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Antidepressants Work, Sort of—Our System of Care Does Not

Ronald Pies, MD

As Yogi Berra would have put it, "It was déjà vu all over again." The media were abuzz once again with headlines like "Report Questions Benefits of Antidepressants" and "Are Antidepressants Any Better Than a Sugar Pill?"—eerily similar to the headlines we saw last year, after the meta-analysis of antidepressant treatment by Kirsch et al[1] appeared. Many psychiatrists will recall that the Kirsch et al[1] study was widely covered in the lay press, as it seemed to debunk the efficacy of antidepressants in all but the most severely depressed patients—and even in that subgroup, drug-placebo differences were attributed to "…decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication."[1] In short, not a very impressive showing.

This time, the media buzz was due to another meta-analysis by Fournier et al,[2] which reached a similar conclusion. The authors examined 6 randomized, placebo-controlled studies of antidepressant treatment in adult outpatients (n = 718), using the Hamilton Depression Rating Scale (HDRS). Fournier et al[2] concluded that "…The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms." However, in contrast to Kirsch et al,[1] the authors found that, for patients with very severe depression (HDRS score ≥23), "…the benefit of medications over placebo is substantial."[2]

To their credit, a number of print and online sources consulted outside experts, who pointed out numerous limitations in the design of the Fournier et al[2] study. For example, David Hellerstein, MD (cited in Gever[3]) noted that the only 2 antidepressants studied—paroxetine and imipramine—have more adverse effects than several newer antidepressants and that this may have affected compliance and dropout rates. Moreover, Hellerstein noted, none of the 6 studies lasted more than 11 weeks, and the imipramine dose was subtherapeutic (100 mg/d) or less than optimal (100–200 mg/d) in 2 of the 3 imipramine studies. Finally, Hellerstein pointed out that the duration of illness before entering the trials was not addressed and that short-duration depressive bouts may be highly susceptible to a strong placebo effect.[3] It should also be noted that the Fournier et al[2] studies were of outpatients only—a group generally less "sick" than those we see on the wards.

AQ1

Similarly, Richard A. Friedman, MD,[4] writing in the January 10, 2010, health Section of the *New York Times*, noted that 6 studies using just 2 antidepressants "… is not many studies if your goal is to answer a broad question about the efficacy of antidepressants as a class." Indeed, Friedman[4] quotes one of the authors of the study, Robert J. DeRubeis, PhD, as saying, "Of course, we can't know that these results generalize to other medications."[4] Moreover, Friedman[4] pointed to a critical design feature of the Fournier et al[2] meta-analysis, that is, "…they decided to exclude a whole class of studies, those that tried to correct for the so-called placebo response." That is, the Fournier et al[2] meta-analysis did not examine studies involving a placebo "washout" period. Friedman[4] goes on to say that

An analysis that eliminates such studies is bound to show a comparatively small average difference between drug treatment and placebo treatment. Not surprisingly, this is just what happened in the recent analysis. But in randomized clinical trials that try to correct, or wash out, the placebo effect, patients with mild to moderate depression respond to antidepressants at rates nearly identical to patients with severe depression (who tend to have a much lower response to placebos).[4]

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Friedman[4] also notes that "…the real test of an antidepressant is not just whether it can lift someone out of depression; it is whether it can keep depression from returning…" and that "…on average, the risk of relapse in patients who continue on an antidepressant is one half to one third of those who are switched to a placebo".[4] (In a letter responding to Dr. Friedman, DeRubeis and Fournier noted that "...many approved antidepressants vary little in effectiveness" and that their meta-analysis deliberately "aimed to estimate the difference between the effects of medications and placebos."[4a])

As I'll note later, the long-term benefits of antidepressant treatment may not be as robust as we think. But there may be reasons not directly tied to antidepressants that explain why studies of these agents have yielded disappointing results in recent decades. For example, in the February 2007 issue of this journal, Kobak et al[5] pointed out that if the interviews producing HDRS scores are not performed skillfully, the results of the study may be distorted. Kobak et al[5] cited several instances in which poor interviewing technique led to outcomes showing little difference between antidepressant and placebo; conversely, good interviewing technique led to a more robust improvement rate ("effect size") for the antidepressant. It is not clear how competently the HDRS interviews were conducted in the studies that composed the Kirsch et al[1] and Fournier et al[2] meta-analyses.

