Are Antidepressants Effective? What's a Clinician to Think?

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Questions about the efficacy of antidepressant drugs in depression have been raised as a result of 2 recent reports.[1,2] Turner et al.[1] reviewed industry-sponsored clinical trials (randomized controlled trials; RCTs) submitted to the FDA and found that positive RCTs were more likely to be subsequently published than negative trials. The authors suggested that published data overestimate the effectiveness of antidepressants. Kirsch et al.[2] found that RCTs of antidepressants that enrolled more severely depressed patients yielded larger effects than trials of less severely depressed patients and questioned the clinical significance of the magnitude of drug effects for less severely depressed patients. Reaction of the media to these reports has tended to sensationalize the findings and makes dispassionate appraisal of the findings difficult. The intent of this brief review is to put these findings in perspective.

The implication that clinicians may have been misled by unpublished data seems overstated. Data from antidepressant trials reported to the FDA were first reviewed and published by Khan et al. in 2000.[3] In 2002, Khan et al.[4] noted that in recent antidepressant trials reported to the FDA, only 45 of 93 (48%) active antidepressant arms were significantly superior to placebo. In another 2002 article, Khan and colleagues[5] also noted that pretreatment severity predicted greater change with medication, less change with placebo, and larger drug-placebo differences. Also in 2002, Thase[6] pointed out that the average drug-placebo difference in industry-sponsored antidepressant RCTs was relatively modest and that because of the so-called file drawer effect (failure to publish negative data), reliance on the published literature overestimated meta-analytic appraisals of treatment effects. Thus, information regarding the efficacy of antidepressants has been available to clinicians for a number of years.

Early Findings From the Treatment of Depression Collaborative Research Program

The suggestion that antidepressants are more effective or only effective in severe depression is not a new concern. In a report from the National Institute of Mental Health–funded Treatment of Depression Collaborative Research Program published in 1989,[7] all active treatments—imipramine, cognitive behavior therapy, and interpersonal therapy—were more effective than clinic visits with placebo; however, in the less severely depressed patients, active treatments were not significantly more effective than clinic visits with placebo. By contrast, among the more severely depressed patients, the placebo rate fell and both interpersonal psychotherapy and imipramine were significantly more effective than placebo. In patients with greater Global Assessment of Severity scores, the difference between remission rates with imipramine and placebo was especially robust (60% vs. 8%; imputed from Figure 2, p. 977).[7]

The foregoing findings suggest that in less severely depressed, uncomplicated patients, clinical management with placebo is an effective intervention. Frank and Frank[8] have discussed the importance of attention and reassurance and the symbolic importance of placebo. Fawcett and colleagues[9] further detailed the "ingredients" of clinical management in a manual for RCTs. As the editorial accompanying the Elkin[7] report noted, "Both psychiatrists and primary care clinicians should now be alerted to take such supports [the supportive elements of clinical management] seriously as an intervention."[10(p983)] Here, the clinical and research implications of the findings diverge. Clinicians might do well to maximize the effect of nonspecific supportive interventions. The usual research aim is to reduce placebo effects; in fact, reduction in the number of ratings and time spent with the patient has been suggested.[11]

Moderators of Antidepressant Response

The findings regarding severity and response raise the question of whether there are other factors that moderate or predict differences in response to drug and placebo. Some of these factors, reviewed in prior reports,[12–14] may have to do with trial design. For example, Khan et al.[12] found that clinical trials with fewer treatment arms and flexible rather than fixed dosing schedules had larger drug-placebo differences. Nelson et al.,[15] in a meta-analysis of late-life depression studies, found that response rates and drug-placebo differences were greater in the 10- to 12-week trials compared with the 6- to 8-week trials, and these differences appeared clinically meaningful. The number needed to treat dropped from 20 in the shorter trials to 8 in the 10- to 12-week trials. Thus, trials with fixed dosing schedules, several treatment arms, and, in the case of older patients, shorter durations may *underestimate* response rates and drug-placebo differences. Others have noted that the expectation of receiving placebo in placebo-controlled RCTs is associated with lower response rates than in double-blind drug comparisons without a placebo.[16] Consistent with this, Walsh et al.[14] found that drug-placebo differences are declining over time, largely because the magnitude of the placebo response is growing. These trends suggest that expectation of benefit, the characteristics of the participants selected, and/or other aspects of patient enrollment have changed in a manner that has selectively enhanced placebo response rates.

Other patient characteristics also may moderate antidepressant response. In a secondary analysis of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), Glassman et al.[17] found that, among depressed patients who had experienced a myocardial infarction (MI), those whose first depressive episode followed the MI were quite responsive to clinical management with placebo and that sertraline did not add benefit; however, in patients with a history of recurrent depression that predated the MI, placebo rates were lower, response to sertraline increased, and drug-placebo differences were robust. Other patient characteristics that have been associated with larger drug-placebo differences include a lower percentage of females in the sample[12] and greater chronicity of the depression.[18–20]

Efficacy for Prevention of Relapse and Recurrence

When considering the value of antidepressants in depression treatment, clinicians should keep in mind the potentially important role of these medications in the prevention of relapse and recurrence. The benefits of drug treatment for this purpose have been consistent and robust. Geddes et al.[21] performed a meta-analysis of 31 relapse prevention studies that included 4410 patients. Antidepressants reduced the odds of relapse by 70%. The pooled relapse rates were 41% for placebo and 18% for antidepressants. The efficacy of

antidepressants for relapse prevention is well established.

Efficacy of Antidepressants Relative to Psychotherapy

Because evidence-based psychotherapies represent an alternative for acute phase treatment of depression, the discussion of antidepressant efficacy begs the question of whether psychotherapy is more effective than antidepressants. The question is best addressed with head-to-head comparison studies. Several reviews of these studies have been published.[22–25] These reviews find antidepressants and psychotherapy comparable. In addition, when psychotherapy is compared with clinical management and placebo, the difference between psychotherapy and the control is similar in magnitude to drug-placebo differences.[7,24,25] This observation is similar to the analysis of 21 psychotherapy studies by Baskin et al.,[26] who examined differences in the magnitude of effects depending on the nature of the control group. When the control provided minimal patient contact, such as a waitlist, the effect size of psychotherapy was moderate in size, 0.49. When the control group was structurally similar in terms of elements such as number of visits, length of sessions, and format (individual or group), but differed in terms of the active ingredients of the specific therapy, the effect size was small, 0.15. This is a crucial point since many early studies of psychotherapy used waitlist controls that differ substantially from supportive clinical management provided in antidepressant trials.

Summary

In summary, while controlled clinical trials of antidepressants in depression support the efficacy of these agents, the magnitude of their effects is small. Drug-placebo differences appear to be declining over time, in part related to rising placebo response rates. These findings have been available for some time. The evidence-based psychotherapies represent alternative treatments that are comparable in efficacy to antidepressants in moderately depressed outpatients. When compared with adequate controls, these psychotherapies also have small effect sizes. The most robust effects of the antidepressants in depression are realized in the prevention of relapse and recurrence. For the clinician, determination of moderators that will help to identify those individuals who will have a more robust response to specific treatments, whether antidepressants or psychotherapy, is a priority.

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