Depression With Physical Symptoms: Treating to Remission

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Depression is a recurrent, often chronic disease consisting of psychological and physical symptoms that are frequently undiagnosed or inadequately treated. While psychological symptoms have been shown to respond to current antidepressants, physical symptoms may not be as responsive. Treating both psychological and physical symptoms of depression may lead to a higher percentage of patients reaching remission. *(J Clin Psychiatry 2003;64[suppl 7]:24–28)*

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (DSM-IV)[1] classification of major depressive disorder (MDD) has traditionally focused on the psychological symptoms of depression, e.g., depressed mood, lack of interest, excessive guilt, suicidal thoughts, feelings of worthlessness, and indecisiveness. Although these psychological symptoms are key features of the disorder, the rate of MDD in populations that primarily complain of physical symptoms, such as fatigue, sleep and appetite disturbances, muscle tension, headaches, and general symptoms of pain, may have been underestimated.[2] To exacerbate the problem, diagnostic criteria for MDD list only 3 criteria for physical symptoms: sleep disturbance, appetite disturbance, and fatigue or loss of energy, with no mention of painful physical symptoms.[1] Because the typical presentation of MDD may not be with classical psychological symptoms, patients may become frequent visitors to primary care settings with vague physical complaints such as headache, backache, stomachache, joint and muscle aches, and chronic fatigue.[2–4] In 1985, Bridges and Goldberg[5] estimated that as many as 1 in 5 new consultations in primary care were for physical symptoms for which no specific cause could be found. The search for a medical cause for the physical complaint typically leads to underrecognition and undertreatment of psychiatric disorders.[2,6] Further, patients may assign greater importance to treating the physical symptoms than to treating the mood disturbance itself. Therefore, in order to achieve adequate treatment response and genuine remission, both the psychological and physical symptoms must be identified and resolved.

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ASSESSING PHYSICAL SYMPTOMS

The instruments that help clinicians and researchers the most in identifying physical symptoms associated with mood disorders tend to be long questionnaires that are broad-based and track "state" versus "trait" measures.[2,7] Kellner's 92-item Symptom Questionnaire,[7] for example, has shown excellent sensitivity to detect change in physical symptoms following antidepressant treatment,[8] and the 90-item Hopkins Symptom Checklist (SCL-90)[9] includes items that target degree of distress of physical symptoms.[2] The obvious disadvantage of both of these instruments is their length.

The use of sensitive scales in clinical practice to assess such physical symptoms is uncommon, and conventional scales used to measure depression in clinical trials rarely include significant numbers of physical symptoms.[2] The Montgomery-Asberg Depression Rating Scale (MADRS)[10] is a 10-item clinician-rated scale that includes only 3 physical symptoms (decreased appetite, insomnia, and fatigue). The Hamilton Rating Scale for Depression (HAM-D),[11] typically administered in its 17-item version (HAM-D-17), includes a greater number of physical symptoms (insomnia, decreased appetite/weight loss, fatigue, somatic/anxiety symptoms) than the MADRS. While psychological symptoms account for up to 38 points of the possible total score of 56, physical symptoms account for up to only 18 points (32% of the total score). Furthermore, the HAM-D places a greater emphasis on sleep and appetite disturbances, which can account for up to 10 of the total 18 points related to physical symptoms.[2] These issues are not unique to the HAM-D and the MADRS. Most depression scales tend to concentrate on psychological symptoms,[12] and some of the best-studied physical symptom instruments are focused on somatiza-

tion and hypochondriacal concerns and are not predictive of depression.[7]

Unfortunately, many of the definitions of remission used in the literature[13–15] suggest that a HAM-D score ≤ 7 is consistent with remitted MDD. Yet, a patient with a HAM-D score ≤ 7 may still be suffering from physical symptoms that are not tracked adequately by the scale itself. A recent study[16] from our group showed that patients who remitted following 8 weeks of antidepressant therapy (HAM-D-17 score ≤ 5) had significantly ($p < .03$) lower physical symptom scores at endpoint compared with patients who responded (50% or greater reduction in HAM-D score from baseline to endpoint) but did not achieve remission.

