EDITORIAL

Do Antidepressant Medications Work?

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INTRODUCTION

Antidepressants are among the most widely prescribed medications in the U.S.[1] In part, this may be related to the apparent increase in the prevalence of depression, which has been noted since the mid-20th century.[2] In addition to treating the various types of depression (such as major depression, dysthymia, and sometimes bipolar depression), antidepressants are widely used in anxiety disorders, fibromyalgia, and pain management.[3]

The burgeoning use of antidepressants has also been influenced by managed care insurance programs, which are generally more willing to pay for relatively inexpensive pharmacotherapy rather than more expensive psychotherapies.[4] This is also part of a widespread trend to focus on the biological aspects of psychiatric disorders. Antidepressants are frequently prescribed by primary care and other non-psychiatric physicians who have access to a very large number of patients. Pharmaceutical companies have invested heavily in the development of antidepressants and have aggressively marketed them to psychiatrists, other physicians, and the general public.

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CONTROVERSIES IN PRACTICE

In recent years, antidepressant medications have become increasingly controversial, receiving widespread coverage in the popular media as well as within medical circles. This development is in the context of a general re-evaluation of the utility of psychiatric medications, including antipsychotic, stimulant, and anti-dementia drugs.

Dr. Marcia Angell, former editor-in-chief of the *New England Journal of Medicine* and a critic of the pharmaceutical industry, in a pair of articles published in *The New York Review of Books* (within which she reviewed several books critical of psychiatry), supported the view that the effectiveness of antidepressants is limited.[5,6] In a far-ranging critique of psychiatry and psychopharmacology, she also highlighted the questionable practices of the pharmaceutical industry in promoting psychiatric medications, especially for off-label indications. She suggested that the appearance of an epidemic of psychiatric illness might have to do with broadened diagnostic criteria, partly designed to maximize the utilization of medications.

Dr. Angell (and others) also questioned the closeness between psychiatry and the pharmaceutical industry. Others have noted the (now supposedly banned) historical tendency of the industry to suppress negative studies and information about antidepressants and other medications.[7,8] The question of suicidality associated with antidepressants, especially among children and adolescents, has added to the level of concern.

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Adverse effects of newer antidepressants, although generally less problematic than those associated with older drugs such as the tricyclic antidepressants, can still be considerable. These may include weight gain and sexual side effects such as erectile dysfunction and a reduced ability to achieve orgasm. Psychiatrists as well as other physicians and mental health professionals are understandably concerned. Are antidepressants safe and effective? Are they overprescribed?

A large number of placebo-controlled trials of various antidepressants have been published, most showing efficacy compared with placebo. Many of these studies are relatively small and short-term in nature. An important issue is that of efficacy as the gold standard. Efficacy is defined as a statistically significant advantage of a treatment over placebo. A drug such as an antidepressant may be efficacious in the pharmacological sense, yet the magnitude of the effect might not be sufficient to be clinically meaningful.[9] This is not only a criticism of antidepressant research; it also embodies something of a value judgment: how much effectiveness is enough? It appears that this criticism is equally applicable to a variety of non-psychiatric medications in common use. Is it fair to put psychiatric drugs under a more powerful microscope than other medication types?

Some of the recent controversy has been fueled by the use of meta-analyses. A meta-analysis combines the results of multiple studies in order to amplify their power (achieving a sufficiently large sample size to be able to more definitively answer a particular research question). Meta-analyses are useful tools, but they have their own limitations and sources of bias; they may also be conducted in various ways that can render different results. For example, the choice of the studies included in the analysis can greatly skew the results. Meta-analyses are capable of illustrating broad averages, but they cannot address individual response; lumping studies together tends to obscure the effects on subgroups.

A much discussed meta-analysis performed by Kirsch et al. (cited by Dr. Angell as part of her review of his 2010 book) showed limited efficacy for antidepressants, especially in milder cases of depression.[10,11] Kirsch, an expert on the placebo response, has suggested that this could be responsible for the apparent benefits. Kirsch's methodology has been questioned, and several other recent meta-analyses have shown much more robust antidepressant action, in some cases only for more severe depression and in some cases across the board.

A meta-analysis by Fournier et al. concluded that the benefit of antidepressants, when compared with placebo, increases with the severity of depressive symptoms, from minimal (or nonexistent) in mild cases to substantial in severe depression.[12] Gibbons et al. performed a meta-analysis of antidepressant trials involving fluoxetine (Prozac, Eli Lilly) and venlafaxine

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(Effexor, Wyeth/Pfizer) to examine the effect on depression as well as suicidality. They concluded that fluoxetine and venlafaxine decreased suicidal thoughts and behavior in adult and geriatric patients and that depressive symptoms were reduced. No evidence of increased suicide risk was found in adolescents receiving active medication, and their depression responded to treatment. No relationship was found between symptom severity and response.[13] Leucht et al. compared meta-analyses of psychiatric and general medical medications and concluded that psychiatric drugs were not less effective than other drugs.[14]

Another problem in antidepressant research is that of a large placebo response, rendering even robust responses to medication less impressive. The reasons for this finding (which appears to be more evident in the recent past) are unclear and are widely debated. One explanation is that depressed patients are suggestible and that even placebo treatments are apt to be helpful.[15] In fact, the whole question of the placebo response in psychiatry and other branches of medicine is worthy of much more investigation.

Regardless of one's position on the merits of antidepressants, there is no doubt that many patients do not respond sufficiently to pharmacological therapies. Treatment-resistant depression (often defined as failure to respond to at least two well-conducted antidepressant trials) is extremely common. The Star*D trial, the largest study of the effectiveness of depression treatments (including medications and cognitive–behavioral therapy), revealed a response rate of 50% to 55% after two sequential treatment interventions, with response rates falling to 25% or less for subsequent interventions.[16] Research that evaluated combinations of antidepressants and psychotherapy has generally shown some advantage for combined treatment.[17]

RECOMMENDATIONS FOR IMPROVED CARE

Given the controversy surrounding antidepressants and their effectiveness, how is the clinician to proceed? Here are some pragmatic suggestions:

1. The choice of medication versus psychotherapy (or lifestyle changes such as exercise) represents a false dichotomy. Research suggests that approaches combining medication and psychotherapy enhance clinical outcomes for some patients.

2. For milder forms of depression, beginning with nonpharmacological therapies is an appropriate choice for many patients. The preferences of the patient, the previous history (if any), and the accessibility of psychotherapy may all play a role in treatment selection. For example, cognitive–behavioral therapy, a modern and innovative form of psychotherapy developed for depression, has been shown to be effective in a number of studies. It involves a pragmatic focus on identifying and addressing negative patterns of thought and behavior in the "here and now," in contrast to traditional therapy approaches.[18]

3. Treatment choices may be modified as the therapy proceeds. A patient who does not respond to one approach, such as psychotherapy alone, might be a candidate for the addition of medication.

4. For those with more severe pathology, such as most hospitalized patients and patients with suicidal, psychotic, catatonic, or melancholic symptoms, antidepressant medication is clearly indicated.

CONCLUSION

Further research into the effectiveness of the currently available antidepressants is required to resolve these controversies. Ultimately, however, better treatment options, including new medications as well as improved access to psychotherapies, are urgently needed.

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