Physical Symptoms of Depression: Unmet Needs

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The burden of depression on society is sizable. Innate to this burden are underdiagnosis and undertreatment of unipolar and bipolar major depressive disorder in all parts of the health care system in part due to underrecognition of the physical symptoms that commonly are core components of major depressive disorder. Physical pains especially complicate the diagnosis of depression. Many patients de-emphasize psychosocial symptoms while emphasizing pains as their primary or sole complaints. There is a high correlation between the number of physical symptoms reported and the presence of depression. Additionally, patients with residual physical and emotional symptoms following treatment for depression appear to be at higher risk of relapse compared with those who have no residual symptoms. Complex genetic vulnerabilities underlie the depressive diathesis, and stress appears to be an accentuation for the gene expression that sets off episodes of depression in persons with these predispositions. If underdiagnosis interferes and acute treatment is not implemented early and effectively for initial episodes of depression and maintained after remission, individuals with genetic vulnerabilities may experience a pattern of recurrences, cycle acceleration, and increased severity. Serotonin and norepinephrine may be shared neurochemical links that tie depression and physical symptoms together. Thus, it is reasonable to hypothesize that antidepressants that incorporate both serotonin and norepinephrine reuptake inhibition might be a more efficacious treatment approach for patients with physical symptoms of depression. *(J Clin Psychiatry 2003;64[suppl 7]:5–11)*

World Health Organization (WHO) data have confirmed that the international burden of depression is enormous and growing. This disorder is projected to be the second leading cause of disease in the world by the year 2020.[1]

Depression has an earlier symptom onset than is commonly understood by most practicing clinicians, and as a result, the disease often progresses insidiously for years before it is detected and intervention is begun. Because early detection and effective intervention can decrease the severity of depression over the long-term and lessen risk of recurrence,[2] it is imperative that physicians be aware of the initial symptoms that indicate depression might be present. While more than 40 antidepressants from different classes with different mechanisms of action are available to treat depression, only 30% to 40% of patients taking these antidepressants will achieve full remission.[3] Patients who are seeking treatment from their primary care physician for physical symptoms frequently have depression. Pain especially can serve as an initial early indicator of depression. Continued physical symptoms or lingering pain despite acute treatment might alert clinicians that a patient is at higher risk for recurrences, since this has been demonstrated when such individuals were compared with those who have no residual symptoms.[4] Diffuseness of pain and the extent to which pain interferes with activities are two characteristics that strongly predict depression.[5] Arguably, the underrecognition of depression in those with physical symptoms may be the single most common reason why psychiatric illnesses frequently go undetected in the general practice setting.[6] Therefore, clinicians need to recognize the significance that physical symptoms, one of which is pain, can have in the early detection and management of major depressive disorder if they are to effectively treat it and lessen its huge burden and costs.

THE BURDEN OF MAJOR DEPRESSIVE DISORDER

In 1996, the WHO updated its evaluations of the burdens and disabilities associated with the world's major diseases. The findings were revealing. Disability, for example, was classified as any restriction or loss of ability to perform due to impairment, and WHO data estimated that 11% of all disability was due to major depressive disorder.[1] There are obvious pieces of evidence supporting the high morbidity of major depressive disorder (Figure 1).[7]

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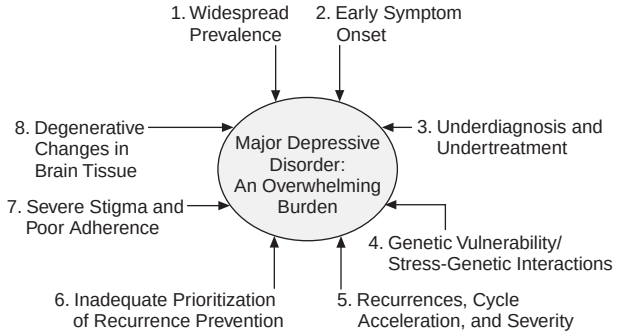
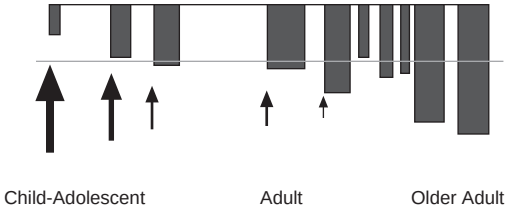
Figure 1. Contributors to the High Morbidity of Major Depressive Disorder and Treatment-Resistant Depression[a]



[a]Adapted with permission from Greden.[7]

Figure 2. Influence of Stress on the Lifetime Course of Untreated Depression[a]



[a]Adapted with permission from Greden.[7] Shaded boxes designate depressive episodes. Line indicates depressive episodes that meet the criteria for major depressive disorder. Arrows designate stressors. Size of arrows and boxes signifies estimates of severity.

