

Lithium, valproate, and suicide risk: Analysis of 98,831 cases

Dan Giurca, MD

The current academic psychiatry paradigm reinforces that lithium reduces suicide risk, more so than other medications, including valproate. However, data from multiple sources contradict this “evidence-based” belief.

Data do not support lithium’s supposed advantage

An 8-year prospective study in Sweden by Song et al¹ tracked 51,535 patients with bipolar disorder from 2005 to 2013. In their conclusions, the authors of this study omitted some surprising numbers that contradict the dominant paradigm. There were 230 (1.089%) completed suicides in the lithium group (N = 21,129), 99 (1.177%) in the valproate group (N = 8,411), and 308 (1.195%) in the “other medication” group (N = 25,780). This difference of .088% is too small (95% CI, -.180% to .358%) to substantiate the purported advantage of lithium over valproate. More important is that in terms of suicide-related events, the medication group excluding lithium and valproate had 2,018 (7.8%) events vs lithium 2,142 (10.1%) and valproate 1,105 (13.1%). The difference of 2.3% is statistically significant (95% CI, 1.8% to 2.8%). These numbers reflect fewer suicide-related events with psychiatric medications other than lithium and valproate. Compounding the problem is a design flaw in which 3,785 patients were counted twice in the lithium and valproate groups (21,129 + 8,411 + 25,780 = 55,320, which is more than the 51,535 patients in the study). By falsely inflating the denominator (N) for the lithium and valproate groups, the respective published rates are deceptively lower than the actual rates. Song et al¹ did

not provide an adequate explanation for these findings and omitted them from their conclusions.

In *Schatzberg’s Manual of Clinical Psychopharmacology*, the authors cited Song et al¹ but omitted these findings as well, and stated “lithium is clearly effective in preventing suicide attempts and completions in bipolar patients.”² In *Stahl’s Essential Psychopharmacology*, the author wrote “lithium actually reduces suicide in patients with bipolar disorder.”³ In a review article, Baldessarini et al⁴ stated “the overall risk of suicides and attempts was five times less among lithium-treated subjects.” These claims are contradicted by the data from Song et al.¹ In contrast, in a double-blind, randomized clinical trial of 98 patients with bipolar disorder and past suicide attempts who were randomly assigned to treatment with lithium or valproate, Oquendo et al⁵ did not find any difference between lithium and valproate in preventing suicide events, and concluded “it is perhaps continuity of treatment—any treatment—that attenuates risk of suicidal behavior in bipolar disorder.”

In an overlapping period, National Poison Data System (NPDS) data of single substance exposures painted a different

Dr. Giurca is a locum tenens psychiatrist, New York State Office of Mental Health, Albany, New York.

Disclosures

The author reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0296

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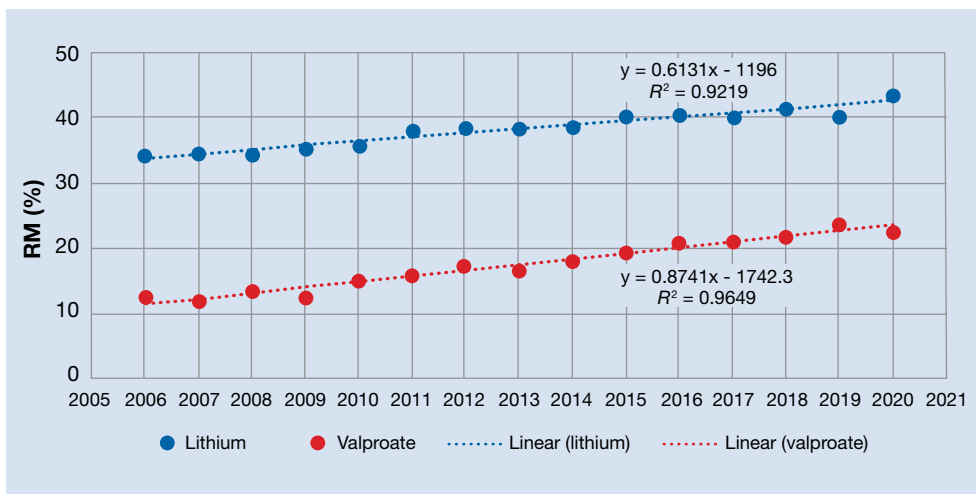
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If lithium truly reduces suicide risk 5-fold, it would be seen in a sample of 98,831

Figure

Time series analysis of relative morbidity of lithium vs valproate



RM: relative morbidity
Source: Reference 6

picture in the United States.⁶ During 2006-2013, the lithium group (N = 26,144) had 32 deaths (all causes) (.122%), and the valproate group (N = 25,630) had 16 deaths (.062%). During 2006-2020, the lithium group (N = 52,262) had 55 deaths (.105%), and the valproate group (N = 46,569) had 31 deaths (.067%). Clearly there is a major disconnect between lithium’s advertised ability to reduce suicide risk and the actual mortality rate, as evidenced by 98,831 cases reported to NPDS during 2006-2020. One would expect a lower rate in the lithium group, but data show it is higher than in the valproate group. This underscores the common fallacy of most lithium studies: each is based on a very small sample (N < 100), and the statistical inference about the entire population is tenuous. If lithium truly reduces suicide risk 5-fold, it would be seen in a sample of 98,831. The law of large numbers and central limit theorem state that as N increases, the variability of the rate progressively decreases. This can be easily demonstrated with computer simulation models and simple Python code, or on the average fuel economy display of most cars.

What about the relative lethality?

The *APA Textbook of Suicide Risk Assessment and Management* stated that it is important

to consider the relative lethality (RL) of prescription medications.⁷ The RL equation (RL = 310x / LD50) represents the ratio of a 30-day supply of medication to the human equivalent LD50 for a 60-kg person (x is the daily dose and LD50 is the rat oral lethal dose 50).⁸ Time series analysis shows that the lithium relative morbidity (RM) is consistently double that of valproate (*Figure*⁶). Regression models have shown high correlation and causality between RL and RM.⁹⁻¹¹ It is surprising that valproate (RL = 1,666%) has a lower RM than lithium (RL = 1,063%). This paradox can be easily explained with clinical insight. The RL equation compares medications at the maximum daily dose, but in routine practice valproate is commonly prescribed at 1,000 mg/d (28% of the maximum 3,600 mg/d). Lithium is commonly prescribed at 1,200 mg/d (67% of the maximum 1,800 mg/d). Within these dosing parameters, the effective RL is valproate 463% and lithium 709%. The 2020 RM is valproate 22% and lithium 43%.¹² The COVID-19 pandemic did not affect the predicted RM. Confirming these numbers, Song et al¹ acknowledged “greater safety in case of overdose for valproate in clinical practice.” Baldessarini et al⁴ asserted “the fatality risk of lithium overdose is only



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moderate, and very similar to modern antidepressants and second-generation antipsychotics.”⁴ This claim is contradicted by the RL equation and regression models.⁷⁻¹¹ Lithium’s RL is 19 times higher than that of fluoxetine, and 30 times higher than that of olanzapine.⁸ Lithium’s RM is nearly identical to amitriptyline (42%), vs fluoxetine (12%).¹²

Data-driven analysis shows that lithium has higher rates of morbidity and mortality than valproate, as evidenced by 98,831 NPDS cases during 2006-2020. These hard numbers speak for themselves and contradict the dominant paradigm, which proclaims lithium’s superiority in reducing suicide risk.

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