Major Depressive Disorder: Remission of Associated Symptoms

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Major depressive disorder (MDD) is a highly prevalent disease often associated with significant medical comorbidity. However, limited data are available examining the associated symptoms of MDD, especially the painful physical symptoms that frequently occur in patients. The presence of these physical symptoms greatly reduces a clinician's ability to recognize and diagnose MDD, ultimately leading to poor treatment outcome. While the treatment goal of MDD is complete remission of all symptoms and the patient's return to full-functioning capacity, if physical symptoms persist, the patient does not achieve functional recovery. Severe consequences have been associated with incomplete remission and residual symptoms, including greater disability and health care costs, plus the increased risk of relapse, morbidity, and mortality. In the treatment of MDD, the noradrenergic, serotonergic, and dopaminergic neural pathways have been found to be affected by depression. More specifically, these neural pathways may correlate with certain psychological and physical symptoms of depression. By studying the effects of antidepressant medications on specific neurotransmitters, antidepressant therapies could be matched to treat specific symptoms of depression. To achieve the goal of remission, clinicians must first determine the best rating method to identify and accurately evaluate the physical symptoms of depression in addition to the core mood symptoms. Therefore, further studies are needed to aid our assessment of physical symptoms and to meet the challenge of effectively matching treatments to a patient's specific symptoms. *(J Clin Psychiatry 2006;67[suppl 6]:27–32)*

Major depressive disorder (MDD) is a common occurrence among patients in primary care and medical inpatient settings, frequently presenting with medical comorbidity.[1–4] While 6% of primary care patients experience depression, the prevalence is higher (12%) among medical inpatients, illustrating this increased comorbidity of depression with medical illness.[4] Depression is especially high among patients with neurologic illness—40% to 50% in Parkinson's disease, 40% in Huntington's disease, and 15% to 50% in Alzheimer's disease.[5]

As a multifaceted systemic illness, MDD manifests through a variety of emotional (e.g., depressed mood, hopelessness, anhedonia) and physical (e.g., fatigue, pain, psychomotor) symptoms.[6,7] While the literature has focused on the comorbidity of MDD with Axis I, II, and III disorders,[2] little attention has been concentrated on associated symptoms of MDD such as physical and psychomotor symptoms, fatigue, anhedonia, and lack of motivation.

This article will examine the associated symptoms of MDD including physical symptoms, anxiety, fatigue, lethargy, and others. The role of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) will also be discussed through looking at the neurologic pathways affected by depression and the effect of treatment on these neural targets. Finally, the selection of treatments will be discussed, focusing on the potential benefits of treatment matching and the use of agents with multineurotransmitter effects.

PHYSICAL SYMPTOMS OF DEPRESSION

Kroenke et al.[7] demonstrated that multiple physical symptoms may indicate the presence of MDD, especially as the number of physical symptoms increases. Up to 65% of patients with MDD report the presence of painful physical symptoms.[8,9] In fact, more than two thirds of depressed primary care patients present exclusively with physical symptoms as the main reason for their visit.[9,10] The National Ambulatory Medical Care Survey (1989 summary)[11] showed that somatic symptoms, such as back pain, abdominal pain, and headache, result in increased clinical visits each year in the United States.

The presence of physical symptoms negatively impacts both diagnosis and treatment outcome for depression,

resulting in frequent underrecognition and inadequate treatment.[8,9] For example, the recent National Comorbidity Survey Replication[12] showed that only 32.7% of patients with a mental disorder (mood, anxiety, impulse control, and/or substance disorder) received at least minimally adequate treatment, meaning that two thirds received inadequate treatment. The survey[13] also found an average delay between onset of depressive symptoms and seeking treatment for those symptoms of 8 years. Both findings could help explain the overall increased frequency of clinical visits for somatic symptoms found by Bair and coworkers.[8,9] Therein lies the paradox—despite a greater presentation of physical symptoms in depressed patients, depression is still often misdiagnosed. Kirmayer et al.[14] assessed primary care physicians' recognition of depression based on patients' style of clinical presentation (psychosocial, somatic, or other complaints); whereas over 75% of patients (N = 685) exhibited somatic symptoms, only 22% of true somatizers were accurately diagnosed. Comparatively, 17% of patients presented with psychosocial symptoms, resulting in the correct diagnosis of 77% of these patients. Therefore, the attributes of somatization reduce a physician's ability to recognize depression, which can lead to poor treatment outcome.

Additionally, the presence of physical symptoms in patients with depression is associated with greater functional disability.[7–9] Kroenke et al.[7] surveyed 1000 adult primary care patients to determine how the number and type of physical symptoms exhibited by patients related to psychiatric disorders and functioning. Functional status was measured in 6 domains: physical functioning, social functioning, role functioning, mental health, bodily pain, and general health perceptions. The data showed that as the number of somatic symptoms increased, so did the prevalence of mood disorders. In addition, the number of physical symptoms was highly correlated with the level of dysfunction in all 6 domains.

