Commentary

A Radical Proposal to Address the Problem of the Lack of Generalizability of Placebo-Controlled Studies of Antidepressants

Mark Zimmerman, MD‡*  

In the current issue of the Journal, Blanco and colleagues examine the generalizability of neuroimaging studies of psychiatric disorders and find that most studies select individuals with “pure” forms of the disorder of interest and exclude the large percentage of individuals with comorbid disorders. The authors suggest that the sample selection procedures of these studies limit the applicability of this research toward understanding the pathophysiology of the patients seen in clinical practice (most of whom do not have pure forms of disorders).

In the introduction of their article, Blanco and colleagues note that concerns about generalizability, or external validity, have previously been raised with regard to treatment studies of psychiatric disorders. Their article thus expands the scope of concerns about generalizability, and they most likely foreshadow a future debate about whether the empirical literature is sufficiently robust and generalizable to incorporate and pay for the testing of biomarkers in routine clinical practice.

In present day clinical practice, a more salient concern than problems with the generalizability of neuroimaging studies is the limited external validity of treatment studies. I will therefore use the invitation to write this commentary as an opportunity to make a radical proposal that could nudge the industry toward conducting treatment studies that have greater clinical applicability.

During the past decade, my clinical research group has studied the generalizability of antidepressant efficacy trials (AETs). We found that most depressed patients seen in our outpatient practice would not have qualified for an AET, a result that has been independently replicated a number of times. Thus, for most patients seen in clinical practice, we do not know if medication works. Of course, many of our patients get better after initiating antidepressants, but we do not know how often this is due to the nonspecific therapeutic aspects of treatment rather than the direct chemical action of the antidepressant molecule. Demonstrating an active medication is superior to placebo has proven to be difficult, and strategies have been discussed and proposed to increase the likelihood of “detecting a signal.” However, as a practicing psychiatrist, I am humbled to realize that most of the patients I treat would not qualify for an AET; therefore, most of my prescriptions of antidepressants are predicated upon “a leap of faith.”

The only approach I can envision that will motivate the pharmaceutical industry to change its strategy of recruiting a highly selected group of patients into treatment studies is to impose a countervailing force that would impact revenues. Specifically, if health insurance companies limited prescriptions to patients upon whom antidepressants have proven effective, then I would predict that physician behavior would change abruptly and dramatically, and the resulting financial consequence of this change would alter how patients are recruited into industry-funded AETs. Health insurance companies can easily accomplish this change in prescribing habits by modifying the information required on medication preauthorization forms.

The primary purpose of medication preauthorization is to reduce cost by limiting the prescribing of expensive brand name medications. To be sure, I do not like completing preauthorization forms. As a busy psychiatrist who sees many patients and prescribes many medications, I find the completion of preauthorization forms to prescribe certain medications to be an annoyance. Preauthorization is most commonly required for medications that are not yet available in generic equivalents, and the preauthorization forms are usually limited to 2 questions—one about prior failed treatment efforts (with generic medications) and the other to verify that the patient has the diagnosis for which the medication is indicated. The latter question is designed to limit the off-label use of medication.

Antidepressants are one of the most frequently prescribed classes of medications, and most antidepressants are available in generic formulations. Yet during the past 8 years, 4 medications (vortioxetine, vilazodone, desvenlafaxine, and levomilnacipran extended release) have received approval from the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD), and generics are not yet available. The question I would like to raise herein is whether insurance companies would be justified in expanding the information requested on a preauthorization form to include questions reflecting the inclusion and exclusion criteria used to select patients into the AETs that established the medications’ regulatory approval. Another way of putting this—Should insurance companies limit authorization to the patient subgroup for whom the medication has been demonstrated to be effective? I would argue that the FDA has failed to follow its own guidelines regarding the proper labeling of antidepressants and therefore insurance companies would be justified in going...
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studying the efficacy of new medications. The prescription of antidepressants has significantly increased over the past 20 years, and concerns about their overprescription have been raised. It is important to better characterize the depressed patients who are and are not responsive to antidepressant medication and to limit prescribing only to those patients who show greater benefit than that achieved when receiving placebo. Since I am pessimistic that the FDA will suddenly start to follow their own guidelines regarding the labeling of medications, I am suggesting that the health insurance industry, which has a financial stake, step in and enact a change to their preauthorization procedures thereby reducing expenditures on treatments that have not yet been shown to be effective for most depressed patients. I am not implying that the medications are ineffective for these large subgroups of depressed patients. Rather, because of the sample selection procedures in AETs, we simply do not know if the medications are effective in most depressed patients treated in clinical practice. Such a change in the rigor (or should I say burden) of the preauthorization process for recently approved, branded medications would most likely prompt the pharmaceutical industry to conduct studies that have greater external validity because revenues and revenue projections would be negatively impacted.

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REFERENCES


