

It is illegal to post this copyrighted PDF on any website. How Much Is the Debate Over Antidepressant Efficacy and Safety in Bipolar Depression an Artifact of Study Methodologies?

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The use of antidepressants for bipolar depression remains a never-ending controversy, driven at least in part by several mainly sociological factors: (1) the hypothesis advanced in the 1970s and 1980s that antidepressants might, in some bipolar patients, hasten the switch from depression to mania and/or accelerate recurrences^{1,2}; (2) the seemingly widespread uptake of this hypothesis as dogma, leading to (3) condemnation of monoaminergic antidepressants as causal (rather than incidental) to poor outcomes in bipolar disorder,³ plus (4) lack of efficacy seen with some of the few specific antidepressants that were actually studied in placebo-controlled trials for acute bipolar depression; and, lastly, (5) the veritable cessation of randomized trials in bipolar depression with any monoaminergic antidepressants developed after 1999.

In fact, only 3 “modern” antidepressants have ever been studied in placebo-controlled trials for bipolar depression: 3 of 3 trials showed efficacy with fluoxetine (added to either lithium⁴ or olanzapine,⁵ or as monotherapy for relapse prevention in bipolar II depression after an initial acute response⁶); 3 of 3 trials found no advantage for mood stabilizer plus paroxetine versus mood stabilizer plus placebo^{7–9}; and 1 of 1 found no difference from placebo with bupropion added to a mood stabilizer.⁷ Strikingly, until now, there have been no other placebo-controlled trials with any antidepressants for bipolar depression. Nevertheless, these initial studies produced an echo chamber effect of claims that antidepressants as a class are ineffective or detrimental. That, in turn, ushered in the field’s self-imposed moratorium on placebo-controlled trials with newer monoaminergic agents (such as desvenlafaxine, mirtazapine, nefazodone, levomilnacipran, vilazodone, vortioxetine, and transdermal selegiline). It is therefore no small credit to the field that, in this issue, Ghaemi and colleagues¹⁰ now provide the first placebo-controlled trial of adjunctive citalopram in bipolar depression.

At first glance this report seems to be yet another negative trial, with no discernible effect (either good or bad) as

compared with placebo. On closer inspection, several points bear on this study’s interpretation. First, both the citalopram and placebo groups showed initial improvement in acute depression; however, the high placebo response rate makes it hard to tell if this trial is truly a negative trial or, rather, a failed trial. The magnitude of improvement in depression severity scores from baseline after 6 weeks with citalopram was an impressive 52.2%, a percentage of symptom reduction entirely on par with that seen in the US Food and Drug Administration (FDA) registration trials of lurasidone (50.3%–50.8% across dosing ranges)¹¹ and cariprazine (49.2%–49.7% across dosages)¹² for bipolar depression. But the present study of citalopram captured a greater degree of improvement from baseline with placebo (44.5%) as compared to lower percentages of improvement with placebo seen in trials with those FDA-approved treatments.

Bipolar depression has a peculiarly and vexingly high placebo response rate—on average, 39% across trials, apparently driven to some degree by low baseline severity and longer study durations.¹³ Ghaemi et al¹⁰ rightly controlled for these potential confounders in an exploratory but underpowered regression and found an improvement that numerically (but nonsignificantly) favored citalopram over placebo. In a separate subgroup analysis, fully half of their bipolar II participants who received placebo responded. Placebo response rates above 40% in bipolar depression become hard to interpret relative to active drug,¹³ making it hard to know whether their finding of citalopram’s nonsuperiority to placebo affirms perceptions that “SSRIs do not help bipolar depression” or, rather, reminds us that “low baseline severity and statistical underpowering do not help demonstrate separation from placebo.”

Second, prior lessons were gleaned about the impact of statistical underpowering and low baseline severity as factors that obscure drug-placebo differences when we consider the individually failed trials of lamotrigine for acute bipolar depression. In that database,¹⁴ a signal for lamotrigine emerged only with a sufficiently large pooled study group to control adequately for the moderating effect of low baseline severity on placebo responsiveness. While subject recruitment for randomized bipolar depression trials poses a notoriously difficult and painstaking endeavor, underpowering remains an unavoidable obstacle for making definitive interpretations of failed trials—as pertinent to the present study, which enrolled 20% fewer subjects than their initial power calculations called for.

Beyond a high placebo response rate and statistical underpowering to differentiate failed from negative

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findings, a third critical point involves Ghaemi and colleagues' unconventional decision to ignore subjects' acute antidepressant responsiveness and instead retain all willing subjects in long-term treatment (extending study duration)—eschewing (in fact, condemning) the more traditional trial design of enrichment (in which acute response must be demonstrated before then embarking on long-term relapse prevention). Elsewhere, Ghaemi and Selker¹⁵ disparage enrichment designs as producing “results of questionable validity” that are “tautologous in what they measure,” claiming that because the natural course of mood disorders is often phasic, enriched designs do not actually capture sustained improvement. Yet, ignoring enrichment would be akin to committing hypertensive patients to a long-term antihypertensive regimen without first checking for observable improvement in blood pressure, or undertaking long-term antimigraine or antiepilepsy therapy without first determining whether or not the proposed medication in fact reduces event frequency.

To understand the importance of enrichment in bipolar relapse prevention trials, one need look no further than to randomized trials with lithium and divalproex. The ill-fated pivotal registration trial of divalproex for relapse prevention after acute mania in bipolar I disorder failed to demonstrate an advantage for either divalproex or lithium (the latter included for assay sensitivity) over placebo¹⁶—except, as shown in a later post hoc analysis, when divalproex initially demonstrated acute antimanic efficacy.¹⁷ Specifically in the case of long-term antidepressant treatment for bipolar depression, Amsterdam and Shults⁶ enriched

acute responsiveness for fluoxetine in bipolar II depression and found during subsequent maintenance therapy that fluoxetine monotherapy outperformed placebo and even lithium. Even more compellingly, randomized long-term data from the Stanley Bipolar Network¹⁸ showed that a robust acute antidepressant response was necessary to predict low depression relapse during long-term (1-year) continued antidepressant therapy, while poor initial response led to high depression as well as mania relapse rates.

Clinicians often bemoan that the literature regarding antidepressants for bipolar depression fails to yield definitive guidance on best evidence-based practices. That still-unresolved dilemma may partly reflect the protean, nonstatic nature of bipolar depression as well as the many factors that can moderate antidepressant outcome, such as baseline severity, rapid cycling, subthreshold mixed features, polarity proneness, and bipolar I or II subtype, among others.¹⁹ The present randomized trial of citalopram by Ghaemi and colleagues¹⁰ makes forays to address some of these moderators and, as such, adds to an ongoing and often spirited dialogue. Ultimately, however, the findings remind us more about the methodological design complexities of studying antidepressants rather than reveal fundamentally new definitive conclusions for clinicians hoping for simpler directives about “what to do.” In the world of evidence-based medicine, there are unfortunately no short-cut alternatives to honing one's skills for reading the clinical trials literature with a critical awareness of the methodological nuances and limitations that can obfuscate drug-placebo differences.

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