ACHIEVING REMISSION AND RECOVERY

For over a decade, complete remission of all symptoms (emotional, physical, and motor) with a restoration of full-functioning capability has been the goal of treatment for MDD.[6,15–17] Achievement of full-functioning capacity means the patient returns to work, resumes hobbies and personal interests, and restores personal relationships.[6] However, patients who are deemed to be in partial or complete remission cannot attain functional recovery if their physical or motor symptoms are not fully resolved, nor will patients' ability to concentrate improve if physical symptoms persist.

Risk Factors Associated With Partial Remission

Failure to achieve remission is associated with many negative outcomes. The attainment of response rather than

remission is associated with a substantially greater risk of relapse or recurrence.[18–20] Paykel et al.[19] found that 76% of patients with residual symptoms following partial remission experienced subsequent early relapse. Furthermore, Judd et al.[18] showed that patients who did not achieve remission experienced more severe and chronic future depressive episodes with shorter durations between episodes.

Additional risk factors associated with incomplete remission include persistent impairment and greater morbidity and mortality. Research demonstrates that patients who do not achieve remission continue to suffer from impaired psychosocial functioning in their work and relationships.[21] Patients failing to achieve remission may also be at risk for increased all-cause mortality[22] and morbidity and/or mortality with stroke,[23] type 1 or type 2 diabetes,[24,25] myocardial infarction,[26] cardiovascular disease,[27] coronary heart failure,[28] and human immunodeficiency virus (HIV).[29] Residual symptoms of depression are also associated with a sustained risk of suicide.[30]

Patient Treatment Adherence

Patient adherence to therapy is essential for positive treatment outcome.[31] While two thirds of patients with MDD experience improvement with antidepressant therapy,[32] patient noncompliance with treatment is common.[33] Lin et al.[34] found that approximately 28% of patients (N = 155) stopped taking their medication during the first month of therapy; 44% quit taking them by the third month of treatment. Studies show 2 of the reasons patients stop taking their medications are that they start to feel better or, conversely, they feel their symptoms are not improving.[33,35] Consequently, these patients decide to terminate antidepressant treatment prematurely even though they have not fully recovered. The issue of residual symptoms, especially physical complaints, may play a part in patient noncompliance if patients feel their symptoms are not being resolved. Therefore, clinicians have much to accomplish in this area.

Residual Physical Symptoms

The physical symptoms of MDD are associated with greater disability and health care utilization.[36] Denninger et al.[36] evaluated the relationship between physical symptoms and depression in 148 outpatients with MDD receiving open-label treatment with fluoxetine (20 mg/day) for 8 weeks. A reduction in somatic symptoms correlated significantly (R = 0.345, p < .0001) with improvement in depressive symptoms. Patients who achieved remission, defined as a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score ≤ 5, had significantly lower physical symptom scores at endpoint compared with patients who responded to antidepressant treatment (≥ 50% reduction in baseline HAM-D-17 score) without achieving remission.

Bair et al.[8] found the severity of painful physical symptoms is predictive of poor treatment outcome in depres-

Figure 1. Plausible Brain Structure–Function Links to Depressive Symptoms
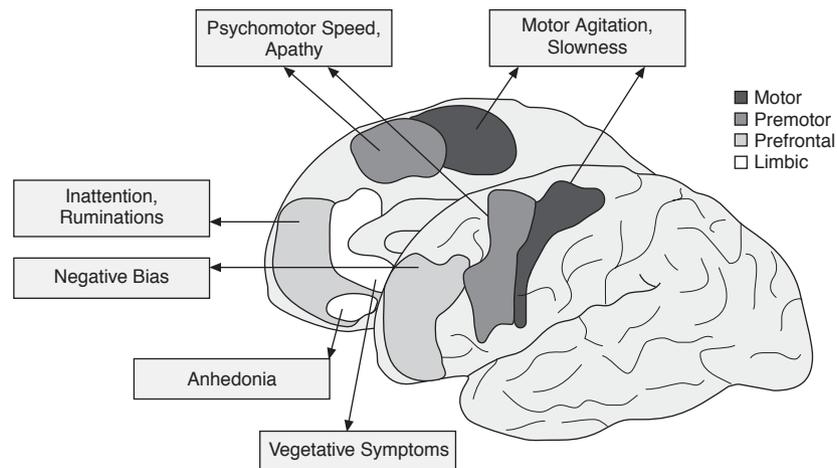
sion. In a study analysis (data from A Randomized Trial Investigating SSRI Treatment [ARTIST]) of 573 clinically depressed patients, two thirds of patients reported pain at baseline. Following 3 months of antidepressant treatment, 24% of patients experienced a poor treatment response. When patients improved, their predominant residual symptoms still continued to be physical in nature unless they began treatment with anxiety as a symptom, in which case anxiety continued to be the predominant symptom.

