Suicide mortality and use of psychotropic drugs in patients hospitalized due to bipolar disorder: A Finnish nationwide cohort study

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**Importance:** Bipolar disorder is a serious mental disorder that affects around 3% of the general population. On average, patients with bipolar disorder die approximately 9 years earlier than the general population and 9–15% of them die by suicide.1,2 Lithium salts have been the cornerstone of treatment for bipolar disorder during the last decades. However, in recent years, the usage of other psychotropics has substantially increased. In particular, some anticonvulsant drugs like valproic acid have partially replaced lithium as the first-line treatment of this disorder. In addition to the main long-term medications, other pharmacological options are often prescribed chronically as an adjuvant therapy or to control some of the symptoms sporadically present in these patients. For instance, in a recent Swedish nationwide registry study, a trend towards the decreased use of lithium and increased use of antidepressants was observed in the treatment of bipolar disorder.4

As suicide constitutes the second most frequent cause of death after cardiovascular disease and is one of the main causes for the premature mortality observed among patients with bipolar disorder,2 it should be one of the key aspects considered when choosing treatment regimens. However, not much comparative data on the effectiveness of different medications in preventing suicide in bipolar patients exist. Thus, it is possible that medication decisions drift towards choosing based on side-effects rather than efficacy.

**Objective:** To study the comparative effectiveness of pharmacological treatments to prevent suicide mortality in a nationwide cohort of Finnish patients with bipolar disorder (n = 18,018).

**Design, setting and participants:** We studied the risk of suicide during 1996–2012 among all patients who had been hospitalized due to bipolar disorder in Finland (n = 18,018; mean follow-up time 7.2 years) using prospectively gathered nationwide databases for hospitalization and dispensed medications. The primary analysis was a Cox proportional hazards model. Analyses were adjusted for the effects of time since diagnosis, order of treatments, current use of other treatments, polypharmacy within medication group, number of suicide hospitalizations within 2 year time interval (indicator of inherent risk of relapse), age at index date, sex, and calendar year of index date.

**Results:** In comparison between use and no use among specific agents reaching nominal statistical significance, lithium (HR 0.33, 95% CI 0.24 to 0.47, p < 0.001) and valproic acid (HR 0.61, 95% CI 0.48 to 0.79, p < 0.001) were associated with a lower risk of suicide in bipolar disorder, whereas antidepressants (HR 1.28, 95% CI 1.02 to 1.61, p = 0.03) were associated with a higher risk of dying by suicide, although this result is not significant when corrected for multiple comparisons (Figure 1). Lithium presented a 42% lower risk for suicide mortality compared with valproic acid (HR 0.58, 95% CI 0.39 to 0.86, p < 0.01) (Figure 2). Use of sedatives and benzodiazepines were also associated with a higher risk, although the results for benzodiazepines did not reach statistical significance (sedatives: HR 1.52, 95% CI 1.02 to 2.21, p = 0.03, benzodiazepines: HR 1.21, 95% CI 0.97 to 1.51, p = 0.10).

**Conclusions and relevance:** Lithium and valproic acid should be considered as treatments of choice for patients with bipolar disorder who are at high risk for suicide. The increased risk associated with antidepressant and sedative use might in part or in full be due to confounding by indication, and further analyses for confounding are warranted and underway. However, it is obvious that lithium and valproic acid are associated with substantially better outcome than antidepressants. Also, as a safety precaution, antidepressant, benzodiazepine and sedative use in bipolar patients with high suicide risk should trigger even closer monitoring for suicidal signals.