

Correspondence

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The evidence for lithium in suicide prevention

We read with interest the recently published meta-analysis of suicide prevention strategies by Riblet *et al.*¹ However, we have some concerns about the authors' conclusion that 'unlike previous reviews,^{2,3} we did not find that lithium significantly reduced suicide'. This statement is at odds with the finding from our own meta-analysis in 2013, which found that lithium was more effective than placebo in reducing the number of suicides.⁴ The difference between the two meta-analyses relies solely on the addition of data from a single non-blind pragmatic trial.⁵ Although the authors do state that 'the results of the summary estimate for lithium became statistically significant after removing a more recent study [Girlanda *et al.*⁵] with several methodological limitations', they fail to point out two key issues with regard to the addition of this trial, on which one of us (A.C.) was co-investigator.

Riblet *et al* fail to highlight that this study was not placebo controlled, unlike all the other studies contributing data to their meta-analysis, and was reported as essentially a failed, underpowered study.⁵ Including this study is, at the very least, highly questionable. Just as the authors reasonably included only randomised controlled trials (RCTs) in their analysis, so we would argue that it is inappropriate to include a non-placebo-controlled trial in a meta-analysis aiming to estimate the efficacy of lithium.

Furthermore, the fact that the addition of data from a single RCT with 53 patients, and just one completed suicide, appears to materially change the estimate of effect serves to highlight the major point that Riblet *et al* fail to discuss. As we have previously noted,⁴ randomised data in this area are sparse and estimates of efficacy are therefore highly unstable. It simply is not yet possible to determine, on the basis of randomised evidence alone, whether lithium does or does not reduce – and this may be an enduring uncertainty, given the low event rate of suicide and the practical and feasibility challenges of conducting adequately powered trials.

Although acknowledging the limitations of the randomised evidence, it is important to note that there are several large-scale observational studies that also find a reduced incidence of completed suicide among those on lithium treatment that is of a size consistent with the randomised evidence.^{6–8} Taking the randomised and observational data together, and in view of the sensitivity of Riblet *et al*'s results to the inclusion or exclusion of a single methodologically heterogeneous trial, we believe that the combined current evidence indicates that lithium probably has a substantial and clinically important anti-suicidal effect.

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Authors' reply: We thank Roberts and colleagues for their thoughtful critique of our meta-analysis.¹ They question our decision to include Girlanda *et al*² in our meta-analysis of trials of lithium for the prevention of death by suicide. Roberts *et al* aptly highlight that the Girlanda *et al* study had several methodological limitations. Although the study was described as a randomised assessor-masked trial, the comparison arm consisted of usual care; in addition, the study did not achieve the target sample size.

Since our meta-analysis evaluated randomised trials of behavioural and pharmacological interventions, we included trials that used usual care, placebo or waiting-list control conditions. Although there are many benefits to using a placebo control condition, a number of legitimate counter-arguments have also been raised, even in the case of pharmacological trials.³ In fact, some authors have suggested that, if a trial is of pragmatic design, a usual-care control may be more appropriate than placebo.³ We had no specific inclusion criteria involving study size. In fact, one advantage of meta-analysis is the ability to pool multiple underpowered studies; consequently, we feel that the size of the individual studies is less relevant. In our original manuscript, we did perform a sensitivity analysis by removing the Girlanda *et al* trial from our analysis because of its multiple methodological limitations. We agree, however, with Roberts *et al* that we should have made it clear to the reader that the Girlanda *et al* trial used usual care, rather than placebo, as the control condition.²

Consistent with the salient points made by Girlanda *et al* in the discussion section of their paper,² we agree that it is important that readers are aware of the results of all randomised trials evaluating lithium for suicide prevention, regardless of the findings or the power of the individual study. In fact, Girlanda *et al* highlighted that it would be important for their results to be