Then, there is the mysterious nature of the placebo response. For example, some evidence suggests that placebo response rates have actually been rising in recent years, as Walsh and colleagues[6] discovered. This "placebo inflation" effect may be due, in part, to recruitment of less severely ill subjects for study. The less ill the subjects, of course, the more likely a placebo is going to work for them. Subjects in many modern studies are often recruited from ads in magazines, rather than from samples of "real" patients, who are often much sicker.

Finally, Sheldon Preskorn makes an interesting theoretical observation, applicable to the findings in both the Kirsch et al[1] and the Fournier et al[2] studies: "The 'finding' that antidepressants do not work as well in mild as in severe depression is a 'floor' effect… you could not show that antidepressants worked in nondepressed individuals, and the lower the severity score, the closer the participants are to the 'floor'" (personal communication, January 19, 2010).

AQ2

There is a larger point to be made about the kind of meta-analyses Kirsch et al[1] and Fournier et al[2] have done. Basically, these studies involve "crunching numbers" on individual trials in which, usually, a single antidepressant was tested over a period of a few weeks. To be sure, the effect sizes (compared with placebo) are often unimpressive in such single-stage trials. But when psychiatrists use a "full court press" and treat depressed patients over many months, using various combination and augmentation strategies, we often see better results with antidepressant medication. For example, the multistage STAR*D studies, sponsored by the National Institute of Mental Health, found that, after the fourth and final pharmacotherapy "hoop" was jumped through, the cumulative rate of remission (full resolution of the depressive syndrome) in patients with resistant nonpsychotic major depressive disorder (MDD) was about 67%.[7] Unfortunately, the nature of the STAR*D study precluded use of a placebo group, and this greatly limits the conclusions we can draw from it. However, the cumulative remission rate of 67% is certainly much higher than historically reported rates of remission with placebo, which average around 25% in a single trial.[8] Preskorn[8] believes that, in general, "…the chance of remission is 1.5 to 2.0 greater if the patient is on an antidepressant versus placebo." Preskorn[8] also points out that whereas placebo is often thought of as "no treatment," it is actually "…a control for the beneficial effects of all the clinical management that a patient receives in such a trial, beyond the investigational medication." Thus, the popular expression "no better than a sugar pill" misrepresents the benefits of a placebo.

In short, I believe the STAR*D studies provide us with decent, although not conclusive, evidence that antidepressants are effective in MDD when administered in a robust, appropriately dosed, multistage strategy. This, in fact, was my experience as a psychopharmacology consultant for more than 20 years: if you made the right diagnosis—for example, excluding cases of covert bipolar depression[9]—and stuck with the patient long enough, you would eventually see significant improvement on one or another antidepressant regimen. But how much of the improvement in my patients was due to pharmacotherapy and how much merely to my supporting and encouraging the patient? How much was due to the natural course of the patient's illness and recovery cycle? There are many confounds in clinical practice. We should be circumspect about "believing our own eyes" and generalizing our impressions to other patient populations.[10] Moreover, as my colleague, Nassir Ghaemi, points out, psychiatrists do not provide "randomized" treatment to their patients. Rather, we are trained to tailor our treatment to what we believe is most likely to benefit a particular patient. That's a far cry from what happens when a patient is enrolled in a study like the STAR*D.