Data from ARTIST[8] also revealed the unmet needs of treatment with selective serotonin reuptake inhibitors (SSRIs) in the physical symptom arena. More than half (59%) of patients still reported residual painful physical symptoms after 3 months of treatment with an SSRI (fluoxetine, paroxetine, or sertraline). Fewer data are available concerning the effect of venlafaxine and duloxetine in treating the physical symptoms of depression; more studies are needed to determine if physical symptoms would remain the predominant component of residual symptoms following treatment with these antidepressants.

LONG-TERM TREATMENT OF MDD

Neurologic Pathways Affected by Depression

Research suggests that depression does not affect a single brain region or neurotransmitter system but instead involves specific integrated neural pathways connecting the neurotransmitters at certain cortical, subcortical, and limbic sites.[37,38] By organizing the dimensions of depression (i.e., mood change, cognitive impairment, motor deficits, and circadian dysregulation), the specific neural circuits affected by depression may possibly be identified and compared for determining potential treat-

ment. For example, the symptoms of mood changes, such as dysphoria, suicidality, anhedonia, and anxiety, may be based on a different neural circuit than the symptoms of motor deficits. Likewise, cognitive impairment and circadian rhythms may be related to different neural circuits as well. Therefore, plausible brain structure–function links to depressive symptoms may exist in the brain, meaning different neural circuits may be involved with different symptoms (Figure 1).

Similarly, different types of depression treatments—pharmacologic, cognitive, and somatic—can regulate specific neural targets, resulting in chemical and molecular changes that can facilitate recovery by returning the brain to a healthy mood state.[37–39] In fact, recent trends in psychopharmacology are again focusing on the role of multiple targets of action in the treatment of depression.[40] Mayberg[41] has studied the importance of these neural circuits in depression, examining pathophysiology, behavioral correlates, and treatment targets (Figure 2).

Furthermore, studies on antidepressant treatments and cognitive-behavioral therapy (CBT) have demonstrated this neural effect.[39,42] Patients treated with paroxetine[39] experienced more limbic changes, whereas CBT responders showed increased prefrontal alterations. Response rates were similar for each group. Mayberg et al.[38] discovered similar effects on the limbic and prefrontal neural circuits through deep brain stimulation of the Cg25WM. Therefore, these studies show that by organizing the depression symptoms at the neural systems level, residual symptoms might be matched to the optimal treatment.

Matching Treatment to Depression Symptoms

Treatment matching following initial diagnosis is an intriguing theory. For example, if a patient presents with

Figure 2. Importance of Neural Circuits in Depression: Pathophysiology, Behavioral Correlates, and Treatment Targets[a]
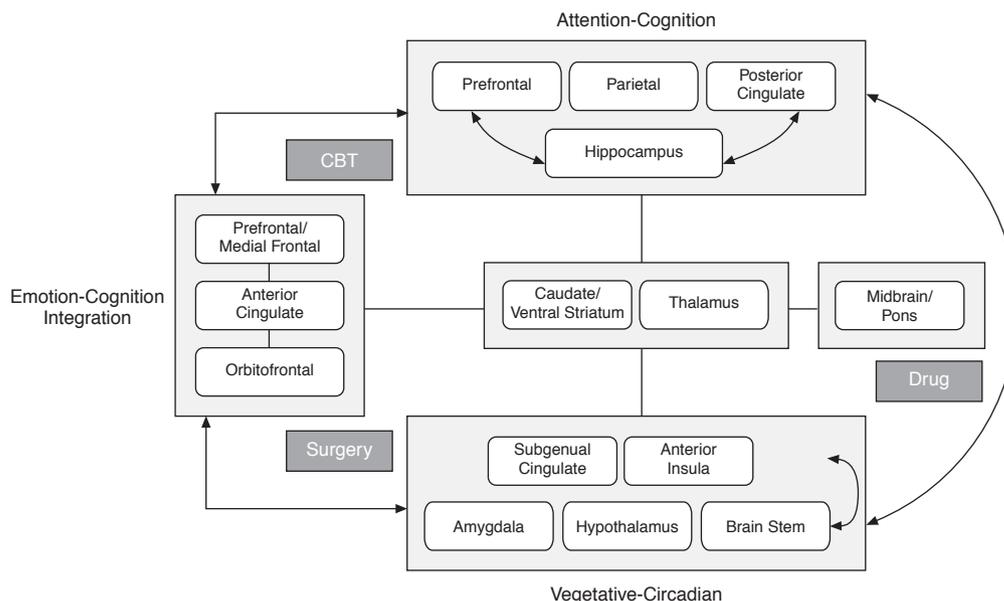
[a]Adapted from Mayberg,[41] with permission. In this model, remission occurs when there is modulation of dysfunctional limbic-cortical interactions (black arrows), which is facilitated by different types of treatment.
Abbreviation: CBT = cognitive-behavioral therapy.

