Drs Sidor and MacQueen Reply

To the Editor: We appreciate the opportunity to address the comments by Drs Cruz and Vieta pertaining to our meta-analysis examining the role of antidepressants for the acute treatment of bipolar depression.[1] It is not the role of systematic reviews to provide treatment recommendations[2,3]; rather, our results provide a "snapshot" of the current state of clinical trials. If individual studies themselves do not provide high quality evidence, then even an appropriately conducted meta-analysis will not provide the information necessary to allow clinicians to draw firm conclusions. In the absence of replicated high quality randomized controlled trials (RCTs), it is the role of the systematic review to summarize the literature to date and the role of the clinician and those making clinical practice guidelines (CPGs) to reach conclusions based on their grading of the evidence presented and their assessment of the relevance of that information for their particular populations of interest (eg, clinicians and CPGs may need to consider whether the evidence we summarized is relevant to those with bipolar disorder II as well as to those with bipolar disorder I or whether patients with rapid-cycling illness have been adequately included and described in studies to date).

We agree with Drs Cruz and Vieta that the 2010 EMBOLDEN II study comparing paroxetine to placebo[4] provides compelling evidence for the lack of efficacy of an antidepressant in bipolar depression. As our meta-analysis did not include data from this trial, we have taken this opportunity to update our meta-analysis to include these most recent results. Consistent with the trends we previously reported, inclusion of the EMBOLDEN II results further reduced the effect size of clinical response when comparing antidepressant to placebo treatment (relative risk [RR] = 1.13; 95% CI, 0.99–1.30; $P = .08$). Using a random-effects model, as suggested by Drs Cruz and Vieta, even further reduced the effect size to RR = 1.17; 95% CI, 0.88–1.57; $P = .28$. Inclusion of recent high quality RCTs, such as the EMBOLDEN II study, supports our assessment that the extant literature does not provide strong support for the notion that antidepressants are efficacious for the acute treatment of bipolar depression.

We are not certain about Drs Cruz and Vieta's comment that inclusion of switch and remission rates adds nothing to the meta-analysis. These two outcomes are important to consider in terms of both treatment efficacy and antidepressant safety. A unique feature of this meta-analysis was our consideration of liberal switch criteria and how they alter safety outcome. The results highlight a gap in some previous trials and suggest that future studies should measure the occurrence and impact of subthreshold mood switches that may occur with the administration of an antidepressant. This focus is consistent with an increased awareness of the need to evaluate and report relevant "harms" that may be associated with specific treatment strategies, as knowledge of potential harms associated with treatments should enhance the ability of clinicians to select not only effective, but safe and acceptable treatment options.[5]

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