, but criteria not explicit.
Tondo 2001[82]	2000	To compare suicide rates with and without long-term lithium treatment in major affective disorders.	22 (on lithium) and 13 (not on lithium)	Randomised and observational	Mixed group of mood disorders (bipolar disorder, major depression and schizoaffective disorder).	Criteria outlined by the authors (based on Rosenthal [92])
Burgess 2001[84]	2000	To assess the effect of lithium on outcome in mood disorders (suicide and self harm considered as part of a range of outcome measures)	9 (data on suicide from only 4 studies)	Only RCTs	RCTs comparing lithium with placebo in the maintenance treatment of mood disorders.	Cochrane criteria
Baldessarini 2003[14]	2002	The effect of lithium treatment on rates of suicide and self harm	42 (on lithium) and 22 (not on lithium)	Randomised and observational (3 were RCTs)	Bipolar disorder and major depression	Not reported
Geddes 2004[12]	2003	To assess the efficacy and acceptability of lithium for relapse prevention in bipolar disorder (suicide was considered as one of the outcomes)	5	Only RCTs	RCTs comparing lithium with placebo in the maintenance treatment of bipolar disorder with at least 3 months of follow-up	Cochrane criteria

Cipriani 2005[25]	2005	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	32	Only RCTs	Mixed group of mood disorders (unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, and rapid cycling)	Cochrane criteria
Baldessarini 2006[24]	2005	To assess the risk of suicide and self-harm whilst on lithium treatment	45 (31 included in meta-analysis)	Randomised and observational (5 RCTs included in meta-analysis)	Mixed group of mood disorders (major depression, bipolar disorder, dysthymia, schizoaffective disorder, and rapid cycling)	Criteria outlined by the authors (based on Rosenthal [92])
Cipriani 2006[85]	2005	To assess the effects of lithium versus antidepressants for the long-term treatment of recurrent affective disorder (suicide was considered as one of the outcomes)	8	Only RCTs	Mixed group of mood disorders (bipolar disorder, major depression and schizoaffective disorder).	Cochrane criteria
Guzzetta 2007[33]	2006	To assess the effect of lithium on suicide and self harm rates in those with major depressive disorder	8	Randomised and observational	Major depressive disorder only	Not reported
Baldessarini 2009[91]	Not stated.	To compare suicide risk during long term (at least 6 months) lithium vs anticonvulsants in patients with bipolar disorder	6 studies with control groups (3 were RCTs, n=538)	Randomised and observational	Bipolar disorder	Not reported
Cipriani 2013[26]	2013	To assess whether lithium has a specific preventive effect for suicide and self harm in people with unipolar or bipolar disorder	48	Only RCTs	Major depression and bipolar disorder (also analysed separately)	Cochrane risk of bias tool

Yerevanian 2013[89]	2013	To assess the impact of psychotropic drugs (including lithium) on suicide and suicidal behaviors.	Systematic search (Medline only), but results presented in a narrative way	Randomised and observational	Bipolar disorder	Not reported
Hawton 2015[34]	2014	To identify all randomised controlled trials of pharmacological agents or natural products for self-harm in adults	7 (one RCT of lithium)	Only RCTs (comparing pharmacological treatments or natural products with placebo or alternative drug treatment)	Individuals with a recent (within six months) episode of self harm resulting in presentation to clinical services.	Cochrane risk of bias tool and GRADE
Tondo 2016[83]	2015	To assess the rate of suicide attempts in bipolar disorder. Those on long-term lithium were specifically excluded	101	Not specifically stated. Mainly observational.	Bipolar disorder	Not reported
Zalsman 2016[90]	2014	To assess the effect of all types of suicide prevention strategy on suicidal behaviour.	1797 in total	Mix of systematic reviews (23), met-analyses (12), RCTs (40), cohort trials (67), population investigations (22).	Suicide prevention strategies of any type. No psychiatric diagnosis specified.	Categorised for level of evidence according to Oxford criteria
Riblet 2017[93]	2015	To assess the effectiveness of all types of intervention in preventing suicide	72 RCTs and 6 pooled analyses of RCTs in total (6 trials of lithium were considered)	RCTs and pooled analyses of RCTs	Suicide prevention strategies of any type. No psychiatric diagnosis specified.	Cochrane risk of bias tool

