

Lithium and suicide in mood disorders: Updated meta-review of the scientific literature

Katharine A Smith^{1,2} | Andrea Cipriani^{1,2} 

¹Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

²Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

Correspondence

Andrea Cipriani, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK.

Email: andrea.cipriani@psych.ox.ac.uk

Objectives: Suicide and suicidal behaviour are increased in mood disorders, particularly bipolar disorders. Observational studies and small randomized controlled trials (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 PubMed, PsycINFO, and the Cochrane Library systematically for systematic reviews and meta-analyses of RCTs of lithium and suicide and self harm published between January 1980 and June 2017. In the case of multiple publications on the same topic, only the most recent or most comprehensive review was considered.

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 and heterogeneity in terms of participants, diagnoses, comparators, durations, and phase of illness, 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 anti-suicidal effects of lithium have been consistently reported over the past 40 years. The most robust evidence comes from RCTs, but these results are also discussed in the context of the difficulties in conducting high quality studies in this area, and the supporting evidence that observational and non-randomized studies can also provide. Given this evidence, however, the use of lithium is still underrepresented in clinical practice and should be incorporated more assertively into current guidelines.

KEYWORDS

bipolar disorder, lithium, meta-analysis, mood disorders, randomized controlled trial, self harm, suicide, systematic review, unipolar depression

1 | 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 in 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 disorders¹² and is superior to other mood stabilizers,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 randomized) 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 organization in the USA and compared rates of suicide attempt and suicide death in those taking lithium with rates in those taking valproate. They showed a greater anti-suicidal effect in those taking lithium. The risk of suicide was 2.7 times higher (95% confidence interval [CI] 1.1-6.3) during treatment with valproate than during treatment with lithium. Corresponding hazard ratios for non-fatal attempts were 1.7 (95% CI 1.2-2.3) for attempts resulting in hospitalization and 1.8 (95% CI 1.4-2.2) 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 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 criticized 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 from 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 randomized 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 their relationship to lithium treatment.

2 | 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 1 January 1980 and 1 June 2017. No age or language restrictions were applied and the following keywords were used: *lithium, suicide, self harm, suicide attempt, non-suicidal self-injury, depression, bipolar and mood disorder*. In the 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.

3 | 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 that 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 randomized 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?

3.1 | 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 were published by the same group of authors (Cipriani and colleagues) initially in 2005, with an updated review published in 2013.^{25,26} Both of these reviews used a similar methodology and combined results from RCTs lasting at least 3 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 their initial review,²⁵ Cipriani and colleagues found 32 RCTs with 1377 patients randomized to lithium and 2052 to other compounds,

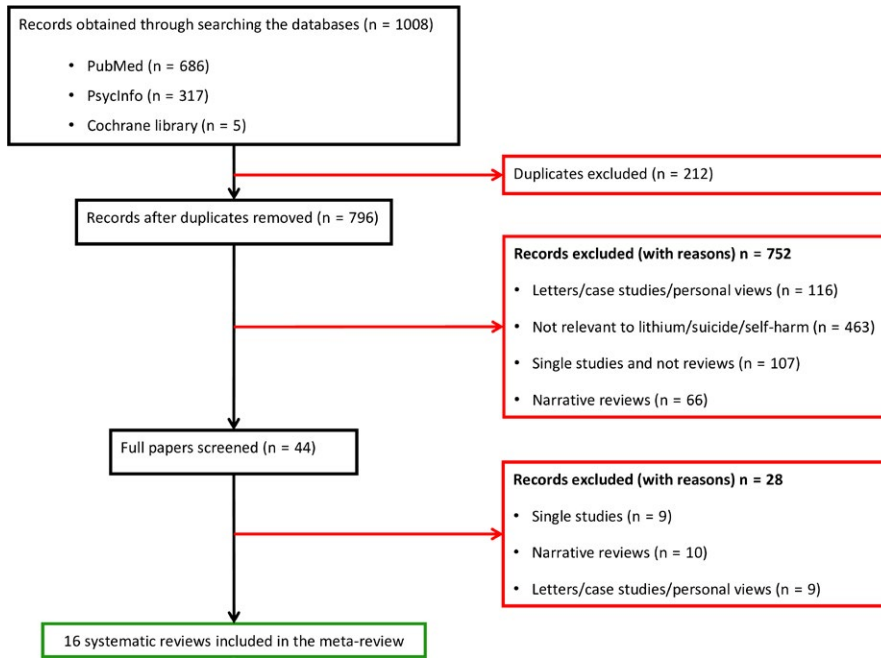


FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow chart of selected studies.⁸⁶ Black boxes present screened data, green boxes present selected studies and red boxes present excluded studies (see Table 1 for full details)

