LETTERS TO THE EDITOR

Clinical Trials of Antidepressants: "Enrichment Strategies"

LE Miller[1]

To the Editor: I read with great interest the article by Merlo-Pich and colleagues titled "A New Population-Enrichment Strategy to Improve Efficiency of Placebo-Controlled Clinical Trials of Antidepressant Drugs."[1] Because one in two clinical trials of US Food and Drug Administration–approved antidepressants fails,[2] the authors suggest that the efficiency and accuracy of studies should be improved to reduce the frequency of failed and uninformative trials. They further propose that the exclusion of data from sites showing extremely high or extremely low placebo effects may help to achieve this goal. After the authors applied a *post hoc* enrichment-window model, the probability of a successful antidepressant trial increased from 50% to 90%. I respectfully disagree with the premise of this article. Instead, I argue that, in order for antidepressant trials to demonstrate greater benefit, the efficacy of the drug itself should be "enriched," thereby avoiding the need for data manipulation and cherry picking to arrive at a biased conclusion. The article is particularly concerning because three of the four authors clearly have a vested interest in the success of these trials. We would all do well to remember that the goal of clinical trials is to arrive at the truth, not necessarily to achieve success.

CONFLICT OF INTEREST
The author declared no conflict of interest.

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2. Turner, E.H., Matthews, A.M., Linardatos, E., Tell, R.A. & Rosenthal, R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N. Engl. J. Med.* **358**, 252–260 (2008).

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The Placebo Response Is Part of Good Medicine

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To the Editor: Merlo-Pich *et al.*, in their article "A New Population-Enrichment Strategy to Improve Efficiency of Placebo-Controlled Clinical Trials of Antidepressant Drugs," published an enrichment strategy to increase the probability of a positive outcome with a therapeutic agent in depression.[1] By using statistical modeling, they conclude that this can be achieved by excluding centers at which a high placebo response is observed. Unfortunately, the authors do not discuss what value such trials would have for clinical practice or regulatory processes. The placebo response is a highly complex biological and psychological set of reactions by a patient to a therapeutic intervention in the context of a "therapeutic encounter." In the recent excellent review by Finniss *et al.*,[2] the therapeutic relationship between the physician and the patient is highlighted as a key factor in determining the frequency and extent of placebo response. A caring physician who takes time to explore a patient's needs and expectations is likely to elicit a higher placebo response, and that is an essential component of the therapeutic encounter across cultures and history. Not all doctors are equally skilled or patient or have sufficient time to foster such a therapeutic relationship. Although the patient characteristics are clearly also important, the move to exclude the centers themselves rather than only the patients with high placebo response would tend to suggest that the common element that leads to these high placebo responses has more to do with the staff and medical culture of a specific center than with the characteristics of individual patients. Hence, if a pharmaceutical is found to work only where low standards of medical skill result in a low placebo response, this is not a valid positive finding for the drug but rather a negative finding for the medical culture of the center.

Such a trial would provide little evidence to determine the clinical utility of the drug, and its value is therefore questionable. The high placebo response in clinical trials is a well-documented problem; however, other measures to reduce it—for example, avoiding excessively optimistic information and consent documents—might be more appropriate than the methods suggested in this article.

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The author declared no conflict of interest.

1. Merlo-Pich, E., Alexander, R.C., Fava, M. & Gomeni, R. A new population-enrichment strategy to improve efficiency of placebo-controlled clinical trials of antidepressant drugs. *Clin. Pharmacol. Ther.* **88**, 634–642 (2010).
2. Finniss, D.G., Kaptchuk, T.J., Miller, F. & Benedetti, F. Biological, clinical, and ethical advances of placebo effects. *Lancet* **375**, 686–695 (2010).

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