Suicide risk and lithium

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The study by Katz and coauthors[1] adds to the literature on anti-suicide properties of lithium in patients with mood disorders. The RCT enrolled a large number of participants with major depression or bipolar disorder, most with clinically complex presentations - profiles commonly seen in the veteran populations. The trial was prematurely terminated following futility analysis. What conclusions can be drawn? The findings contrast with a bulk of naturalistic and epidemiological data showing an evident suicide-protective effect of lithium.[2] We concur with the accompanying editorial by Baldessarini and Tondo[3] indicating that several factors, including low serum levels of lithium as well as the high rates of psychiatric comorbidity, and the brief treatment exposure among the others, might be responsible for these findings. To wit, Ahrens et al.[4] concluded that the mortality reducing effect of lithium can take up to two years. As suicide risk varies over time, the study duration may have been too short to capture a true pharmacological effect.

Additionally, two aspects might help in the interpretation of the trial results. First, it is unclear why patients with high personal risk of suicide (≥ 6 previous lifetime episode) were excluded from the recruitment. Such patients are exemplars of a high suicide risk phenotype in whom lithium is likely to exert its antisuicidal effect more substantially. Together with the very high rates of substance use (which might dilute the effectiveness of any pharmacological treatment), this factor might have contributed to a potential bias in the patient selection. The second aspect reflects the possibility that RCTs might not be the most appropriate methodology to assess lithium antisuicidal properties. Indeed, meta-analytical estimates of the reduction of suicide risk under lithium are of large magnitude (7 fold decrease) pointing to a very large signal to noise ratio[5] unlikely to be influenced by bias or factors other than a treatment effect. Since the noise is constituted by the accuracy of the diagnosis, RCT recruiting complex clinical presentations might enlarge the denominator making problematic to detect the signal (treatment effect), as well as impacting on sample size estimates. So, can we conclude that lithium is of no benefit in those at the risk of suicide or is it the effect restricted to a narrower patient population? The table in the Baldessarini and Tondo commentary suggests that lithium reduces suicide rates, but most studies listed are on more selected patients. Mood disorders are most likely heterogeneous, as is their response to the treatment.

References

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