and reported a reduction in the rate of suicide (odds ratio [OR] 0.26, 95% CI 0.09-0.77), a reduction in the rate of suicide and self harm combined (OR 0.21, 95% CI 0.08-0.50) and a 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 6674 randomized 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 (OR 0.38, 95% CI 0.15-0.95). Lithium showed less clear benefits in preventing deliberate self harm than placebo (OR 0.60, 95% CI 0.27-1.32). 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 >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 came to a somewhat different conclusion.⁹³ The authors investigated all strategies for suicide prevention, and in their analysis of the effect of lithium included only six trials. They included a new study (by Girlanda and colleagues)⁹⁴ which had been published after the 2013 review by Cipriani²⁶ and also included another study with no suicidal events in either the lithium or placebo groups.³⁹ Their overall conclusion was that, although four of the six studies they included suggested a benefit for lithium (with overall numbers of 1 suicide in 313 patients in the lithium group vs 6 suicides in 306 patients in the control group) the result was not statistically significant. The decision to include the study by Girlanda et al⁹⁴ 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 randomized, 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 these data. Whilst the authors of the 2017 systematic review⁹³ 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

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 et al 2001 ⁸¹	2000	To assess the risk of suicide or self harm in patients with affective disorders on long-term lithium	33	Randomized and observational	Mixed group of mood disorders (bipolar disorder, major depression and schizoaffective disorder)	Reported, but criteria not explicit
Tondo et al 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)	Randomized and observational	Mixed group of mood disorders (bipolar disorder, major depression and schizoaffective disorder)	Criteria outlined by the authors (based on Rosenthal ⁹²)
Burgess et al 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 et al 2003 ¹⁴	2002	To consider the effect of lithium treatment on rates of suicide and self harm	42 (on lithium) and 22 (not on lithium)	Randomized and observational (3 were RCTs)	Bipolar disorder and major depression	Not reported
Geddes et al 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 et al 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 et al 2006 ²⁴	2005	To assess the risk of suicide and self harm whilst on lithium treatment	45 (31 included in meta-analysis)	Randomized 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 et al 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 et al 2007 ³³	2006	To assess the effect of lithium on suicide and self-harm rates in those with major depressive disorder	8	Randomized and observational	Major depressive disorder only	Not reported
Baldessarini et al 2009 ⁹¹	Not stated	To compare suicide risks during long-term (at least 6 months) treatment with lithium vs anticonvulsants in patients with bipolar disorder	6 studies with control groups (3 were RCTs; n = 538)	Randomized and observational	Bipolar disorder	Not reported

Study ID	Year of search	Aim	Total studies included	Type of studies included	Inclusion criteria	Quality of evidence
Cipriani et al 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 et al 2013 ⁸⁹	2013	To assess the impact of psychotropic drugs (including lithium) on suicide and suicidal behaviours	Systematic search (Medline only), but results presented in a narrative way	Randomized and observational	Bipolar disorder	Not reported
Hawton et al 2015 ³⁴	2014	To identify all randomized 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 6 months) episode of self harm resulting in presentation to clinical services	Cochrane risk of bias tool and GRADE
Tondo et al 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 et al 2016 ⁹⁰	2014	To assess the effect of all types of suicide prevention strategy on suicidal behaviour	1797 in total	Different study types including systematic reviews (23), met-analyses (12), RCTs (40), cohort trials (67) and population investigations (22)	Suicide prevention strategies of any type. No psychiatric diagnosis specified	Categorized for level of evidence according to Oxford criteria
Riblet et al 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

GRADE, grading of recommendations assessment, development and evaluation; RCT, randomized controlled trial.

methodological challenges with the study by Girlanda et al⁹⁴ (which are recognized and thoroughly discussed by the authors) should call into question the inclusion of this study in such a systematic review.