Major depressive disorder has high worldwide prevalence and impact. Kessler et al.[8] reported that more than 15% of the population are at risk for major depressive disorder over their lifetimes, and that risk is approximately 1.7 times higher in women than in men. Overall, an estimated 340 million individuals worldwide and 18 million in the United States have major depressive disorder at any given time.[8] The economic burdens are enormous. People with depression have health care costs—excluding mental health care expenses—that are 2 to 3 times higher than those of nondepressed people.[9] Few major disorders have a negative health impact that can parallel that of major depressive disorder.

Perhaps more importantly, early symptom onset, underdiagnosis, and undertreatment are primary contributors to the burden of major depressive disorder. Frequently, individuals who are later determined to have major depressive disorder in adulthood experienced symptom onset in adolescence or young adulthood but received inaccurate diagnoses. Specifically, only a minority of patients receive an accurate diagnosis and adequate treatment, and this pattern has persisted worldwide for decades.[1] Undiagnosed individuals appear to be at greater risk of developing increased severity, recurrences, acceleration of episodes, and even treatment resistance than individuals whose major depressive disorder is recognized and successfully treated at an earlier age. This hypothesis is partially supported by research that indicates that subclinical depressive symptoms during teenage years strongly predict subsequent adult major depressive disorder, resulting in as much as a 2- to 3-fold increased risk.[10] In controlled studies, symptom remission rates for depression are typically less than 50%,[11,12] which means that a sizable number of patients are left with considerable symptomatology because they have responded only partially to treatment or have not responded at all. While linkages remain to be confirmed, recent neuroscience studies suggest that underdiagnosis, undertreatment, and eventual chronicity may contribute to accelerating lifetime progression via underlying brain morphological changes.[13]

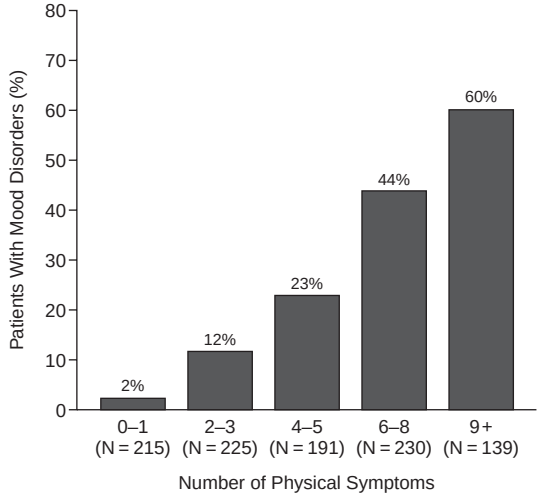
Major depressive disorder and bipolar disorder are complex genetic disorders. Data suggest that when those with underlying genetic vulnerabilities encounter stressful life events such as death, divorce, financial upheaval, trauma, or assault, depressive episodes may emerge, reappear, or become accentuated, adding to the burden of major depressive disorder. Maintenance antidepressant treatments may prevent episodic recurrences or worsening.[7] If maintenance antidepressant treatments are not in place for individuals with such genetic diatheses, and what are often unavoidable stressors appear, they may precipitate not only repeated flare-ups, but perhaps increased sensitivity to future stressful events. Eventually, even minor stressors may hypothetically lead to severe depressive episodes (Figure 2),[7] or recurrences may develop even in the absence of stressors. In essence, a vicious cycle emerges.

Stigma and poor adherence contribute to the inadequate treatment cycle, expanding the gateway to the continued progression of the disease. This pattern of recurrences, cycle acceleration, and increasing severity may eventually culminate in the suppression of brain neurogenesis, neuronal atrophy, cell death,[14] and hippocampal dysfunction[15] as evident in magnetic resonance imaging changes.[16] More studies and better integration of clinical, neuroimaging, genetic, and stress assessments are needed to confirm whether and how these neurochemical changes contribute to the development and disability of major depressive disorder, but the mosaic appears to be emerging into a picture. Sadly, the picture is one of disability unless early detection and intervention are prioritized.