AQ3

Nonetheless, I agree with my colleague, David Osser, MD, who—along with many other experts and clinicians—believes that the benefits of antidepressants have been "oversold" (personal communication, January 14, 2010). Certainly, when one looks at the typical "Big Pharma" antidepressant advertisement—frequently adorned with chirping birds and butterflies—one is keenly aware of being sold a bill of goods! The recent revelations of unpublished negative studies of antidepressants have further eroded confidence in what clinicians and patients have been "sold," as regards the benefits of these agents.[11] Furthermore, a careful inspection of the STAR*D data leaves one with greatly restrained enthusiasm for antidepressants, particularly as long-term maintenance agents. As Ghaemi[12] has noted in a careful reanalysis of the STAR*D maintenance data, only a quarter of the overall sample maintained their remission after 1 year. Ghaemi[12] concludes that "…there is much less long-term benefit with antidepressants in unipolar depression than has often been assumed…."

Even in the acute treatment phases of STAR*D, the results were generally disappointing. As Sheldon Preskorn[8] notes, "…the remission rates went down progressively with each subsequent level of the STAR*D treatment, such that only 11% of patients who entered level 4 achieved remission status. In fact, almost 40% of patients who entered STAR *D remained clinically ill after almost a year of treatment…." Preskorn[8] argues that we should not be surprised by these downbeat results, because the drugs used in the STAR*D study all have very similar effects on neurotransmitters. Preskorn[8] compares the study to treating infected patients with "penicillin variant #1 through penicillin variant #8 and wondering why progressively fewer get better." Essentially, one is concentrating penicillin nonresponders in each subsequent arm of the study. Preskorn[8] believes that "…an analogous situation appears to apply to STAR*D" and points to the urgent need for "…truly novel medications that work via different mechanisms of action." Amen to that!

At the same time, Ghaemi[12] calls our attention to what may be an "…excessively broad concept of major depression." Indeed, the current *Diagnostic and Statistical Manual of Mental*

Disorders, Fourth Edition (*DSM-IV*) construct of MDD is so elastic, one can wrap it around almost anyone with depressive symptoms: from those with 1 major depressive episode lasting just 2 weeks, to those with 10 years of highly episodic depressive bouts, lasting a month of longer. Some patients in the latter group may actually be part of the bipolar spectrum and relatively poor responders to antidepressants alone.[12] The disappointing STAR*D results might reflect, in part, this heterogeneity. In addition, some of the findings from STAR*D may be explained by genetic heterogeneity in major depression, with some evidence linking citalopram responsiveness to variants in *HTR2A*, *GRIK4*, and *KCNK2* genes.[13]

As the *DSM-V* emerges from its present fog of controversy, we shall see if the criteria for MDD are made more stringent and selective. My own view—admittedly, not yet backed up by the requisite epidemiological studies—is that the 2-week minimum for MDD should be increased to 3 to 4 weeks. This may prove a somewhat less sensitive, but perhaps more specific time frame for diagnosing "true" MDD, in contrast to transient, spontaneously remitting depressive reactions. (On the other hand, for reasons beyond the scope of this editorial, a number of mood disorder specialists believe the so-called bereavement exclusion for MDD ought to be eliminated.[14,15])

ANTIDEPRESSANT OR PSYCHOTHERAPY?

As a clinician, I still tend to believe my eyes—at least up to a point. And, over the past nearly 30 years, I have seen hundreds of patients improve, and maintain their improvement, on antidepressants—once properly diagnosed and adequately treated. For some patients, antidepressants are literally lifesaving medications. "Evidence-based medicine" is not intended to negate our careful, clinical observations—but it should compel us to reexamine our assumptions and prejudices. We are now faced with mostly unimpressive results from 2 recent meta-analyses[1,2] and the STAR*D, at least as regards the less severe end of the depression continuum. Although these studies have significant limitations, they cannot be ignored. There is also the matter of harm avoidance. Allowing for their heterogeneous pharmacodynamics and adverse effects, it's fair to say that newer antidepressants (selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors) are relatively safe, but far from innocuous, medications. Their potential for metabolic, cardiac, sexual, and other adverse effects is now well established.[16]

For all these reasons, I believe we should generally reserve antidepressants for moderate-to-severe cases of major depression that exceed the 2-week minimum duration required by *DSM-IV*. There are good reasons to prioritize antidepressant treatment for depressed patients with features of melancholia, both as defined in the *DSM-IV* and in more sophisticated, neurobiologically based formulations.[17] Indeed, a recent review[18] concluded that "The research data, in the aggregate, suggest that the presence of melancholia predicts a poor response to psychotherapy and placebo and a relatively good response to antidepressants and ECT." In contrast, for most cases of briefer (<3 weeks), mild-to-moderate, nonmelancholic depression, I believe psychotherapy should be our first-line treatment.

