

# The Role of Divalproex Plus Olanzapine in Outpatient Mixed-Episode Bipolar I Disorder

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In the 1970s and 1980s, randomized trials in bipolar disorder focused on the treatment or prevention of acute mania, with little recognition that certain illness subtypes might significantly influence treatment outcomes. The article in this month's issue of the *Journal* by Houston and colleagues, comparing outcomes for bipolar mixed episodes treated with olanzapine or placebo added to divalproex, builds on retrospective and post hoc analyses from older studies that suggested that one such subtype, mixed episodes, may hold special importance for predicting acute response to a mood stabilizing agent.<sup>1,2</sup> However, before one can embrace as fact any hypothesis generated from post hoc analyses, prospective randomized studies are essential in order to formally test their validity—a lesson learned in the case of rapid cycling, another illness characteristic that once was thought to distinguish poorer response to lithium than divalproex based on post hoc<sup>3</sup> or open-label<sup>4</sup> studies, which was refuted only through prospective randomized data.<sup>5</sup> Particularly when an illness characteristic is thought to confer a negative prognosis and greater treatment resistance, such as mixed episodes, prospective data are scientifically indispensable.

Houston et al present the first prospective randomized trial focusing specifically on mixed-episode bipolar patients and affirm differential treatment outcomes: in this instance, a superior reduction in both manic and depressive symptoms with the combination of olanzapine plus divalproex than with divalproex alone. The authors took great care to assure optimization of blood valproate levels and document an inadequate response to divalproex monotherapy prior to initiating the second agent—methodological advances over most previous randomized studies of combination therapy in acute mania. Inclusion of effect sizes and numbers needed to treat or harm afford readers a more practical way to assess the meaningfulness of treatment outcomes. Moreover, by defining response or remission by yoking reductions in both Young Mania Rating Scale and Hamilton Depression Rating Scale scores, the authors provide a composite measure of global symptom improvement—and remind us of the need for a unified instrument in order to

rate symptom change in mixed episodes, and reckon the relative degree of symptom reduction for one illness pole versus the other.<sup>6</sup>

Complex combination therapy has become increasingly common across most phases of bipolar disorder, although most combinations are not necessarily evidence based.<sup>7</sup> Olanzapine plus divalproex represents one of the few well-studied dual combinations in both short-term<sup>8</sup> and long-term<sup>9</sup> studies. In acute mixed episodes, modern practice guidelines typically advise adding antipsychotic drugs to traditional mood-stabilizing agents (such as lithium or divalproex) when presenting symptoms involve high severity or psychosis. Experts on both sides of the Atlantic advocate their addition after an incomplete antimanic response to a traditional mood stabilizer alone.<sup>10</sup> Houston and colleagues focused solely on outpatients with mixed episodes that were mostly nonpsychotic—a group that is most likely managed more often in outpatient than in inpatient settings given the current health care climate, as compared to a decade or longer ago. However, since neither imminent danger nor efforts to avert hospitalization were immediate concerns (no subjects in either randomized arm required hospitalization), herein lies the most difficult inference to draw: For a drug that has become almost synonymous with managing illness “urgency,” how should clinicians decide *which* bipolar I mixed-episode patients are best served by such an augmentation strategy, and when does the magnitude of potential benefits outweigh the risks?

The reduction in Young Mania Rating Scale scores for subjects taking divalproex plus olanzapine was about 2.5 points lower than in those taking divalproex alone, a difference corresponding to a medium effect size (0.423). By contrast, although the observed difference between treatment arms in mean Hamilton Depression Rating Scale scores was statistically significant, the relatively small between-group effect size (0.298) suggests only a modest clinical advantage for reducing depression symptoms during mania, and depression symptoms improved more slowly than mania symptoms. Both treatments yielded a favorable, low number needed to treat for response (but not remission, in either arm). However, as compared to subjects taking divalproex alone, those also taking olanzapine gained 2.64 kg more weight and had nearly a 7-point rise in fasting glucose levels over 6 weeks (as compared

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to a slight decline from baseline fasting glucose levels in recipients of divalproex alone). In the absence of psychosis, hospitalization, or imminent danger, one must determine when the demonstrable benefits of olanzapine augmentation offset the potential for greater metabolic burden and other adverse effects, as well as potential implications for treatment adherence and ongoing therapy.

Simultaneously, one must also consider the paucity of established, effective combination therapies for mixed episodes in bipolar disorder apart from adding a second-generation antipsychotic to lithium or an antimanic anticonvulsant. Monotherapies seldom yield robust efficacy in complex forms of bipolar disorder. Rather surprisingly, combinations of traditional mood stabilizers (lithium, divalproex, and/or carbamazepine) have not been systematically studied in randomized trials for acute manic or mixed episodes, particularly after an initial inadequate response to a single agent. Lamotrigine has not been studied as monotherapy or combination therapy in acute mixed episodes, and its more prominent antidepressant than antimanic efficacy, plus gradual titration schedule, render it a less compelling option when mania accompanies depression in bipolar disorder. The addition of an antidepressant to an antimanic drug appears to only worsen mania symptoms without appreciably improving depressive symptoms in bipolar patients with concomitant mania and depression.<sup>11</sup>

Mixed episodes carry prognostic implications that extend beyond solely the need to control immediate symptoms. They often involve greater morbidity and comorbidity,<sup>2</sup> slower recovery rates,<sup>12</sup> greater functional impairment,<sup>13</sup> and risk for recurrent suicidality<sup>14</sup> as compared to pure manic or depressed-phase episodes. Treatment outcomes are often suboptimal—in part, perhaps, because mixed episodes are often misidentified as “pure” depressed phases of bipolar disorder,<sup>15</sup> which may in turn become aggravated by antidepressant cotherapy.<sup>11,16</sup>

It may be useful, and scientifically most accurate, to differentiate the goals of acute treatment versus those of continuation therapy (relapse prevention) or maintenance phases (ie, prevention of recurrences or new episodes) and to distinguish risk-benefit analyses as being unique to each phase of treatment. In the acute phase, the speed with which a therapeutic regimen is optimized can significantly predict time to recovery.<sup>17</sup> Multivariate analyses elsewhere also suggest that the duration of time spent in an acute mixed episode—but not the severity of baseline mania symptoms per se—significantly predicts the time until a next new episode.<sup>18</sup> In this respect, the urgency with which one approaches treatment of any mixed episode, regardless of initial symptom severity, holds relevance for longer-term outcome.

Nowadays, the reporting of pharmaceutical company-sponsored clinical trials understandably can incur greater scrutiny than federally or other funded research, although adequately powered clinical trials in bipolar disorder funded

by any entity, pharmaceutical or otherwise, have become few and far between. The pros and cons of using atypical antipsychotics in general, especially in nonpsychotic disorders, also have become a growing focus of public and media attention—consequently demanding thoughtful deliberation when practitioners choose from agents that differ in their breadth of spectrum and require repeated assessment of risks and benefits over time. The results presented by Houston and colleagues provide a straightforward, methodologically rigorous appraisal of the relative advantages and disadvantages in combining 2 of the most extensively studied agents for a difficult but commonly seen subtype of bipolar I disorder. Such data provide vital evidence to inform optimal decision making in routine clinical practice.

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