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### Adjunctive Mood Stabilizers Are Not the Same as a Placebo-Only Arm in Bipolar Depression Trials: Reply to Terao

**To the Editor:** I agree with Dr Terao's observation that a comparator arm of mood stabilizer plus placebo is clearly not the same as placebo alone, and indeed the threshold for demonstrating clinical significance in an adjunctive antidepressant clinical trial requires showing a meaningful effect above and beyond that of a comparative intervention sans antidepressant. The extent to which drugs we colloquially call "mood stabilizers" (MSs) exert antidepressant properties remains complex and a matter of debate. Lamotrigine, for example, exerts modest but more potent antidepressant than antimanic efficacy, while lithium and divalproex each are associated with relatively more robust antimanic than antidepressant effects, and the acute and prophylactic antidepressant properties of carbamazepine remain largely undemonstrated.<sup>1</sup> The study of adjunctive citalopram by Ghaemi et al<sup>2</sup> was not powered to parse relative differences among antidepressant properties across MS cotherapies, and certainly the MS comparator group for citalopram did not constitute placebo alone. Obvious ethical problems would make it difficult to randomize acutely depressed or otherwise severely ill bipolar patients to placebo alone.

The fundamental dilemma in concluding from this study that citalopram conferred no value for treating bipolar depression lies in the extremely large response seen in the mood stabilizer plus placebo comparator group, for whatever reason it occurred; based on Montgomery-Asberg Depression Rating Scale (MADRS) scores reported in the study, I calculate a very large within-group effect size (Cohen *d*) of 1.403 for subjects in the MS plus placebo arm. Perhaps the dramatic within-group effect size for the MS plus placebo group does indeed reflect the underappreciated antidepressant properties of lithium and other mood stabilizers, although one must acknowledge that previous randomized trials in bipolar depression have found more modest effects for subjects assigned to MSs plus placebo. A recent network meta-analysis<sup>3</sup> reported only a small effect size (standardized mean difference

[SMD]) for lithium monotherapy in acute bipolar depression of  $-0.24$ , with a nonsignificant confidence interval (CI). Lamotrigine's SMD in that meta-analysis was similarly low ( $-0.07$ ) and with nonsignificant CIs, while a nonsignificant SMD for carbamazepine favored placebo over active drug.<sup>3</sup>

It remains paradoxical that mood stabilizers to treat acute bipolar depression yield remarkably small effect sizes and yet the placebo effect in bipolar depression trials remains strikingly high.<sup>4</sup>

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Published online: June 22, 2021.

**Potential conflicts of interest:** Dr Goldberg has been a consultant for BioXcel, Otsuka, Sage, Sunovion, Medscape, and WebMD; has been on the speakers bureau for Allergan, Intra-Cellular Therapies, Otsuka, and Sunovion; and has received royalties from American Psychiatric Publishing, Inc, and Cambridge University Press.

**Funding/support:** None.

*J Clin Psychiatry* 2021;82(4):211r13919b

**To cite:** Goldberg JF. Adjunctive mood stabilizers are not the same as a placebo-only arm in bipolar depression trials. *J Clin Psychiatry.* 2021;82(4):211r13919b.

**To share:** <https://doi.org/10.4088/JCP.211r13919b>

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