PHYSICAL SYMPTOMS INCLUDING PAIN IN DEPRESSION

Physical symptoms are a key feature in this depressive profile. DSM-IV, other nomenclatures, and most general descriptions pertaining to depression that date back to Hippocrates have listed gastrointestinal problems, sleep

Figure 3. Numerous Physical Symptoms More Strongly Suggest Mood Disorder Than Fewer Physical Symptoms[a]



[a]Reprinted with permission from Kroenke et al.[17]

disturbances, headaches, appetite changes, fatigue, and aches and pains of a diffuse nature as common features of depression. Additionally, Kroenke et al.[17] noted that as the number of physical complaints increases, so does the likelihood of a mood disorder. Depression is commonly comorbid with chronic pain, occurring in approximately 50% of patients who have chronic pain.[18]

Physical Symptoms, Pain, and Diagnosis

Despite these historical traditions, physical complaints appear to complicate the diagnosis of depression, contributing to the challenge facing primary care physicians and psychiatrists when patients present for evaluation. Patients with depression often report physical symptoms, notably pain, as their primary or sole complaint in lieu of mentioning psychosocial symptoms. Such a presentation, when coupled with time limitations, may prevent the attending physician from identifying the unsuspected, underlying depression. Because physical symptoms are frequently the chief or sole complaints of the patient, many physicians do not consider the possibility of an underlying mood disorder. Lesse[19] reported that 30% of patients with depression experience physical symptoms for more than 5 years before receiving the proper diagnosis.

Simon et al.[20] exemplified how frequently primary care physicians are faced with the tendency of patients to report physical and not emotional symptoms. Their international study included 1146 patients from 15 primary care centers in 14 countries on 5 continents. These patients underwent structured assessments of depressive and somatoform disorders and met diagnostic criteria for major depression. Study results indicated that 791 (69%) of the initial 1146 patients reported physical symptoms as the reason for their visit to the physician, and 126 (11%) denied experiencing psychological symptoms of depression when directly questioned. Patients who lacked an ongoing relationship with their primary care physician were more likely to report physical symptoms than patients with a personal physician, who displayed a greater propensity to report emotional symptoms.

Table 1. Relationship Between Common Physical Symptoms and Psychiatric Disorders in Primary Care Patients[a]

Physical Symptoms	All Primary Care Patients With This Symptom (%)	Percentage With This Symptom and With Mood Disorder
Joint or limb pain	59	34
Back pain	41	38
Headache	36	40
Chest pain	21	46
Abdominal pain	19	43
Fatigue	58	40

[a]Reprinted with permission from Kroenke et al.[17]

Primary care physicians diagnose depression more accurately when patients present with psychosocial symptoms. Psychosocial complaints typically alert primary care physicians to mood disorders and enable them to make a more expedient and accurate diagnosis of the depression. Kirmayer et al.[21] studied 75 patients with major depression or an anxiety disorder who presented with physical symptoms; only 17 (22%) were recognized as having a psychiatric disorder by the physician when they presented with predominantly physical symptomatology, compared with 58 (77%) who were psychosocial symptom presenters. Kirmayer and colleagues concluded that there was a distinct pattern of "recognition reduction" when depression was accompanied by physical symptom presentation.

Physical pain tends to be a primary patient complaint in the earlier stages of depression. Longitudinal studies are lacking, but in later stages there may be a greater likelihood that, although the patient may still have coexisting physical symptoms, they will be more inclined to simultaneously report emotional or mood symptoms. In such circumstances, physicians may wish to historically search for evidence of prior episodes.

Correlation of Physical Symptoms and Depression in Patient Reports

Kroenke et al.[17] utilized an inverse correlative approach to study what physical symptoms are frequently reported by patients who have psychiatric disorders. The study, which included 1000 adult clinic patients, determined that the presence of any physical symptom increased the likelihood of a mood or anxiety disorder by 2- or 3-fold (Figure 3) and indicated that physical symptoms had a strong association with psychiatric disorders (Table 1). Among the sample, 34% to 46% of patients with physical pain were found by standardized criteria to have a mood disorder. Only 2% of patients with no physical symptoms

or with only 1 physical symptom were determined to have a mood disorder; that percentage jumped to 60% when the patient had 9 or more physical symptoms. Overall, there was a high correlation between physical symptoms and psychiatric disorders. These study results do not imply causality, but demonstrate that physical symptoms and psychiatric disorders frequently coexist.

In a cross-sectional study at a general medical primary care practice in rural New England, Gerber et al.[22] assessed the relationship between specific physical complaints of patients and underlying depressive symptoms. Researchers screened 1042 patients for depression using the Hopkins Symptom Checklist 49-item depression scale and had physicians fill out a form recording specific chief complaints, and amplification and clarity of complaint presentation style. Study results indicated that complaints revealing a high positive predictive value (PPV) for depression were sleep disturbances (PPV 61%), fatigue (PPV 60%), multiple (3 or more) complaints (PPV 56%), nonspecific musculoskeletal complaints (PPV 43%), back pain (PPV 39%), shortness of breath (PPV 39%), amplified complaints (PPV 39%), and vaguely stated complaints (PPV 37%). The researchers concluded that depressed patients are common in primary care and that the aforementioned physical complaint presentation styles and physical symptoms are frequently associated with underlying depression.

