Antidepressant Effects of Combined Mood Stabilizers May Account for High Placebo Response Rates

To the Editor: I read with much interest a recent JCP article in which Ghaemi et al[1] reported that citalopram, added to standard mood stabilizers, does not have clinically meaningful benefits versus placebo for either acute or maintenance treatment of bipolar depression. In an editorial, Goldberg[2] criticized the article because of the high placebo response rate, which was above 40%.

Although Ghaemi et al[1] themselves attributed the high placebo response rate to nonpharmacologic reasons such as natural remission of bipolar depression, it should be noted that all patients (in both the placebo and citalopram groups) concurrently started taking mood stabilizers (lithium, divalproex, carbamazepine, or lamotrigine) or were already taking mood stabilizers for at least 4 weeks prior to study entry. Therefore, some patients in the placebo group began receiving not only a placebo but also a mood stabilizer. Thus, the antidepressant effect of the mood stabilizer might have contributed to these patients' improvement. In addition, the other patients in the placebo group already receiving a mood stabilizer might have been asked to take medicine (ie, placebo and mood stabilizer) more regularly just before study entry, which probably led to the elevation of serum levels of the mood stabilizer, and thereby the antidepressant effect of the mood stabilizer might have contributed to their improvement.

In Ghaemi and colleagues' study,[1] the most commonly used mood stabilizer was lithium (24 of 60 patients in the citalopram group and 37 of 59 patients in the placebo group). The efficacy of lithium in the treatment of acute bipolar depression has been demonstrated in several previous studies.[3,4] In any case, antidepressant effects of mood stabilizers as well as natural remission and/or true placebo effect could account for the high placebo response rate. If there had been a third group of patients receiving only a placebo in this study, the above possibilities could have been examined.

REFERENCES

1. Ghaemi SN, Whitham EA, Vohringer PA, et al. Citalopram for Acute and Preventive Efficacy in Bipolar Depression (CAPE-BD): a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2021;82(1):19m13136.
2. Goldberg JF. How much is the debate over antidepressant efficacy and safety in bipolar depression an artifact of study methodologies? *J Clin Psychiatry*. 2021;82(1):20ed13649.
3. Baron M, Gershon ES, Rudy V, et al. Lithium carbonate response in depression. Prediction by unipolar/bipolar illness, average-evoked response, catechol-*O*-methyl transferase, and family history. *Arch Gen Psychiatry*. 1975;32(9):1107–1111.
4. Goodwin FK, Murphy DL, Dunner DL, et al. Lithium response in unipolar versus bipolar depression. *Am J Psychiatry*. 1972;129(1):44–47.

Takeshi Terao, MD, PhD[a,*]

[a]Department of Neuropsychiatry, Oita University Faculty of Medicine, Oita, Japan

**Corresponding author:* Takeshi Terao, MD, PhD, Department of Neuropsychiatry, Faculty of Medicine, Oita University, Idaigaoka 1-1, Hasama-machi, Yufu-city, Oita, 879-5593, Japan (terao@oita-u.ac.jp).

Published online: June 22, 2021.

Potential conflicts of interest: There were no conflicts of interest.

Funding/support: No funding was received.

J Clin Psychiatry 2021;82(4):21lr13919

To cite: Terao T. Antidepressant effects of combined mood stabilizers may account for high placebo response rates. *J Clin Psychiatry*. 2021;82(4):21lr13919.

To share: https://doi.org/10.4088/JCP.21lr13919

Antidepressants Added Nothing to Mood Stabilizers Alone

To the Editor: Dr Terao's letter commenting on our study[1] makes an excellent observation. Indeed, we wanted to see if antidepressants were effective when combined with mood stabilizers, versus mood stabilizers alone. If we had not allowed patients to enter the study unless they already were taking mood stabilizers, as is commonly the case, then the study would have been biased against mood stabilizers. In that case, since all patients had to be depressed, they would have failed their mood stabilizers already, and the resulting study would have been a study of bipolar depression that was treatment-resistant to mood stabilizers. Most clinicians do not practice this way and instead either use antidepressants alone or give antidepressants plus mood stabilizers together. The study design was left flexible so as to be generalizable to this treatment setting. The "placebo" group reflects "mood stabilizer plus placebo," and thus the study results answer the practical question whether antidepressants should be given with mood stabilizers in clinical practice, or whether mood stabilizers alone are just as effective. The answer was that mood stabilizers alone were just as effective, and adding antidepressants provided no further benefit. Whether that benefit from mood stabilizers is a pharmacologic effect, or a natural history effect, or another placebo-based effect is irrelevant. The randomized trial provides causal evidence that adding antidepressants to mood stabilizers, contrary to long-standing and difficult-to-change popular belief, does not provide further meaningful clinical benefit.

REFERENCE

1. Ghaemi SN, Whitham EA, Vohringer PA, et al. Citalopram for Acute and Preventive Efficacy in Bipolar Depression (CAPE-BD): a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2021;82(1):19m13136.

S. Nassir Ghaemi, MD, MPH[a,*]

[a]Department of Psychiatry, Tufts University School of Medicine, and Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

**Corresponding author:* S. Nassir Ghaemi, MD, MPH, Department of Psychiatry, Tufts Medical Center, 800 Washington St, Boston, MA 02111 (Nassir.Ghaemi@tufts.edu).

Published online: June 22, 2021.

Potential conflicts of interest: From October 2017–June 2021, Dr Ghaemi was an employee of Novartis Institutes for Biomedical Research (NIBR), Cambridge, MA. The study discussed in this letter was funded by the National Institute of Mental Health (NIMH) in 2007, with Dr Ghaemi as the principal investigator, and was conducted and completed in 2007–2016, before Dr Ghaemi's employment at NIBR.

Funding/support: The study discussed in this letter was funded by NIMH grant 5R01MH078060-05.

Role of the sponsor: The NIMH had no role in the conduct or publication of the study.

J Clin Psychiatry 2021;82(4):21lr13919a

To cite: Ghaemi SN. Antidepressants added nothing to mood stabilizers alone. *J Clin Psychiatry.* 2021;82(4):21lr13919a.

To share: https://doi.org/10.4088/JCP.21lr13919a

Adjunctive Mood Stabilizers Are Not the Same as a Placebo-Only Arm in Bipolar Depression Trials

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.[1] The study of adjunctive citalopram by Ghaemi et al[2] 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[3] 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.[3]

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.[4]

REFERENCES

1. Ernst CL, Goldberg JF. Antidepressant properties of anticonvulsant drugs for bipolar disorder. *J Clin Psychopharmacol*. 2003;23(2):182–192.
2. Ghaemi SN, Whitham EA, Vohringer PA, et al. Citalopram for Acute and Preventative Efficacy in Bipolar Depression (CAPE-BD): a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2021;82(1):19m13136.
3. Bahji A, Ermacora D, Stephenson C, et al. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: a systematic review and network meta-analysis. *J Affect Disord*. 2020;269:154–184.
4. Nierenberg AA, Østergaard SD, Iovieno N, et al. Predictors of placebo response in bipolar depression. *Int Clin Psychopharmacol*. 2015;30(2):59–66.

Joseph F. Goldberg, MD[a,*]

[a]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York

**Corresponding author:* Joseph F. Goldberg, MD, 128 East Ave, Norwalk, CT 06851 (joseph.goldberg@mssm.edu).

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):21lr13919b

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):21lr13919b.

To share: https://doi.org/10.4088/JCP.21lr13919b