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 randomized evidence synthesized 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 methodological quality (especially of the older ones) was variably performed and reported. 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 colleagues²⁶ specified a minimum treatment period of 3 months in their review, the range varied, with a mean follow-up of 19.1 (standard deviation [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 or 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 in 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 et al¹⁵ ($n = 20\ 638$, discussed above) and Hayes et al²⁹ ($n = 14\ 396$, discussed below) include numbers far

greater than could ever be recruited into a randomized controlled 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, and 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 has overcome these issues by comparing lithium to other mood-stabilizers, antidepressants 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 an RCT still result in relatively small numbers of participants. For example, the researchers in the bipolar affective disorder: lithium/anticonvulsant comparative evaluation 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 for 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 is 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 et al²⁶ 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.

3.2 | 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 subgroup 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 most recent update in 2011 of their original search from 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 6 months preceding trial entry. This excluded a number of studies that included participants with a more distant history of self harm (for example Oquendo et al³⁶) or studies that 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 vs 3/83 in the placebo group) 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 the probability of no event in the lithium group was $<5\%$. Adjusting their analysis for differing person-years of exposure in the two groups, they concluded that the 95% CI of the placebo incidence rate (IR) of suicides of 0.065 (range 0.013–0.190) did not cover the zero IR of the lithium group ($P = .049$). However, the reanalysis in the systematic review³⁴ (0/84 versus 3/83; OR 0.14, CI 0.01–2.68) did not support this claim for statistical significance and concluded that 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 et al³⁶ was excluded from the Hawton et al review because not all patients had reported self harm in the previous 6-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 0.27–1.32).²⁶ Lithium was, however, more effective than carbamazepine in reducing the number of self-harm episodes (OR 0.14, CI 0.02–0.83).

These findings from RCTs are in contrast to the observational data, which suggest that lithium may indeed reduce self harm when

compared to other mood stabilizers.^{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-stabilizing treatments.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 that 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 and 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 USA is currently undertaking a large randomized trial of lithium for suicide prevention, expecting to randomize 1862 veterans with depression (from both bipolar disorder and major depressive disorder) to either adjunctive lithium or placebo, and to follow them for up to 1 year (<https://clinicaltrials.gov/ct2/show/NCT01928446>) and data from this trial will help to inform us further on the effects of adjunctive lithium on suicidal behaviour.

3.3 | Lithium and suicidal ideation

Suicidal ideation and thoughts of hopelessness should be another important area of study with respect to lithium. However, the data are 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 are 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 (S-STs, 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 that 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 experiencing 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.

4 | DISCUSSION

Taken together, the randomized 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 subsyndromal 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 suicide 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 stabilizers do not seem to have the same anti-suicidal 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 stabilization 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 has some ability to 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-stabilizing 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 considered 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 are associated with increased suicide risk²⁴ and are common traits in bipolar disorder. The anti-aggressive properties of lithium are well reported,⁵³ as are reductions in impulsivity.^{54,55} 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 an effect on,³³ or even a worsening of,⁵⁶ symptoms associated with suicide such as agitation, restlessness, 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 may mediate this effect. Kalkman and colleagues, for example, have proposed a role for 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 those with 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 et al studied euthymic patients diagnosed with bipolar disorder, and showed that patients treated with lithium ($P = .007$) and healthy controls ($P = .001$) 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 recognizing 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 effects of clozapine and lithium on suicidal behaviour are related to their pronounced effects on serotonin. Dysfunction in the serotonergic system has been associated with suicidal behaviour⁶¹ 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 anti-suicidal 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.

5 | 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 anti-suicidal action of lithium. Lithium is the only medication in bipolar disorder thus far to have been shown to have a specific anti-suicidal 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 and Müller-Oerlinghausen⁶³ concluded that there was clear evidence of an anti-suicidal effect of lithium, but commented that this had not translated into guidelines or clinical practice. Whilst more recent guidelines have incorporated these recommendations for 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 treatment⁶⁸ 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 <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, closely monitoring serum levels to avoid

sustained periods where lithium levels are high.⁴¹ New innovations such as the lithiummeter⁸⁷ allow the management of lithium levels to be more streamlined and to help patients to adhere carefully to self and clinician-guided monitoring. The lithiummeter 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, optimization 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 from 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 anti-suicidal effect of lithium also seems to be accompanied by a reduction in non-suicide related deaths.

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 anti-suicidal 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 Oxford Lithium Trial (Oxlith),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 disorder⁷⁸ 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 stabilization 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-stabilizing 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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ORCID

Andrea Cipriani  <http://orcid.org/0000-0001-5179-8321>

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