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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 al¹ 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, Goldberg² criticized the article because of the high placebo response rate, which was above 40%.

Although Ghaemi et al¹ 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.

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Antidepressants Added Nothing to Mood Stabilizers Alone

To the Editor: Dr Terao's letter commenting on our study¹ 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.

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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 al² 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-analysis³ 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

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