The addition of olanzapine to valproate or lithium for acute manic or mixed bipolar episodes reduced manic symptoms


**QUESTION:** In patients with acute manic or mixed bipolar episodes, is a combination of olanzapine with valproate or lithium more effective than valproate or lithium alone?

**Main outcome measures:** Severity of manic symptoms (YMRS score), clinical response (improvement of ≥50% in YMRS score), and adverse events.

**Main results:** Analysis was by intention to treat. Patients in the olanzapine combination group had a greater mean decrease in YMRS score than patients in the control group (table). More patients in the olanzapine combination group than in the control group had a clinical response. Olanzapine combination therapy led to increased weight gain, somnolence, tremor, dry mouth, and speech disorder (table). The groups did not differ for dropouts (table).

**Conclusion:** In patients with acute manic or mixed bipolar episodes, the addition of olanzapine to valproate or lithium reduced manic symptoms but increased some adverse events.

**COMMENTARY:** Tohen et al have shown that olanzapine is an effective treatment for mania. Based on the effect size of 0.47, the primary measure of manic symptom reduction indicated that 68% (95% CI 59% to 76%) of patients receiving placebo and lithium or valproate improved less than the average patient receiving olanzapine and lithium or valproate. Patients with mixed and pure mania responded similarly to olanzapine augmentation, but the advantage of olanzapine was not statistically significant in patients with pure mania. It is unclear whether olanzapine augmentation should therefore be reserved for mixed episodes or whether the benefit in pure mania is also clinically important and this analysis merely failed to identify this benefit because of low statistical power. Other antipsychotics have been shown to be effective for acute mania and are used commonly. As such, the next logical question is which antipsychotic is preferred for acute mania.

Although this was an acute treatment trial, antipsychotic treatment often continues for months. As a result, when selecting a treatment for acute mania, clinicians need to consider its effectiveness, safety, and tolerability during maintenance treatment. These issues evoke the debate between newer and older antipsychotics but in a completely different patient population. Long-term use of older agents commonly leads to motor side effects in bipolar patients, although weight gain can be substantial with some newer agents. This may be particularly relevant in bipolar disorder because lithium and valproate also cause weight gain. In this study, olanzapine was associated with a considerable increase in weight relative to placebo (3.1 ± 0.23 kg). Weight gain would be expected to increase with longer use. Clinicians making decisions about whether to use olanzapine or an alternative antipsychotic need to consider this and the related increased risk for weight-related health problems. Making such decisions is complex and should include the patient because individual values will affect treatment acceptance. The results of the 18-month extension trial may be helpful and are expected shortly.

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