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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.

1 Riblet N, Shiner B, Young-Xu Y, Watts B. Strategies to prevent death by suicide: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2017; **210**: 396–402.

2 Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide prevention strategies: a systematic review. *JAMA* 2005; **294**: 2064–74.

3 Zalsman G, Hawton K, Wasserman C, Van Heeringen K, Arensman E, Sarchiapone M, et al. Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry* 2016; **3**: 646–59.

4 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:** 1805–19.

5 Girlanda F, Cipriani A, Agrimi E, Appino M, Barichello A, Beneduce R, et al. 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**: 1–8.

6 Song J, Sjölander A, Joas E, Bergen SE, Runeson B, Larsson H, et al. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. *Am J Psychiatry* 2017; **174**: 795–802.

7 Hayes JF, Pitman A, Marston L, Walters K, Geddes JR, King M, et al. 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**: 630–7.

8 Silverman SL. From randomized controlled trials to observational studies. *Am J Med* 2009; **122**: 114–20.

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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

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'incorporated into future meta-analytical reviews'.[2] A co-author of Roberts *et al*'s letter to the editor (Cipriani) was also a co-author on this publication by Girlanda *et al*.

Ultimately, although we agree that the results of observational studies certainly support a role for lithium in suicide prevention, we feel that there is a clear need for more randomised trials evaluating its efficacy in preventing death by suicide. The substantial effect of a single trial highlights the tenuousness of findings regarding lithium in RCTs. Fortunately, a brief search of clinicaltrials.gov suggests that there is a large trial of lithium for suicide prevention underway (NCT01928446) and another trial that was recently completed (NCT01134731). Notably, a third trial was prematurely terminated (NCT00520026).

1 Riblet N, Shiner B, Young-Xu Y, Watts B. Strategies to prevent death by suicide: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2017; **210**: 396–402.

2 Girlanda F, Cipriani A, Agrimi E, Appino M, Barichello A, Beneduce R, et al. 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**: 1–8.

3 Avins AL, Cherkin DC, Sherman KJ, Goldberg H, Pressman A. Should we reconsider the routine use of placebo controls in clinical research? *Trials* 2012; **13**: 44.

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Where is the argument for the conceptual slippery slope?

I do concur with the position laid down by Brendan Kelly[1] in commentary on the paper by Verhofstadt *et al*[2] and his conclusion that 'we should not kill our patients'. However, one argument he has surprisingly not used is that of a 'slippery slope'. In particular, Beauchamp & Childress[3] specify two versions of this argument. The psychological–sociological one is well-known and is often cited as an argument against euthanasia. However, the conceptual slippery slope is by far the more dangerous and is exemplified here so succinctly. In Verhofstadt *et al* we have 'unbearable suffering' as a concept leading almost effortlessly and uncritically to the euthanasia of psychiatric patients who have no terminal disease. What is so shocking is that this is no sterile philosophical debate: it is in action in a European country and has led to patient deaths. This subjugation demonstrates the biggest risk in the euthanasia debate and should be actively resisted.

1 Kelly B. Invited commentary on: When unbearable suffering incites psychiatric patients to request euthanasia. *Br J Psychiatry* 2017; **211**: 248–9.

2 Verhofstadt M, Thienpont L, Peters G-JY. When unbearable suffering incites psychiatric patients to request euthanasia: qualitative study. *Br J Psychiatry* 2017; **211**: 238–45.

3 Beauchamp TL, Childress JF. *Principles of Biomedical Ethics (4th edn)*. Oxford University Press, 1984.

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Author's reply: I am very grateful to Dr Clifford for his letter. He is entirely correct to highlight the slippery slope. There are several slippery slopes here. Will the practice of euthanasia on the basis of suffering resulting from mental illness alone expand to less severe forms of mental illness, to earlier mental illness and to people without mental illness themselves but who experience substantial suffering as a result of mental illness in someone else (e.g. a family member)? The reason why I did not present the slippery slope argument initially was because the argument can, ironically, become a slippery slope itself, as skilled rhetoricians invoke all kinds of unlikely speculative scenarios with substantial emotional power, but limited practical relevance. Nonetheless, Dr Clifford's point is clearly right and I am especially pleased that he agrees with the central point of my commentary: we should not kill our patients.

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Authors' reply: Given that a recent trend analysis[1] revealed an increase in instances of euthanasia of people with psychiatric disorders since the Belgian law on euthanasia came into effect in 2002 (despite unresolved matters of great concern), Dr Clifford's call not to ignore the potential risks of euthanasia legislation and practice is indeed essential. Since legalised euthanasia affects directly involved actors as well as healthcare systems and (inter)national societies, discussion of slippery slope arguments is necessary to stay alert and prevent ethically unacceptable acts from being accepted.

At the same time, it is important to safeguard against these discussions becoming purely philosophical, uncorroborated or even leading to a slippery slope fallacy, as might be the case if they are not based on scientific evidence. Hence, it is striking that 15 years after Belgium introduced its euthanasia law, euthanasia among psychiatric patients is still underexamined. Our own study[2,3] has concentrated on the reality of clinical euthanasia practice in Belgium and finding ways of improving its transparency and quality.

In an effort to outline this reality, we would like to react to Dr Clifford's assumption that unbearable suffering as a concept might 'lead almost effortlessly and uncritically to euthanasia'. As we stated in the introduction to our paper,[2] unbearable suffering is a necessary but not a sufficient condition for granting euthanasia requests in Belgium (other conditions being the competent patient repeatedly making a voluntary and well-considered request, and suffering being rooted in an incurable medical illness without prospect of improvement[4]). Furthermore, for patients who are not terminally ill, the Belgian euthanasia law stipulates the specific legal requirement of due care that two additional independent physicians, one of whom is specialised in the patient's disorder, must be involved in careful assessment and evaluation of all the legal requirements. Hence, in the context of psychiatric patients requesting euthanasia, consultations with at least one psychiatrist are mandatory.

Our study[2,3] focused on just one of the key criteria, unbearable suffering, as it represents the most subjective and indeterminate criterion in granting euthanasia requests in the absence of an overarching solid definition and psychiatric assessment tool. In order to contribute to vigilance regarding euthanasia practice, especially concerning psychiatric patients, who are a particularly vulnerable group, the assessment of key criteria such as unbearable suffering should be undertaken as comprehensively and accurately as possible.

It is precisely this scientific involvement that might inform both the slippery slope discussion and the questioning of euthanasia as an end-of-life option on grounds of these arguments. In light of