New Approaches to Managing Difficult-to-Treat Depressions

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In a sense, all depression is difficult to treat. Most depressions are episodic conditions that, not infrequently, are slow to fully remit. Most also are complicated by comorbid psychiatric and general medical disorders. However, a minority of such difficult-to-treat depressions are treatment resistant. The most common cause of initial treatment failure is not resistance but undertreatment—that is, an insufficient duration of treatment, a subtherapeutic dosage of antidepressant, and/or poor adherence to the prescribed regimen. Complicating factors such as undiagnosed hypothyroidism or substance abuse can result in apparent treatment resistance unless addressed. Challenging subtypes of illness, including psychotic and bipolar subtypes of depression, are not necessarily inherently refractory but must be met with modified treatment approaches. *(J Clin Psychiatry 2003;64[suppl 1]:3–4)*

THE TERMINOLOGY OF TREATMENT AND TREATMENT-RESISTANT DEPRESSION

Treatment-resistant depression and treatment-refractory depression refer to the same phenomenon. While consensus has yet to be achieved, working definitions of treatment resistance do exist. For example, some suggest that the term *treatment-resistant* should be reserved for patients who fail to respond to 2 adequate trials of different antidepressants. I prefer not to use the term *refractory* until multiple antidepressants and electroconvulsive therapy have failed.

To understand any definition of treatment resistance, one must understand the embedded terminology. An adequate trial is one in which both duration and dosage are sufficient to produce response. Many experts agree that an adequate antidepressant trial should last at least 4 to 6 weeks. A longer trial increases the likelihood of response, while repeated short drug trials may contribute to treatment resistance by shaping a sense of demoralization.[1] Higher dosages of antidepressant, if acceptably tolerated, also generally increase the likelihood of response. A dosage once considered adequate may be inadequate by today's standards.[2] In the era of tricyclic antidepressants, measuring plasma levels sometimes was used to help clinicians to discern whether dosage reflected actual bioavailability and provided an objective measure of adherence. Monitoring plasma levels thus could increase patient response rates.[3] Regrettably, such use of clinical laboratory has fallen by the wayside with the newer antidepressants.

In treatment research, the traditional guidepost has been response, generally registered as a ≥ 50% reduction in scores on standardized rating scales such as the Hamilton Rating Scale for Depression or the Montgomery-Asberg Depression Rating Scale. While of course desirable, response does not indicate ultimate treatment success, especially if the depressive episode was severe. Full and sustained remission, rather than symptom reduction, is the ultimate goal of treatment. Remission describes the virtual elimination of all of the symptoms of the original episode and a full return to functioning. According to the literature,[1,4] only perhaps 25% to 40% of depressed patients achieve full remission with the first course of therapy. Among those who neither remit nor respond is a subset of patients who obtain some symptom relief. These partial responders do not reach acceptable levels of well-being and continue to experience suicide risk, work impairment, and distress.

THE BURDEN OF DEPRESSION

The social, economic, and personal burdens caused by depression are staggering. The prevalence of depression and underdiagnosis, the preponderance of depressed patients in primary care, a relatively early age at onset, and a tendency toward recurrence or chronicity all converge to make depression a costly disorder in many ways. Greenberg et al.[5] used a human capital approach to examine the direct costs of medical and psychiatric care and the indirect costs of suicides and absenteeism/lost productivity at work stemming from unipolar depression, bipolar de-

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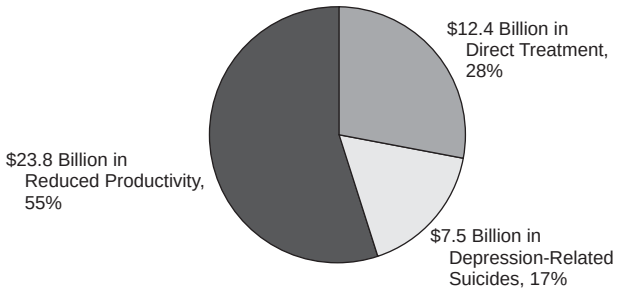
Figure 1. Cost of Depression in the United States in 1990: $43.7 Billion[a]



[a]Data from Greenberg et al.[5]

pression, and dysthymia combined. In 1990, these costs totaled $43.7 billion annually in the United States alone. Direct care costs, however, accounted for only 28% of the total (Figure 1).

