Letters to the Editor

Mixed Features in Bipolar I Disorder and the Effect of Lithium on Suicide

TO THE EDITOR: We read with much interest the article by Song et al. (1), published in the August 2017 issue of the *Journal*, showing that rates of suicide-related events in bipolar disorder were significantly decreased during lithium treatment, but not during valproate treatment, using a long follow-up period and the largest sample ever reported. Surprisingly, however, subgroup analyses showed a nonsignificantly reduced rate of suicide-related events during lithium treatment for patients with bipolar I disorder (hazard ratio=0.85, 95% CI=0.67–1.09) and a significantly reduced rate for patients with bipolar II disorder (hazard ratio=0.62, 95% CI=0.46–0.82). This finding suggests that lithium can prevent suicide in bipolar II disorder but not in bipolar I disorder, which is not in line with our clinical experience.

We wonder if Song et al. used DSM-IV-TR criteria to diagnose all patients with mixed episodes as suffering from bipolar I disorder. As shown by themselves, suicide-related events were not significantly reduced during lithium treatment for patients with mixed episodes (hazard ratio=0.87, 95% CI=0.74–1.03), suggesting that lithium may not be effective for suicide prevention in patients with mixed episodes. If the authors included such individuals in their cohort of patients with bipolar I disorder, the effect of lithium on suicide prevention in bipolar I disorder might have been attenuated to a nonsignificant level.

In fact, other researchers have reported that mixed states had the highest incidence rate of suicide attempts (765 per 1,000 person-years), whereas major depressive episode, depressive symptoms, euthymia, hypomania, and mania had incidence rates of 354, 70, 6, 0, and 0 per 1,000 person-years, respectively (2). In addition, a meta-analysis showed a nonsignificant pooled risk ratio (1.03, 95% CI=0.88–1.20) for comparison of bipolar I disorder relative to bipolar II disorder (3). Therefore, the suicide rate may depend on mixed state and depressive episode but not on bipolar subtype (bipolar I or II).

We recommend that Song et al. rediagnose their patients using a specifier of "with mixed features" (DSM-5), which can be added not only to bipolar I disorder but also to bipolar II disorder. It is likely that the hazard ratio of suicide-related events in patients with bipolar I disorder will be increased to a significant level, whereas that of patients with bipolar II disorder will be decreased but within a significant level. This new conclusion would suggest that lithium may be effective for suicide prevention in both bipolar I and II disorders.

REFERENCES

1. Song J, Sjölander A, Joas E, 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
2. Pallaskorpi S, Suominen K, Ketokivi M, et al: Incidence and predictors of suicide attempts in bipolar I and II disorders: a 5-year follow-up study. Bipolar Disord 2017; 19:13–22
3. Tondo L, Pompili M, Forte A, et al: Suicide attempts in bipolar disorders: comprehensive review of 101 reports. Acta Psychiatr Scand 2016; 133:174–186

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More Efforts Needed to Clarify the Effect of Lithium in Bipolar Disorder: Response to Terao et al.

TO THE EDITOR: We thank Dr. Terao and colleagues for raising important points about our study (1). They have noticed that the reduced rate of suicide-related events during lithium treatment that we saw in persons with bipolar disorder was in fact not statistically significant in the subgroup of patients with bipolar I disorder. They submit that this detail might be explained by including patients with mixed episodes in this group, and they propose that we rediagnose patients according to DSM-5 using the mixed features specifier and rerun analyses.

Unfortunately, our study was based on national registers that do not have symptom-level data available. This precludes us from rediagnosing patients according to DSM-5. However, we have repeated the analyses for the bipolar I and II subtypes of bipolar disorder while excluding patients diagnosed with mixed episodes according to ICD-10 (F316). The results are shown in Table 1.

For all patients without mixed episodes, lithium treatment was significantly associated with reduced suicide-related events. And in line with Dr. Terao and colleagues'