Lithium in the prevention of suicide in adults: systematic review and meta-analysis of clinical trials

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Summary

Controversy exists regarding the efficacy of lithium for suicide prevention. Except for a recent trial that enrolled over 500 patients, available trials of lithium for suicide prevention have involved small samples. It is challenging to measure suicide in a single randomised controlled trial (RCT). Adding a single large study to existing meta-analyses may provide insights into lithium’s anti-suicidal effects. We performed a meta-analysis of RCTs comparing lithium with a control condition for suicide prevention. MEDLINE and other databases were searched up to 30 November 2021. Efficacy was assessed by calculating the summary Peto odds ratio (OR) and incidence rate ratio (IRR) with 95% confidence intervals. Among seven RCTs, the odds of suicide were lower among patients receiving lithium versus control (OR = 0.30, 95% CI 0.09–1.02; IRR = 0.22, 95% CI 0.05–1.05), although the findings were still not statistically significant. The role of lithium in suicide prevention remains uncertain.

Keywords

Lithium; suicide prevention; anti-manic agents; randomised controlled trials; systematic review.

Method

As described in the supplementary Methods (available at https://doi.org/10.1192/bjo.2022.605) we developed a study protocol to identify studies, abstract study data, assess study quality and determine the effect of lithium on suicide. The protocol was posted on PROSPERO (CRD42022295822).

We included studies that randomly assigned adult patients to lithium or a control condition (usual care, placebo or waiting list). We searched MEDLINE (via Ovid), EMBASE, CINAHL, the Cochrane Library’s CENTRAL, and PsycINFO from 1 January 2015 to 30 November 2021 to identify published (including ‘Epub ahead of print’) articles that met our inclusion criteria.

We evaluated the relationship between lithium and suicide using the Peto method. We calculated summary OR with 95% CI and P-values. We used a Poisson regression model with random effects to calculate an IRR for suicides over person-years. We applied GRADE methodology to determine the effect of the quality of the evidence on our findings. All analyses were conducted using STATA version 17 for Windows (StataCorp). Because this was a study of published literature, ethics approval and informed consent were not required.

Results

As shown in supplementary Fig. 1, we identified seven RCTs that randomly assigned adult patients to lithium or a control condition (placebo or usual care) and reported on suicide. The seven studies were all conducted in Europe and North America and enrolled patients with major depressive disorder or bipolar disorder (supplementary Table 1).

Within the identified studies, the odds of suicide were lower for the 568 patients allocated to lithium than for the 570 allocated to a control condition (OR = 0.30, 95% CI 0.09–1.02, P = 0.05) (Fig. 1). The IRR favoured lithium (IRR = 0.22, 95% CI 0.05–1.05, P = 0.06). The findings, however, were not significant.

We did not observe substantial or significant heterogeneity among the included studies (Cochran’s $Q = 3.60, I^2 = 0\%$, $P = 0.61$). On visual inspection, we identified one study with an extremely wide confidence interval. This was the only study that
Our meta-analysis showed that lithium was associated with a 70% lower odds of suicide. Although the finding is promising, the results were not significant. Our results corroborate those of prior meta-analyses as well as that of an individual large trial suggesting that there is insufficient evidence to support that lithium has an anti-suicidal effect. Yet the results of our review emphasise the need to study further the role of lithium for suicide prevention. First, unlike prior meta-analyses, by including over 1000 patients in our analysis, we were able to generate a substantially narrowed precision of the estimate. The trials, however, varied in their target (and actual) lithium levels. Some studies reported poor adherence problems with recruitment.

In a risk of bias assessment, we identified some concerns about the potential effect of study assignment and adherence (supplementary Table 2). This was usually because the authors reported that some participants did not adhere to the study drug. Several studies reported high rates of attrition. A few studies encountered problems with recruitment.

A visual inspection of the funnel plot suggested no evidence of publication bias. The summary estimate included a smaller study that reported a negative result (Fig. 1; supplementary Fig. 2).

According to our GRADE analysis, the certainty of the evidence in favour of lithium was moderate. The finding was important as it pertains to mortality (supplementary Table 3).

**Discussion**

Our meta-analysis showed that lithium was associated with a 70% lower odds of suicide. Although the finding is promising, the results were not significant. Our results corroborate those of prior meta-analyses as well as that of an individual large trial suggesting that there is insufficient evidence to support that lithium has an anti-suicidal effect. Yet the results of our review emphasise the need to study further the role of lithium for suicide prevention. First, unlike prior meta-analyses, by including over 1000 patients in our analysis, we were able to generate a substantially narrowed confidence interval around the IRR estimate. Second, we made a conservative decision to exclude from the analysis a single death due to opioid overdose. There was no indication in the study that this death was classified as a suicide. Experts in the field have raised concerns that some overdose deaths may be misclassified suicides. Related to these concerns, in the suicide prevention literature there is growing interest in addressing self-injury mortality (defined as suicide deaths by any method plus estimated deaths due to accidental or undetermined drug overdose) rather than suicide mortality alone. The inclusion of that overdose death in our study would have generated a significant finding in favour of lithium for self-injury mortality prevention (OR = 0.28, 95% CI 0.08–0.90; IRR = 0.20, 95% CI 0.04–0.93). Lastly, it is worth recalling that a P-value of 0.05 or 0.06 indicates a 5–6% possibility that our results were due to chance rather than an anti-suicide effect of lithium.

There are several proposed theories to explain why lithium might be effective at preventing suicide. One of the many possibilities includes lithium’s role as a mood stabiliser. There is some evidence in the literature that links impulsivity to suicidal behaviour. For example, in a 14-year naturalistic study of patients with affective illness, Maser et al (2002) found that impulsivity was one of the best predictors of suicide after 1-year follow-up (sensitivity 74%, specificity 82%).

It is a strength of our review that we have produced summary estimates for over 1100 patients and improved the precision of the estimate. The trials, however, varied in their target (and actual) lithium levels. Some studies reported poor recruitment, low treatment adherence or high study attrition. Most studies followed patients for less than 1 year. Finally, the generalisability of our results to populations outside of Europe and North America, or patients without depression or bipolar disorder, remains unclear.

Because the findings from our meta-analysis raise questions about the benefit of lithium for suicide prevention, we caution...
Clinicians, researchers and policymakers against dismissing further examination of lithium for suicide prevention.

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Supplementary material

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Data availability

The data sources used in this study are available from the corresponding author on reasonable request.

Author contributions

N.B.R.: conceptualisation, methodology, formal analysis, investigation, software, data curation, validation, visualisation, article drafting, reviewing and editing; Y.Y.-X.: conceptualisation, methodology, formal analysis, investigation, software, validation, article drafting, reviewing and editing; B.S.: conceptualisation, data curation, funding acquisition, project administration, resources, visualisation, article drafting, reviewing and editing; B.V.W.: conceptualisation, data curation, article reviewing and editing, visualisation, supervision.

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Declaration of interest

None.

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