Early symptom change and prediction of subsequent remission with olanzapine augmentation in divalproex-resistant bipolar mixed episodes

Introduction

Patients with bipolar I disorder mixed vs. pure manic episodes may have a more severe course of illness, with slower and less frequent remissions and higher rates of recurrence. Assessment of the prognostic value of early symptom response is of particular importance for this complex and common manifestation of bipolar I disorder. Effective treatment early in the course of illness is a critical component in the long-term management of bipolar I disorder and in achieving earlier and possibly more sustained remission. Interest in using early symptom improvement in both mood and psychotic disorders to predict remission is reflected in a number of analyses, particularly with respect to lack of early improvement as predictive of lack of eventual remission with pharmacotherapy. This approach may be of value in the pharmaco-therapeutic management of bipolar mixed episodes. It is common practice for clinicians who treat bipolar disorder to prescribe from a list of several possible treatment regimens; thus, the ability to predict a lack of remission (for depressive, manic, or mixed episodes) at an early stage of a particular treatment could provide important insights in the clinical management of bipolar disorder.

The paper report results from a post-hoc analysis of data from the olanzapine augmentation arm of a multicenter, randomized, double-blind, placebo-controlled trial in which treatment with either olanzapine augmentation (N= 101, olanzapine mean modal daily dose 14.6 mg) or placebo augmentation of divalproex (N= 101) was evaluated in bipolar I disorder (DSM-IV diagnostic criteria) patients with a current mixed episode that did not respond (defined as HDRS-21score ≥ 16 and YMRS score ≥ 16) to ≥ 14 days of divalproex monotherapy with targeted blood levels of 75-125 μg/mL. One- point decreases in Clinical Global Impression- Severity (CGI-S) total score was examined at 2, 4, 7, and 14 days post- augmentation as potential clinical predictors of remission in the treatment of mixed episodes in patients with bipolar I disorder. Additionally, in an exploratory analysis, prediction of subsequent (Week 6 or last observation) remission was examined, based on improvement in HDRS-21 and YMRS total scores and individual items at the earliest available assessment (on Day 2).

Results

Relationship between remission of manic and depressive symptoms

In the olanzapine augmentation treatment group, there was a strong association between depressive symptom remission and manic symptom remission. Of the100 patients (no post- baseline data were available for 1 patient), 77% were concordant for remission or non-remission for both manic and depressive symptoms. While 39% (16/41) of patients with manic symptom remission failed to also have depressive symptom remission, only 22% (7/32) of patients with depressive symptom remission failed to also have manic symptom remission.

Improvement in CGI-S score in the prediction of remission

Using the ISBD task force recommendation of YMRS ≤ 8 and HDRS-21 ≤ 8 as the definition of remission, a reduction of ≥ 1 point in CGI-S total score with olanzapine augmentation predicted depressive, manic, and mixed symptom remission, with acceptable predictive accuracy at 2, 4, 7, and 14 days. Area-under-the- curve (AUC) metrics from receiver operating characteristics (ROC) analyses were comparable at 2, 4, 7, and 14 days; thus, 1- point CGI-S improvement as early as at 2 days post-augmentation was predictive of endpoint remission. Consistent with the above, a 2- point decrease in both HDRS-21 and YMRS total scores as early as Day 2 yielded a similar pattern of prediction of endpoint remission.

Exploratory analysis of early (Day 2) symptom change in predicting remission

In an exploratory analysis, odds ratios (ORs) and 95% confidence intervals (CIs) for endpoint remission were determined for YMRS and HDRS- 21 individual item scores on Day 2 after randomization to identify potential earlier symptom changes predictive of remission. Insomnia items (early, middle, and and/or late) were predictors of depressive symptom remission for both treatment groups. Additionally, paranoid thoughts, agitation, and somatic/ gastrointestinal symptoms were all statistically significant for predicting depressive symptom remission in the olanzapine + divalproex group; feelings of guilt were a statistically significant predictor for the placebo + divalproex group. Improvement in language- thought disorder or irritability items was associated with significant ORs for prediction of manic symptom remission in the olanzapine + divalproex group. In the placebo + divalproex group, ORs for manic remission were significant for improvement in increased motor activity-energy, content, and speech (rate and amount).

Conclusion

Lack of early clinical improvement in symptoms of mania and depression and associated negative predictive values (NPVs) may indicate a high likelihood of subsequent non-remission in this study population, suggesting that these prognostic parameters may have potential utility in the management of bipolar disorder. Even brief symptom persistence after treatment initiation could suggest a need to reassess treatment strategies in patients experiencing mixed episodes. This analysis showed that there was a trend for sensitivity (true positive rate) and NPVs to improve as the number of treatment days increased, suggesting that early reassessment of patients' post-augmentation of divalproex with olanzapine is important for treatment management. Also, as the PPV was less valuable (tended to decrease) after Day 2, this underscored the value of the Day 2 assessments, especially when considering the potential for persistent symptomatology and adverse events. Therefore, while later time point assessments were important, the Day 2 time point assessment had the greatest clinical utility in these difficult-to-treat patients. This study result, while needing replication, expands current clinical options to monitor early treatment progress of patients with bipolar disorder mixed episodes.

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