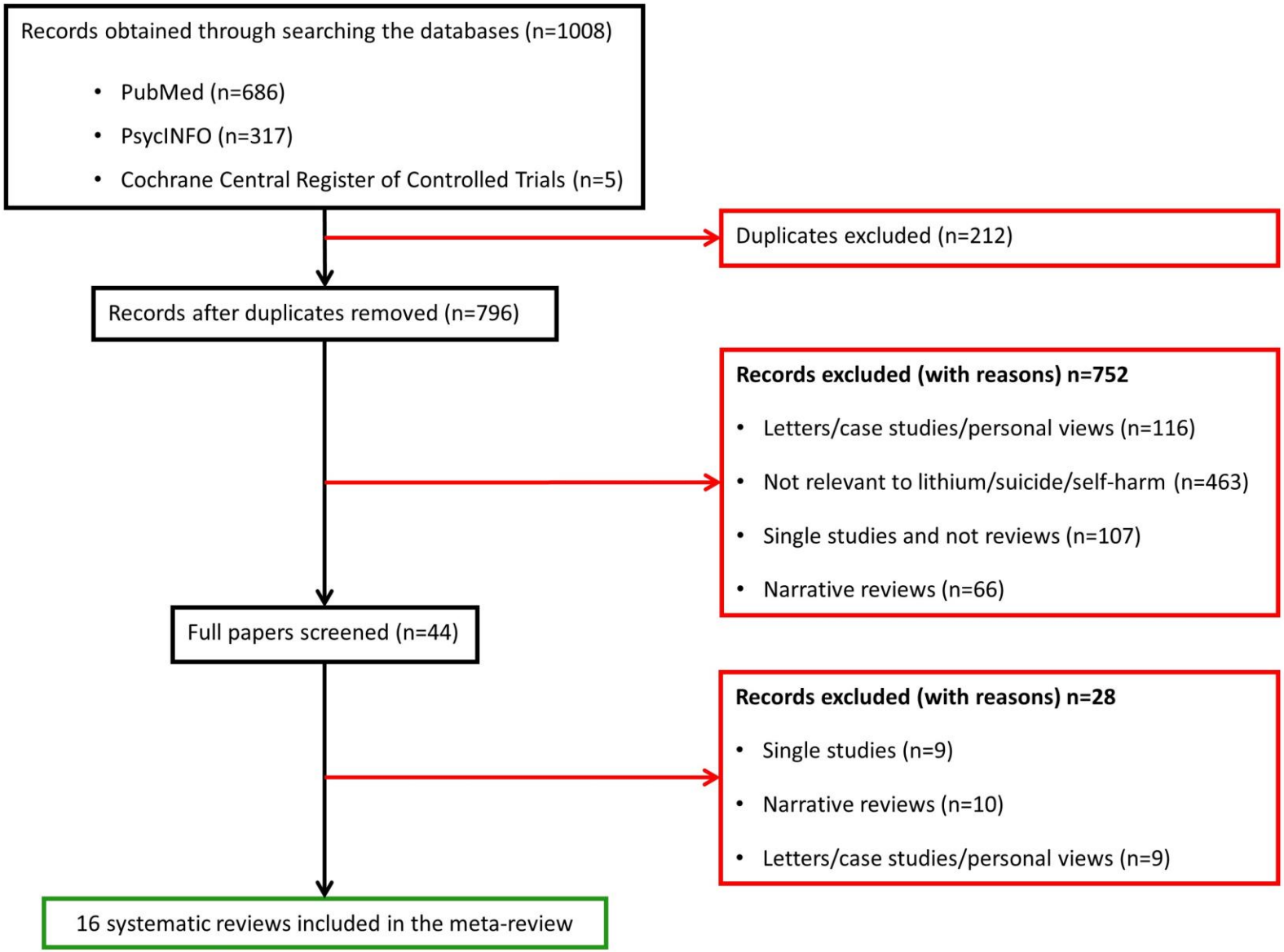

Figure 1. PRISMA flow chart of selected studies.[86] Black boxes present screened data, green boxes present selected studies and red boxes present excluded studies (see Table 1 for full details)