New MDD Treatment Guidelines Fall Short

The American Psychiatric Association recently released new treatment guidelines for patients with major depressive disorder. The guidelines were developed by prominent psychiatrists (who had pharmaceutical industry ties), an independent review panel (without pharmaceutical industry ties), and comments from dozens of experts and organizations (doi:10.1176/appi.books.9780898433878.654001). They are 152 pages in length, and include more than 1,000 references, in addition to a 6-page executive summary. Though comprehensive and useful in many ways, the guidelines have four major potential shortcomings.

First, although the guidelines recommend antidepressant use in mild depression (“An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder”), recent meta-analyses that incorporate all randomized clinical trial data of antidepressants for major depressive disorder (MDD) throw some doubt on the strength of this recommendation (PLoS Med. 2008;5:e45 and N. Engl. J. Med. 2008;358:252-60).

When looked at in terms of drug vs. placebo differences in depression rating scales, the amount of benefit (effect size) was much smaller in reality (including all unpublished studies) than in the published scientific literature. In mild depression in particular, antidepressants are almost identical to placebo (the drug placebo differences are nearly 0), whereas as clinically notable benefits only occur in severe depression (drug/placebo differences are about 5 points).

These differences could be explained in many different ways. There are statistical possibilities: It is always harder to show a small effect size difference as in mild depression than a large one as in severe depression.

It also could be that the extremely broad and heterogeneous MDD category does not represent primarily a disease-like antidepressant-responsive biological depression, as with older concepts of melancholia. Response in severe depression might pick out such melancholia. Second, the discussion of maintenance treatment with antidepressants for recurrent MDD is relatively uncritical (“During the maintenance phase, an antidepressant medication that produced symptom remission during the continuation phase should be continued at a full therapeutic dose”). In the National Institute of Mental Health-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, although acute efficacy was seen in 60%-70% of subjects when all antidepressant classes were used sequentially, about one-half of those persons responded in up to 1 year of follow-up, despite staying on the same antidepressants that had helped them acutely (Am. J. Psychiatry 2006;163:1905-17).

If those who stopped medications because of side effects are included, only about one-third of those patients remained well for up to 1 year. It might be safe to conclude that antidepressants are more effective acutely than in maintenance treatment. The guidelines do not describe these results.

This possibility of limited maintenance efficacy also is supported by an analysis of maintenance randomized controlled trials with antidepressants. These data, presented earlier this year in a poster by Dr. Brian Briscoe and Dr. Rif El-Mallakh at the APA annual meeting in New Orleans, looked at 16 published studies and found that only 1 could be shown to have benefit beyond 6 months of follow-up. In the absence of a critical review of such studies, the maintenance recommendations have a diaphanous quality.

Third, little acknowledgment exists of the risk of probable increased suicidality with antidepressants. Not only that, but the guidelines suggest that a relationship between antidepressants and suicidality does not exist (“A predictive relationship to suicide has never been demonstrated”). This statement is made despite an almost twofold increase in suicidal ideation or attempts in the Food and Drug Administration meta-analysis of multiple randomized controlled trials (in young adults and children, but not older groups) (Arch. Gen. Psychiatry 2006;63:332-9).

Such trials are exactly how predictive relationships are established, because of removal of most confounding factors. Perhaps the work group deliberately used the word “suicide,” rather than “suicide attempts,” since such trials deliberately exclude subjects with notable suicidality, and thus completed suicide did not occur (Am. J. Psychiatry 2004;161:562-3). But about 13% of those who make suicide attempts eventually commit suicide.

Hence, a causative relation is inferable. This risk is not invalidated by less scientifically valid non-randomized epidemiological data suggesting otherwise, because “p” values of the effects of confounding bias in the latter studies (Int. J. Clin. Pract. 2010;64:1009-14). A predictive relationship to suicide prevention, with randomized controlled trials, also has never been demonstrated with antidepressants. Yet, in the absence of direct randomized control trial data one way or the other, the work group appears to presume such benefit, while denying such risk. The controversy is deemphasized in the report, and in fact, is not mentioned in the executive summary.

Fourth, the difficult differential diagnosis between bipolar and unipolar depression is hardly mentioned. No reference is made to the repeated evidence that 30%-40% of patients with bipolar disorder are initially misdiagnosed with MDD (BMJ 2010;340:c854) nor to some data indicating that the single most common cause of treatment-refractory depression is misdiagnosed bipolar depression (J. Affect. Disord. 2005:84:251-7).

Recent meta-analyses of antidepressant randomized controlled trials that incorporate previously unpublished data made available through the FDA archives provide a context that appears to be missing from these guidelines. About 95% of the published scientific literature indicates that antidepressants are more effective than placebo in the acute treatment of MDD.

An equal number of studies, showing that antidepressants were no better than placebo, have not been published. When all the actual studies, published and unpublished, are compiled, about 51% of studies are positive and 49% are negative (N. Eng. J. Med. 2008;358:252-60).

In providing this context, I am not suggesting that antidepressants do not work at all. However, it seems reasonable to conclude that the scientific literature has led the profession to believe that antidepressants are far more effective than they really are. This context is not reflected in the new guidelines.

Any treatment guidelines for MDD face a major problem. In debates about DSM revisions, it has become clear that diagnoses such as DSM-IV MDD are invalid “pragmatically,” based largely on the opinions of DSM leaders about what is “good” for clinical practice, rather than on scientific research (Association for the Advancement of Philosophy and Psychiatry Bulletin 2010;17, www.alien.dowling.edu/~cppering/aap/p/bulletin.htm). Given the way the DSM is created, it might not be surprising to find variable benefits with our treatments.

The fault may lie not in our drugs, but in us, and the ways in which we diagnose and treat.

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LETTERS

Book Review Woes

I found the recent review on the book on addiction quite disappointing (“Is Addiction Really Voluntary,” CLINICAL PSYCHIATRY NEWS, October 2010, p. 8). In the book reviewed, “Addiction: A Disorder of Choice,” author Gene M. Heyman, Ph.D., reportedly presented data supporting the contention that addictive behaviors are borne primarily out of voluntary behavior rather than from disease processes.

Dr. J. Calvin Chatlos, author of the review, commented that the book included “very valid data” that do not support addiction as a chronic disease. The implication of this statement, whether intended or not, is that recent data have cast doubt on the disease model of addiction.

Nothing could be further from the truth.

Contrary to the contention that Dr. Heyman’s ideas presented were novel, I found the examples outlined to be the same tired, flawed arguments that for decades have been used to blame addicts for their condition. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The first flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The second flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The third flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The fourth flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The fifth flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The sixth flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The seventh flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The eighth flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The ninth flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

The tenth flawed contention regarding “data” supposedly challenging the disease concept of addiction pertains to the observation that psychosocial stressors often provoke an addicted individual to modify his or her behavior in ways that promote recovery. This observation is better unique to addiction. I am concerned that concepts presented in this article, if allowed to go unchallenged, might further stigmatize individuals with addictive illness and impede recovery.

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