HOW PHYSICAL SYMPTOMS IMPACT RESPONSE AND REMISSION

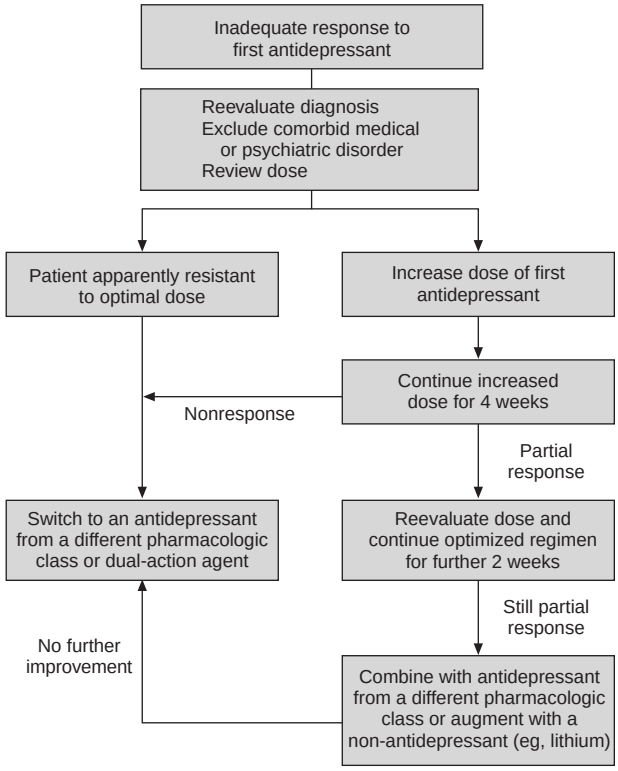
Most patients who are treated for depression fail to reach remission.[17–19] These patients, including those who respond (e.g., experience a ≥ 50% reduction of symptoms), continue to be affected by residual symptoms. These residual symptoms are often physical in nature and include fatigue, sleep disturbances, changes in appetite, and pain. These painful symptoms may be more distressing and disruptive to patients than even the mood symptoms of depression, urging the need for improved methods of treating depression that will result in remission of all symptoms.

Relapse and recurrence after successful treatment of MDD is a common and debilitating outcome.[19] Patients with depression who do not achieve complete remission of their symptoms are particularly vulnerable to relapse.[18–24] In a 15-month study of long-term outcome of treatment of depression, Paykel et al.[20] followed 60 patients diagnosed with unipolar major depression (RDC criteria) to relapse or remission. Thirty-two percent (19/60) reported residual symptoms at remission. Although improvement occurred moderately rapidly, relapse was common. In fact, relapses occurred within the first 10 months of follow-up in 76% (13/17) of patients with residual symptoms but in only 25% (10/40) of patients without residual symptoms.

Data from another study[16] suggest that the degree of physical symptom improvement in depressed patients is significantly correlated with overall reduction of depressive symptoms as measured by the HAM-D-17. Denninger et al.[16] administered the Symptom Questionnaire in concert with the HAM-D-17 before and after 8 weeks of treatment with fluoxetine 20 mg/day. Scores on items measuring physical symptoms decreased significantly following antidepressant treatment, and the degree of reduction in symptoms was significantly correlated with the degree of improvement in depressive symptoms.[16]

These data[16,20] strongly urge the need for improved methods of treating depression that will result in remission without residual symptoms.

Figure 1. The Step-Wise Approach to Management of the Patient With an Inadequate Response to Antidepressant Therapy[a]



[a]Reprinted with permission from Hirschfeld et al.[15]

TREATMENT STRATEGIES FOR MDD WITH PHYSICAL SYMPTOMS

Clinical studies of antidepressant drug treatments have shown that many depressed patients improve with treatment but still do not reach acceptable levels of functioning and well-being.[2,25] Additionally, although psychological symptoms have been shown to respond to antidepressants,[26] it has been hypothesized that painful physical symptoms associated with depression may be less responsive.[2] Hirschfeld et al.,[15] as part of an expert roundtable on the management of patients who fail to respond optimally to antidepressant therapy, developed a step-wise approach to guide clinicians in their treatment decisions (Figure 1). The ongoing Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[27] funded by the National Institute of Mental Health, is determining which treatment options are most effective for patients who fail to benefit adequately after initial treatment with antidepressant therapy. The results of this study will hopefully inform and guide future treatment options for psychiatrists and primary care physicians alike. Strategies under current investigation are shown in Table 1.

Table 1. STAR*D Treatment Options[a]

1.	Augmenting the first antidepressant with other medications or psychotherapy
2.	Changing to a different antidepressant or psychotherapy
3.	Adding psychotherapy or discontinuing the first antidepressant medication while switching to psychotherapy
4.	Switching to another antidepressant
5.	Augmenting the first antidepressant with other medications
6.	Augmenting first antidepressant with other medications or switching to another antidepressant

[a]From the National Institute of Mental Health.[28]
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

In addition to switching, combining, and augmenting various antidepressant therapies, clinicians can employ a number of basic strategies to increase the chance of a patient reaching remission: (1) educate patients about depression and antidepressants, (2) enhance treatment adherence, (3) ensure adequacy of dose, (4) ensure adequacy of treatment duration, (5) choose antidepressant treatments with relatively greater efficacy in specific subtypes or populations, and (6) address residual symptoms (including physical symptoms).