The Global Burden of Disease study launched in 1992 by the World Health Organization adopted the construct of "years lived with disability" to reflect the toll of diseases that do not necessarily cause early mortality.[4] According to this study, neuropsychiatric illnesses were by far the global leaders in years lived with disability, and depression alone accounted for 11% of these years. Likewise, von Korff et al.[6] concluded that only advanced coronary artery disease causes more disability days or days spent in bed than depression.

Clearly, those patients with difficult-to-treat depressions contribute disproportionately to this burden. Untreated, undertreated, or unsuccessfully treated depressive episodes result in both relapse and chronicity, which in turn worsen prognosis and set the stage for future treatment failure.

COMMON CAUSES OF TREATMENT FAILURE

Aside from nonadherence, the most common cause of treatment failure is undertreatment. It is important that the depressed person receives education about the disorder and its treatment, as well as supervision through an adequate trial of an appropriate antidepressant. The clinician must be vigilant against pseudoresistance, which is the misperception of treatment resistance before the patient has received an adequate antidepressant trial.

Many complicating factors render depressed patients difficult to treat. Numerous medical illnesses—and a large number of medications used to treat these illnesses (e.g., antihypertensive agents)—can cause or exacerbate depression, or can interfere with the pharmacologic action of antidepressant drugs.[2] For example, in one study,[7] only 40% of patients with a comorbid medical illness responded to treatment with antidepressants. Comorbid psychiatric conditions may also complicate the treatment of depression, especially if the comorbidity is undiagnosed. Some psychiatric comorbidities, such as the presence of anxiety alongside depression, increase a patient's vulnerability to suicide and so redouble the importance of proper treatment. Many depressed patients have comorbid substance abuse disorders, and in fact, even moderate use of alcohol can interfere with the efficacy of antidepressant drugs.

One of the most important clinical steps in a systematic approach to difficult-to-treat depressions is accurately identifying whether a patient is presenting with a subtype of depression that warrants an alternate treatment approach. Two critical, often overlooked subtypes are psychotic and bipolar depression. As few as 20% of patients with psychotic forms of depression respond to antidepressants alone.[8] In this population, "adequate" treatment involves the combination of an antidepressant and an antipsychotic. Treatment algorithms for bipolar depression, too, have evolved according to the particular characteristics of the illness.[9] In general, bipolar depressions that are not responsive to mood stabilizers alone are treated with the combination of a mood stabilizer and an antidepressant. However, there are not good data on which type of antidepressant should be used. Difficult-to-treat depressions are variable not only across individuals but also between subtypes, and so differential responses to medications should be expected.

In this supplement, Dr. Nelson discusses drug switching, augmentation, and combination therapy in the treatment of difficult-to-treat unipolar depression; Dr. Keck reviews choices for managing bipolar depression, including the use of mood stabilizers, antipsychotics, and antidepressants; Dr. Schatzberg addresses the treatment of psychotic depression; and Dr. Manning discusses diagnosing and caring for patients with difficult-to-treat depression in primary care.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Amsterdam JD, Hornig-Rohan M. Treatment algorithms in treatment-resistant depression. Psychiatr Clin North Am 1996;2:371–386
2. Phillips KA, Nierenberg AA. The assessment and treatment of refractory depression. J Clin Psychiatry 1994;55(2, suppl):20–26
3. Glassman AH, Perel JM, Shostak M, et al. Clinical implications of imipramine plasma levels for depressive illness. Arch Gen Psychiatry 1977;34: 197–204
4. Greden JF. The burden of disease for treatment-resistant depression. J Clin Psychiatry 2001;62:26–31
5. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. J Clin Psychiatry 1993;54:405–418
6. von Korff M, Ormel J, Katon W, et al. Disability and depression among high utilizers of health care. Arch Gen Psychiatry 1992;49:91–100
7. Popkin M, Callies A, Mackenzie T. The outcome of antidepressant use in the medically ill. Arch Gen Psychiatry 1985;42:1160–1163
8. Charney DS, Nelson JC. Delusional and nondelusional unipolar depression. Am J Psychiatry 1981;138:328–333
9. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. Biol Psychiatry 2000;48:558–572