motivation, energy, psychomotor, and cognition symptoms, should an NE or a DA agent be prescribed as opposed to an SSRI? Several studies have demonstrated that treatment with an SSRI[43,44] (i.e. paroxetine, fluoxetine, or sertraline) or a dual serotonin-norepinephrine reuptake inhibitor (SNRI)[45–48] (such as duloxetine) is effective in improving physical symptoms. However, data are not yet complete, and further studies in treatment matching are warranted to look at the effect of antidepressant treatment on noradrenergic, 5-HT, or DA pathways[49] and corresponding physical symptoms.

Recently, interest in DA as associated with depression has reemerged owing to research regarding aripiprazole's affinity for specific DA receptors.[50–52] Sustained hypercortisolism has been linked to a high incidence of depression; it also decreases DA release.[53,54] Symptoms associated with DA neural pathways include pleasure-seeking behavior, attention, sexual function, motor function, emetic reflex, and reward response—common impairments found in most depressed patients.[49,55] In general, DA pathways have been studied more extensively because of these symptoms rather than because of the association with depression. However, DA reuptake inhibition can lead to a reduction in depression, psychomotor activation, and antiparkinsonian effects.[56]

The pathogenesis of depression is more complex than just a deficiency or "imbalance" in neurotransmitter levels. In neurotransmitter depletion studies,[57,58] depressed patients were randomly assigned to either an NE reuptake inhibitor (NRI) (desipramine) or an SSRI (fluoxetine).[57] Patients who had therapeutic responses progressed to selective neurotransmitter depletion testing during 2 sessions of 2 days' duration. The results of the depletion testing correlated with the clinical response to antidepressant treatment. In SSRI responders, 5-HT depletion but not NE depletion caused the return of symptoms.[58] In contrast, 5-HT depletion did not result in the return of symptoms in NRI responders, but NE depletion did. Nondepressed control subjects did not experience symptoms when 5-HT and NE depletion were experimentally induced. These data support the concept that pharmacologic selectivity is accompanied by therapeutic selectivity. Because the etiology of depression is complex, depression may be more directly caused by dysfunction in brain areas or neuronal systems modulated by systems involving 5-HT, NE, or both.

Our challenge in the future will be to match antidepressants with acute symptoms, residual symptoms, and symptoms predictive of relapse. However, to address this challenge, a better measurement system may be needed to assess physical symptoms. Commonly used clinician rating scales on depression symptom severity include the HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS), the Inventory of Depressive Symptomatology (IDS), the Snaith Hamilton Anhedonia Scale, and the Visual Analog Scales (VAS) for Pain. It is difficult to determine the best scale to use; however, the IDS appears to have better psychometric properties and can distinguish between several physical symptom categories.

The MADRS and HAM-D are good measures used by most clinicians, and the MADRS may have better psychometrics than the HAM-D. While the HAM-D does measure physical symptoms, somatic and gastrointestinal symptoms are combined, as well as retardation and psychomotor symptoms. In addition, other issues have arisen with the HAM-D regarding rating retardation and agitation symptoms within the same week. Therefore, to identify people with residual symptoms, it is necessary to measure symptoms within the response or remission category.

Selection of Antidepressant Treatment

Several factors should be contemplated when selecting an appropriate antidepressant. Treatment should maximize the likelihood of remission with the first choice of therapy by evaluating the agent's mechanism of action and clinical evidence demonstrating the agent's efficacy in achieving remission with the elimination of all emotional and physical symptoms of depression. Additionally, the choice of antidepressant should take into account the medication's safety and tolerability profile, ease of use (dosing frequency, titration, ability to administer with/without food, etc.), and the direct and indirect cost. The patient's personal and family treatment history can also help guide treatment selection.

CONCLUSION

Since MDD is a major public health issue with a high rate of comorbidity, remission of all symptoms, especially physical symptoms, is a clinical priority. Painful physical symptoms often contribute to and complicate the diagnosis of depression. Better recognition and treatment of these symptoms may increase a patient's chance of achieving remission. While much has been accomplished in the examination of specific neural pathways associated with depression, the identification of symptoms of depression correlating to these neural pathways, and the effects of antidepressant medication on the physical symptoms of depression, further studies are needed before clinicians can effectively match antidepressant treatment to specific physical symptoms of MDD.

REVIEW QUESTION

Do you routinely screen your depressed patients for the presence of physical symptoms? If so, how do you address these symptoms when developing a patient's treatment regimen?

Drug names: aripiprazole (Abilify), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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

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