Educate patients. Clinicians should explain to patients that depression is a medical illness that is associated with changes in brain functioning and that clinicians typically prescribe antidepressants to help the brain function better. Psychoeducational materials and an emphasis on the importance of communication and collaboration will help set the stage for meaningful dialogue and appropriate treatment strategies.

Enhance treatment adherence. Adequate follow-up with patients (office visits or phone contacts) leads to better adherence to treatment. The use of antidepressants that have relatively greater tolerability and fewer side effects also affects adherence, but it is important to discuss side effects that may occur during antidepressant treatment and strategies to manage them, in the event of their occurrence.

Ensure adequacy of dose. Antidepressant medication should be initially administered at a dose within the recommended therapeutic range; however, some patients respond to subtherapeutic doses while others may require doses well above the therapeutic range in order to respond. Monitoring blood antidepressant levels may be useful for patients who are not responding and do not report side effects.

Ensure adequacy of treatment duration. Most patients require 6 to 12 weeks of treatment to achieve adequate response.[29] On the other hand, studies[29,30] have shown that minimal improvement by week 4 or 5 leads to a very small chance of response. In fact, Nierenberg et al.[30] demonstrated that nonresponse as early as week 4 predicted poor outcome at week 8. These studies suggest that, in general, clinicians must consider taking action if symptom improvement is not robust by weeks 5 or 6. In addition, an improved long-term outcome for patients may be achieved by the use of longer courses of treatment, which may ultimately enable recovery from depressive symptoms.[17]

Choose antidepressant treatments with relatively greater efficacy in specific subtypes or populations. While any antidepressant can result in remission of all symptoms in some patients,[4] chances of remission may be enhanced by choosing agents with relatively greater efficacy in a specific depressive subtype. For example, dual-action antidepressants, acting to inhibit the reuptake of both serotonin and norepinephrine, have performed better than single-action selective serotonin reuptake inhibitors (SSRIs) in evoking remission among patients with melancholic endogenous severe depression.[4,31,32]

Address all residual symptoms, in particular physical symptoms. Clinical experience using tricyclic antidepressants (TCAs) for the treatment of chronic pain has shown that TCAs appear to have greater analgesic efficacy than SSRIs.[2,33–37] In addition, anecdotal case reports suggest that serotonin-norepinephrine reuptake inhibitors also possess analgesic properties,[2,33,35] consistent with data indicating that both serotonin and norepinephrine exert analgesic effects via descending pain pathways.[2,38–40] These pathways may regulate the painful physical symptoms of depression, and when targeted by serotonin and norepinephrine reuptake inhibitors, relieve these symptoms as well.

Antidepressant Treatment Options

TCAs formed the mainstay of antidepressant treatment until the 1990s, and SSRIs have dominated treatment over the last decade.[41] However, the poor tolerability associated with TCAs and concerns about the efficacy of SSRIs in severe, melancholic MDD have led to the search for alternative agents. Attention has recently focused on antidepressants that affect norepinephrine and/or serotonin compared with single-action agents in the treatment of depression with physical symptoms.[31] A number of dual-action reuptake inhibitors that may have a greater chance of eliminating painful physical symptoms and lead to remission of depression include most TCAs, venlafaxine, milnacipran (which is approved in Europe and Japan and is being tested in the United States for use in fibromyalgia), and duloxetine (which is in the final stages of approval in the United States).[4,34,41,43–45]

Mirtazapine, a noradrenergic and specific serotonergic antidepressant that acts by antagonizing the adrenergic α_2-autoreceptors and α_2-heteroreceptors as well as by blocking 5-HT_2 and 5-HT_3 receptors, appears to be useful in patients suffering from depression with sleep disturbance.[42] Mirtazapine enhances the release of norepinephrine and 5-HT_{1A}–mediated serotonergic transmission. Its dual mode of action may conceivably be responsible for its rapid onset of action.[46]

Venlafaxine was the first in a new class of serotonin-norepinephrine reuptake inhibitors. Like some TCAs, ven-

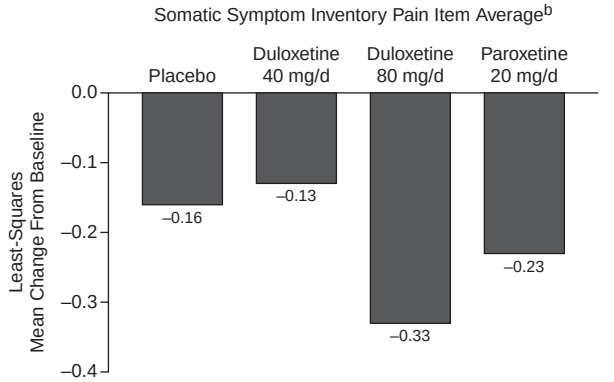
lafaxine inhibits reuptake of both serotonin and norepinephrine. It accomplishes this without affecting other nontherapeutic receptors and may be associated with an earlier onset of action and higher remission rates than SSRIs in severe, melancholic MDD.[29,37,41] Barkin and Fawcett[37] reported that venlafaxine may be particularly useful in the adjunctive treatment of chronic pain.

