



Major Depressive Disorder: Understanding the Significance of Residual Symptoms and Balancing Efficacy with Tolerability

Larry Culpepper, MD, MPH,^a Philip R. Muskin, MD,^b Stephen M. Stahl, MD^{c,d,e}

^aDepartment of Family Medicine, Boston University School of Medicine, Boston Medical Center, Boston, Mass; ^bDepartment of Psychiatry, Columbia University Medical Center, New York, NY; ^cDepartment of Psychiatry, University of California San Diego, San Diego;

^dNeuroscience Education Institute, Carlsbad, Calif; ^eDepartment of Psychiatry, University of Cambridge, Cambridge, United Kingdom.

ABSTRACT

INTRODUCTION: Major depressive disorder is a complex and frequent psychiatric condition that poses significant challenges to both the patients who experience it and the physicians who treat them. The goal of therapy is for patients to achieve remission, which requires identifying and measuring symptoms at the outset and throughout treatment to document both response and resistance to treatment. A number of validated instruments are available both for diagnosis of and response to treatment. Many factors affect a patient's ability to achieve remission, but although many patients do achieve remission, a significant number continue to have residual symptoms that cause functional impairment.

METHODS: Review of the literature for treatment of major depression, including mechanisms of action, individualized treatment optimization, residual symptom reduction, and minimization of side effects.

RESULTS: For sustained remission, all symptoms must be treated until they are undetectable. Patients who do not achieve remission after adequate treatment trials should be evaluated for adherence to treatment, as well as comorbid psychiatric and medical disorders. In these cases, consideration should be given to changing therapy by switching, combining, or augmenting initial therapy, as well as referring some patients to a psychiatrist for treatment with specialized modalities. Linking symptoms with malfunctioning brain circuits and neurotransmitters provides a targeted approach for achieving sustained remission. Neurobiology also provides a rational basis for combination therapy in patients with treatment-resistant depression, because it can aid selection of different drugs with different mechanisms of action or of multifunctional/multimodal antidepressant drugs that target more than 1 molecular mechanism.

DISCUSSION: Recent advances and better understanding of neurobiology provide a rational basis for individualizing treatment of patients with major depression.

© 2015 Elsevier Inc. All rights reserved. • *The American Journal of Medicine* (2015) 128, S1-S15

KEYWORDS: Efficacy; Individualized Treatment; Major depression; Measurement based care; Multimodal antidepressants; Residual Symptoms

Major depressive disorder is widespread, with an estimated 12-month prevalence of 6.7%.¹ It is associated with significant costs in quality of life and lost work productivity

largely due to absenteeism/sick days, short-term disability, and performance deficits.^{2,3} The estimated economic burden of depression in 2000 was 83.1 billion dollars, of which 51.5 billion dollars were workplace costs.⁴ Treating depression is cost-effective because the cost of treatment is offset by increased work productivity associated with symptom remission.²

Major depressive disorder is complex. If one considers the diagnostic criteria—depressed mood or apathy/loss of interest plus ≥ 4 additional symptoms (**Figure 1**)—there are >60 forms of major depressive disorder given the various

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Requests for reprints should be addressed to Larry Culpepper, MD, MPH, Department of Family Medicine, 1 BMC Place, Boston, MA 02118.

E-mail address: laculpep@bu.edu

possible unique combinations of symptoms.⁵ Effectively treating patients with major depressive disorder to complete resolution of all symptoms presents a challenge to physicians. All antidepressant drugs have similar efficacy rates, but response among patients varies.

As our understanding of the neurobiology of major depressive disorder has increased, individualizing treatment to improve outcomes has improved. It is now recognized that psychiatric symptoms correlate with malfunctioning brain circuits. An understanding of a patient's symptom profile is key to individualizing treatment because different symptoms may reflect differences in underlying neuropathology, including differences in neurotransmitter-related abnormalities. Such understanding supports the selection of medications or other treatments that have the mechanisms of action appropriate for the patient. Applying neurobiology principles provides a rationale for individualized treatment selection.

