

Review: long term lithium treatment lowers suicide risk in major affective disorder

Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. *Acta Psychiatr Scand* 2001 Sep;104:163–72.

QUESTION: In patients with a major affective disorder, is long term lithium treatment associated with a lower suicide risk?

Data sources

Studies were identified by searching *Current Contents*, Medline, PsycLIT, and PubMed from the 1960s. Pertinent publications (since 1949) were also searched, and experts were contacted.

Study selection

Studies were selected if they examined lithium treatment in patients with bipolar manic depressive disorder, major affective disorder (including recurrent major depression), or schizoaffective disorder, and included data for estimating suicide rates.

Data extraction

Data were extracted on patient diagnoses, study design, number of suicides, total number of patients at risk for suicide, at-risk exposure times, and study quality. Study quality was assessed by using a quality scoring scale (maximum score 7, which referred to the highest quality score) and expressed as a percentage of the maximum.

Main results

22 studies (5647 patients, 33 473 patient y at risk, mean quality rating 47%, 3 randomised trials) were identified that included data on suicide risk data during maintenance lithium treatment (weighted mean treatment duration 6.02 y). 13 studies also provided suicide risk data on 1439 patients who were not receiving lithium treatment (mean duration of observation 5.03 y). Based on a random effects model (22 studies), the overall weighted suicide rate during lithium treatment was 0.16%/year (95% CI 0.13% to 0.20%/y), and the weighted suicide rate when not receiving lithium treatment was 0.88%/year (CI 0.63% to 1.12%/y). 12 studies that reported suicide rates with and without lithium treatment, in which events occurred in the control group, showed higher suicide risks when not receiving lithium treatment than when receiving treatment (weighted risk ratio 8.85, CI 4.14 to 19.1, $p < 0.0001$; random effects model).

Conclusion

In patients with a major affective disorder, long term lithium treatment lowers suicide risk.

COMMENTARY

The question of whether prophylactic lithium reduces the risk for suicide in mood disorder is clinically important because of the high rate of suicide in mood disorder and the lack of evidence that other treatments (such as antidepressants) affect suicide rates. All research in suicide prevention faces the common challenges of the rarity of suicide (even in high risk groups) and the ethical constraints of clinical trials on suicide. Good evidence on this question has been difficult to obtain.

The meta-analysis by Tondo *et al* involves a careful search for all relevant clinical trials. It concludes that patients with mood disorder who use lithium have lower rates of suicide than those who do not use lithium. This finding concurs with other recent reviews.^{1 2}

The major limitation of this meta-analysis is that it is not confined to randomised controlled trials. In fact, several of the included studies did not use parallel control groups at all. This raises the issue of the comparability of patients who did and did not take lithium. For example, some of the studies used control groups comprising patients who had dropped out of lithium treatment. Such patients probably differ substantially from patients who continued to take lithium; patients who were able to tolerate the discipline of lithium treatment may have been at lower inherent risk for suicide than those unable or unwilling to comply.

Thus, although the size of the antisuicidal effect found in the meta-analysis is striking, to what extent the reduction in risk with lithium is a treatment effect rather than a between-patient difference remains uncertain. If lithium does exert a true treatment effect, the mechanism of action is unclear. It could be either a direct antisuicidal effect or an effect secondary to prevention of relapse. Only the large-scale randomised controlled trials in non-selected groups of patients that compare lithium with another effective maintenance treatment and that use suicide (or a suitable proxy) as an outcome measure will give a clearer answer to this question.

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- 1 Crundwell JK. Lithium and its potential benefit in reducing increased mortality rates due to suicide. *Lithium* 1994;5:193–204.
- 2 Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. *Acta Psychiatr Scand* 1999;100:406–17.

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Sources of funding:
National Association
for Research on
Schizophrenia and
Affective Disorders;
Theodore and Vada
Stanley Foundation
(LT); National
Institutes of Health;
Bruce J. Anderson
Foundation; McLean
Private Donor
Neuropsychopharmacology
Research Fund.

Abstract and
commentary also
appear in
*Evidence-Based Mental
Health*.