In preclinical trials, Wong and Bymaster[47] reported that dual inhibitors of serotonin and norepinephrine uptake (venlafaxine, milnacipran, and duloxetine) showed properties of inhibiting reuptake of both monoamines in vitro and in vivo in the following order of decreasing potency: duloxetine, venlafaxine, and milnacipran. All 3 agents exhibited low affinity at neuronal receptors of neurotransmitters, suggesting low side effect potential.

Several studies[2,41–45,47,48] have shown that the use of duloxetine, in particular, may be particularly efficacious in treating both depression and painful physical symptoms among MDD patients. A recent study[49] pooled efficacy data from 2 identical, double-blind, parallel-group, placebo-controlled studies of duloxetine (60 mg q.d.). Subjects with MDD were randomly assigned to placebo (N = 251) or duloxetine (N = 244) for up to 9 weeks. Response was defined as a 50% reduction in 17-item HAM-D total score from baseline to endpoint, while remission was defined as a 17-item HAM-D total score ≤ 7. The Visual Analog Scale (VAS) for overall pain was also used to assess degree of pain. The means for VAS overall pain score were statistically significant ($p < .001$), representing an approximately 4-fold greater change in remitters. The depression remission rate for pain responders was twice the rate of remission on pain nonresponders (36.2% vs. 17.8%, $p < .0001$).[49] Greater improvements in pain outcomes were also associated with more favorable outcomes on the Clinical Global Impressions of Severity (CGI-S) and Patient's Global Impression of Improvement (PGI-I), and patients whose painful physical symptoms resolved demonstrated higher rates of remission.[49] In a recent dose-finding study, Goldstein et al.[48] reported that 80 mg/day of duloxetine was superior to 20 mg/day of paroxetine, 40 mg/day of duloxetine, and placebo in treating the painful physical symptoms of depression (Figure 2). Detke et al.[45] found similar results in a study of 267 patients with MDD randomly assigned to receive duloxetine (60 mg/day) or placebo in a 9-week multicenter, double-blind, parallel-group clinical trial. Duloxetine reduced overall pain, back pain, shoulder pain, and time in pain while awake significantly more than placebo. Global measures of improvement showed that duloxetine 60 mg/day appears to be a safe and effective treatment of MDD.

More trials of dual reuptake inhibitors against other agents are needed to establish whether dual reuptake inhibitors consistently perform better in terms of remission and elimination of residual symptoms, particularly physical symptoms.[47]

Figure 2. Efficacy of Duloxetine on Painful Physical Symptoms in Depression[a]



[a]Data from Goldstein et al.[48]
[b]Pain-related items #2, 3, 9, 14, 19, 27, and 28.

DISCUSSION

The lack of a systematic assessment of all the symptoms of MDD, including those physical and somatic symptoms that are not part of the DSM-IV definition of the disorder, hinders the efforts of researchers and clinicians in determining whether differential responsiveness exists across antidepressant drugs. More controlled trials and new drug treatments and approaches are needed to better resolve physical symptoms in depressed patients. The most urgent needs in terms of research include (1) define outcome shaped by current nosology of depression; (2) address the lack of information about what happens to patients globally in terms of outcome; (3) broaden outcome measures, including quality of life and functioning; and (4) develop clinical trials that measure systematically how much better patients get psychologically, behaviorally, and physically following antidepressant treatment.

Further studies are also needed to investigate the effects of the use of antidepressants in patients with a primary diagnosis of a pain-related disorder not necessarily associated with mood disorders, e.g., chronic fatigue, chronic back pain, irritable bowl syndrome, and fibromyalgia.[37,50] Although research has shown that certain mental health interventions are effective in treating patients suffering from unexplained physical pain, these treatments are not always provided or are used inadequately.[37]

Clinicians must marshal the different treatment options to increase their patients' chances of achieving sustained remission from depression and resolution of painful physical symptoms.

Drug names: fluoxetine (Prozac and others), mirtazapine (Remeron), paroxetine (Paxil), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, duloxetine and milnacipran are not

approved by the U.S. Food and Drug Administration for use in the United States.

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