DEFINING TREATMENT OUTCOMES: IMPORTANCE OF RESIDUAL SYMPTOMS

Over the last 3 decades, the desired outcome for the treatment of major depressive disorder has shifted from response to remission (**Table 1**).⁶ The definition of response— $\geq 50\%$ reduction in total symptom severity—allows for the presence of significant residual symptoms, which may predispose patients to recurrence, chronicity, and suicidality. The optimal outcome for patients with major depressive disorder is now considered to be symptomatic remission, a marker of wellness that is critical to return to premorbid level of functioning. It may be defined as minimal residual symptoms as measured by a $\geq 80\%$ reduction in symptomatology using one of the accepted rating scales or as an absolute cutoff score, such as ≤ 7 on the 17-item Hamilton Rating Scale for Depression (HAM-D).

The concept of remission more closely matches, but falls short of, what patients are trying to achieve with treatment. The factors most frequently identified by patients as being very important for achieving remission with treatment are listed in **Table 2**.⁷ These factors relate to the concept of well-being, which is defined as having achieved at least 1 item in each of 6 dimensions, including environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, and positive relations with others.⁸ Recovery from a major depressive episode also is

suggested as a desirable treatment outcome. However, the definition of recovery includes the criterion that the patient remains in full remission despite discontinuation of treatment, which may not be reasonable given the chronicity of and biological basis for major depression in many patients.⁸

Patients who achieve full remission are more likely to return to normal psychosocial functioning.⁹ Thus, the consequences of not achieving remission are many, affecting both the course of the disease and the healthcare and societal costs (**Table 3**).¹⁰⁻¹² Patients who achieve remission but have residual symptoms are more likely to relapse than those without residual symptoms (**Figure 2**).^{13,14} A literature review that assessed the burden of treatment-resistant depression in the United States concluded that up to 20% of patients with depression are treatment resistant and that annual added societal costs related to treatment-resistant depression are in the range of \$29 to \$48 billion.¹⁶

Patients who respond to treatment— $\geq 50\%$ reduction in symptoms—are more likely to have significant functional impairment

than those who achieve remission.^{9,17} Nonetheless, some patients who attain symptomatic remission also experience significant functional impairment after treatment.^{9,17-19} Although a criterion for major depressive episodes is functional impairment, clinical studies almost universally have relied on symptoms or symptom profiles as outcome measures.¹⁸ Patients may report improvement in global functioning measures with treatment, but changes in specific functional domains (eg, social, occupational, physical) generally have not been studied. An analysis of the literature concluded that functional outcomes tend to be less responsive to treatment than are symptom outcomes.¹⁸ The presence of some residual symptoms, such as core mood symptoms, correlate more strongly with functional impairment in patients who achieved remission than do other residual symptoms.¹⁹

The degree of remission appears to influence the improvement in the level of functionality. The accepted definition of remission on the 17-item HAM-D, a cutoff of ≤ 7 , is now considered too high, because global psychosocial functioning and quality of life are still impaired.²⁰⁻²² Scores of ≤ 5 ²⁰ and even 0 to 2²² are suggested as better target scores for identifying normal levels of functionality. Even patients who scored ≤ 7 on the HAM-D did not consider themselves to be in remission.²¹

CLINICAL SIGNIFICANCE

- Treatment to remission of depression is key to recovery of full function and preventing relapse.
- Even in remission patients experience residual symptoms that impair functioning.
- Individualized treatment matching therapy to specific symptom clusters may be most effective.
- Matching treatment to symptoms targets dysfunctional brain networks and their neurotransmitters.
- Multimodal treatment is often required to target multiple neurotransmitters.
- Multimodal antidepressants may provide less adverse effects than use of multiple single modality antidepressants.

Download English Version:

<https://daneshyari.com/en/article/2722443>

Download Persian Version:

<https://daneshyari.com/article/2722443>

[Daneshyari.com](https://daneshyari.com)