

**The Gap Between the Randomized Controlled Trial-Based Evidence and Real-World Practice in Switching Strategies of Major Depressive Disorder**

**To the Editor:** Switching to an antidepressant in a different pharmacologic class, which is often employed in clinical practice for major depressive disorder (MDD) patients who have not responded sufficiently to an initial antidepressant, usually yields better clinical outcome. However, some randomized controlled trials (RCTs) and RCT-based meta-analyses designed to test the efficacy of switching therapies suggest that switching to another antidepressant may not be superior to continuing the initial antidepressant.<sup>1</sup> Three reasons account for the gap between the conclusions of traditional clinical trials and our clinical experience in the real-world setting.

The first—and main—reason for this gap is the use of inappropriate inclusion criteria for nonresponders to initial antidepressant treatment. In a study by Bose et al,<sup>2</sup> depressive patients who did not respond (<50% Montgomery-Asberg Depression Rating Scale improvement) to 2 weeks of 10 mg/d of escitalopram were randomly assigned to further treatment in a protocol evaluating the efficacy of 20 mg/d escitalopram versus switching to 60 mg/d duloxetine. In clinical practice, it is difficult to reduce MDD symptoms by 50% in 2 weeks with a moderate dose of antidepressant. Patients meeting such criteria for nonresponse are therefore not true nonresponders and could achieve significant improvement in either the antidepressant continuation group or the switching group. Similarly, in Souery and colleagues' study,<sup>3</sup> achieving 50% total score reduction on the Hamilton Depression Rating Scale after 4-week treatment would have been difficult. Additionally, one study<sup>4</sup> did not clearly define the concept of nonresponse, only indicating that some of the patients previously treated with a selective serotonin reuptake inhibitor (SSRI) were switched to duloxetine. Inaccurate definition of nonresponse has therefore impaired the superiority of switching strategies, and a considerable proportion of patients could see clinical benefit if the dose were escalated or therapy time were extended longer until the onset of antidepressant action occurred. The most recent meta-analysis<sup>5</sup> of the antidepressant dose-response relationship has also shown that SSRIs are more efficient at higher doses, so it makes sense that patients experience continuous improvement after dose escalation in broad analysis, which may weaken the clinical benefit of switching strategies.

Second, doses of switching antidepressants should be comparable and flexible during the study. One trial compared the efficacy of continuation of venlafaxine 75–375 mg/d with that of switching to fluoxetine 25/50 mg/d.<sup>6</sup> According to Hayasaka and coworkers' findings,<sup>7</sup> fluoxetine 40 mg/d is equivalent to venlafaxine 149.4 mg/d. So, it is no surprise that venlafaxine at a higher dose is more effective than fluoxetine.

Third, randomization and blinding were used in most studies cited by this meta-analysis, so we should pay attention to analogous “placebo effects” in such antidepressant switching studies. When nonresponders who had little treatment response to initial antidepressant therapy were randomly assigned in double-blind fashion to an antidepressant continuation group, patients' expectations for symptomatic improvement may have yielded the additional antidepressant effect. Hence, another form of “placebo effect” did exist in this setting, and it is interesting to compare the efficacy difference between the blind setting and the open-label setting.

To summarize, because of obvious flaws in study design, the existing evidence cannot conclude that switching strategies were not superior to initial antidepressant continuation. Further studies are needed to affirm whether switching antidepressants is more effective than continuation of the initial antidepressant.

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**Dr. Bschor and Baethge Reply**

**To the Editor:** We greatly appreciate the comment by Chen and Mei regarding our systematic review and meta-analysis on switching antidepressants. Their views provide a welcome opportunity to clarify important points.

Chen and Mei criticize some of the studies included in the meta-analysis on methodological grounds. In 3 of the 8 studies selected,<sup>1-3</sup> they find fault with the definition or rate of nonresponse. Of note, 2 of those studies<sup>1,2</sup> are not part of our prespecified primary analysis, which we labeled “strict analysis,” as opposed to our post hoc “broad analysis” (both meta-analyses unequivocally found no advantage of switching the antidepressant in comparison to continuation of the so far insufficient antidepressant).

In addition, Chen and Mei may have missed Petrescu and coworkers<sup>2</sup> clear definition of nonresponse as a MADRS score > 20 and a CGI-S score ≥ 3 after 6 weeks of selective serotonin reuptake inhibitors (SSRI) treatment. Also, Bose and colleagues<sup>1</sup> definition is unusual, rather than wrong, because there is no universally agreed upon definition of nonresponse. What is more, even if one follows Chen and Mei’s argument, one would not expect the switching arm to be statistically and clinically significantly inferior, which indeed is the case.<sup>1</sup>

As regards the study that we *did* include in our strict analysis,<sup>3</sup> we cannot follow Chen and Mei’s view that the response criterion is artificially high. In fact, at approximately 55%, subjects did respond at a very common rate. Again, this study reported a statistically and clinically significantly superior effect of continuation relative to switching.

To support their view that different doses of antidepressants may have put switching at a disadvantage, Chen and Mei cite a systematic review and meta-analysis by Jakubovski et al<sup>4</sup> as showing a dose-response relationship in SSRI treatment. Again, it is important to note that this argument does not apply to our strict analysis with its negative result for switching. However, by design, Jakubovski and coworkers’ study cannot support a dose-response relationship of SSRIs because in the studies included, patients were not randomized to different doses of SSRIs. On the contrary, Jakubovski et al compared different studies that employed different doses—in effect treating the trials as observational studies. Even so, the effect they found was clinically insignificant: a standardized mean difference of 0.08 is less than half of what is usually considered low. Further, we have just finished a systematic review and meta-analysis on randomized controlled trials comparing different doses of antidepressants after failure of an antidepressant monotherapy and found no advantage of higher doses for SSRIs.<sup>5</sup>

In the same vein, Chen and Mei claim that Corya et al<sup>6</sup> used noncomparable doses of venlafaxine and fluoxetine in their study. We cannot agree: For a fair comparison, optimal doses of both antidepressants should be used. This is the case with a mean of 275.4 mg/d in the venlafaxine arm and of 37.5 mg/d in the fluoxetine arm. As detailed above, higher fluoxetine dose are not more effective than standard doses, and 37.5 mg/d can already be considered high-dose.

We do, however, agree with Chen and Mei that placebo effects contribute to antidepressive effects seen in double-blind studies. But it seems illogical to us that such a placebo effect should be at work in continuation arms only.

Chen and Mei emphasize the gap between the results of our meta-analysis and the positive effects seen in patients who switch antidepressants. This is a valid point, but not difficult to explain: Depressed patients show a high placebo response,<sup>7</sup> and, naturally, most get better over time.<sup>8,9</sup> This is what makes the randomized trial design scientifically so invaluable. Improvement is to be expected when patients switch antidepressants, but, as the randomized controlled trials summarized in our meta-analysis show, not to a larger extent than among patients continuing their initial treatment.

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