Fortunately, we have reason to be optimistic about the psychotherapies. There is good evidence that both cognitive-behavioral therapy and interpersonal psychotherapy are effective in the treatment of depression, although cognitive-behavioral therapy may be preferred in severe depression.[19] Although psychodynamically oriented psychotherapy for major depression is backed by fewer controlled studies, there is evidence that this, too, may be effective.[20] Of course, there are many instances in which the combination of psychotherapy with medication may be the best overall approach to moderate-to-severe depression.

THE SYSTEM IS BROKEN

Richard I. Shader, MD, reminded me (personal communication, January 19, 2010) that there is considerable variability in the expertise and style of psychotherapists, even with so-called manualized treatment. And, alas, according to a recent editorial lambasting psychologists,[21] the most effective, evidence-based psychotherapies for depression are not often provided. Furthermore, few primary care physicians—who provide about 80% of antidepressant treatment in this country[22]—have the time or training to provide psychotherapy. Equally unfortunate, the use of psychotherapy by psychiatrists has declined significantly in the past decade.[23]

Now, what is the result when most antidepressant treatment is out of the hands of psychiatrists and left to our beleaguered colleagues in primary care—who have perhaps 12 to 20 minutes to evaluate and treat a depressed patient? In my own experience as a psychopharmacology consultant, I have observed a kind of "twin peaks" phenomenon in the general outpatient population: antidepressant therapy is either (*a*) lacking, or inadequately dosed, in patients who clearly merit medication; or (*b*) prescribed in an ill-conceived polypharmacy regimen (say, fluoxetine plus citalopram) for patients who may not need an antidepressant at all. Such irrational polypharmacy is not confined to primary care physicians—I have seen it on occasion even in patients referred from other psychiatrists, although usually in cases of "treatment-resistant depression." Antidepressant polypharmacy may be particularly injurious when the patient in question has what I have called "pseudoresistant bipolar depression."[9] In my experience, many such patients wind up in a chronic state of agitated dysphoria with "mixed" affective features,[24] often accompanied by symptoms of a low-grade serotonin syndrome, for example, restlessness, tremor, insomnia, and gastrointestinal complaints.

I believe that the net result of these distorted medical practice dynamics is that many patients with depression—particularly some minority groups—are not being provided with adequate care. In fact, a recent study[25] suggests that many patients with depression are not getting any kind of care at all. As the lead author, Hector Gonzalez, MD, put it in an interview with the *Wall Street Journal*: "Few Americans with depression actually get any kind of care, and even fewer get care consistent with the [best practice] standards of care."[26] Gonzalez et al found, in particular, that Mexican American and African American individuals meeting 12-month major depression criteria "…consistently and significantly had lower odds for any depression therapy and guideline-concordant therapies."[25]

So, where do we go from here? In my experience, a sustained, multistage antidepressant regimen often produces remission in most patients with (unipolar) major depression, and by no means should we abandon this approach. But even for many of these responders, the beneficial effects are neither robust nor long-lasting. "Remission" based on the HDRS score, after all, is not the same as full social and vocational recovery. Psychiatrists need to stop focusing on the well-known limitations of available antidepressants. Rather, we need to redouble our efforts aimed at developing more creative antidepressant strategies, based on novel mechanisms of drug action. We then need to determine how best to integrate these new biological approaches with psychosocial therapies. Most important, we need to begin providing accessible, affordable,[27] and evidence-based care to all who seek treatment for their depression.

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AUTHOR DISCLOSURE INFORMATION

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