

## Response to “Strategies to prevent death by suicide: meta-analysis of randomised controlled trials”

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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' conclusions that “unlike previous reviews, [2,3] we did not find that lithium significantly reduced suicide.”

This statement is at odds 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] Whilst the authors do state that ‘the results of the summary estimate for lithium became statistically significant after removing a more recent study with several methodological limitations [5]’, they fail to point out two key issues with regards the addition of this trial, on which one of us, AC, was co-investigator.

Riblet et al fail to highlight that this study was not placebo controlled, unlike all 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 author’s reasonably included only randomised controlled trials 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 randomised controlled trial 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 whether lithium does or does not reduce the risk of suicide on the basis of randomised evidence alone - 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.

While 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 in those on lithium treatment of a size consistent with the randomised evidence [6, 7]. 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 antisuicidal effect.

#### References:

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