Physical Symptoms, Pain, and Depressive Recurrences

Physical symptoms and pain not only serve as initial early indicators that depression may be present but after acute treatment, continued physical symptoms also can alert clinicians that a patient is at risk for recurrence. Paykel et al.[4] studied 64 patients having major depression, treated them with antidepressants, and monitored them every 3 months until remission and thereafter. Of the 60 patients who had remitted after 15 weeks, 19 (32%) had residual symptoms. Results indicated that residual symptoms appeared to be more common in patients with more severe symptoms, but notably 94% of those depressed patients who experienced lingering symptoms had mild to moderate physical symptoms. A total of 57 of the patients who had achieved remission were then followed up systematically for another 12 to 15 months to identify relapse rates.[4] Results of this second study phase indicated that residual symptoms were strong predictors of subsequent early relapse, occurring in 13 (76%) of the 17 who had experienced residual symptoms and only 10 (25%) of the 40 patients who had experienced no residual symptoms. This study revealed a correlation between the degree of physical and emotional symptom improvement and the ability for patients to achieve remission, and patients with residual symptoms appeared to be at a higher risk of relapse compared with those who had no residual symptoms. Lingering physical symptoms and pain, even in the presence of improvement for some psychological symptoms, should indicate to a physician that a patient may not have achieved complete remission of depression.

NEUROCHEMISTRY OF PAIN IN DEPRESSION

A growing database suggests that serotonin and norepinephrine may share neurochemical mechanisms that tie depression and physical symptoms together.[23,24] Through the noradrenergic and serotonergic systems, chronic pain and depression appear to share a common biological pathway. When a nerve ending is stimulated due to an injury, for example, a response signal is transferred peripherally and subsequently registered in key central nervous system limbic areas that are conventionally associated with pain recognition. Hypothetically, in the descending inhibitory pathway the sensitivity of how the response is modulated is controlled by a balance of norepinephrine and serotonin. The modulatory roles played by norepinephrine and serotonin are part of the body's endogenous analgesic system, and together may alter downward feedback. Therefore, one possible explanation for the correlation between pain and depression is that patients with major depressive disorder characterized by both emotional and physical symptoms may have neurotransmitter dysregulation that contributes to the characteristic constellation of mood and cognitive symptoms, and also may accentuate pain sensitivity in descending inhibitory pathways.

Emerging data regarding the neurochemistry of pain have led some investigators to hypothesize that antidepressants that incorporate both serotonin and norepinephrine reuptake inhibition might be more efficacious than selective serotonin reuptake inhibitors (SSRIs) for patients with physical symptoms and depression.[25] Serotonin reuptake inhibition alone has demonstrated some evidence of relieving chronic pain. Blier and Abbott[26] reported that the relief of chronic pain effected by some antidepressants may be mediated in part by the blockade of peripheral 5-HT receptors. They suggested that the serotonin system may be endowed with different adaptive properties in various parts of the body, which, along with the multiplicity of serotonin receptors, makes this network important in many disorders. Available data indicate that agents with dual serotonergic and noradrenergic activity appear to have the most consistent benefits in pain syndromes—sometimes even in the absence of depression.[27] This might explain why tricyclic antidepressants have historically demonstrated better effectiveness in treating physical symptoms associated with depression than antidepressants with more selective actions, such as SSRIs.

Understanding the shared neurobiology of pain and depression can offer psychiatrists, physicians, patients, families, and third-party carriers one giant step toward meeting improved diagnosis, earlier intervention, reduction of stigma, better long-term adherence, improved quality of life, and reduced costs.

NEED FOR REMISSION

Failure to attain remission is another major factor linked with physical symptoms that contributes to the burden of major depressive disorder. While more than 40 antidepressants from different classes—some with different mechanisms of action, many with different pharmacokinetics or pharmacodynamics—are available to treat depression, only 30% to 40% of patients taking these antidepressants achieve full remission.[3,28] Remission should ideally be defined as a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of less than 7; yet, test subjects in most studies do not achieve that. It is estimated that 50% to 70% of people with depression achieve some improvement but fail to achieve complete remission of their emotional and physical symptoms.[29] Complete remission should be the determinant of success, and current data suggest that most patients are not receiving adequate treatment for their depression.

Remission appears to significantly improve overall quality of life for patients with major depressive disorder. Those with partial improvement may also experience improvement in quality of life; however, residual symptoms precipitate lower physical and social functioning and significantly detract from these patients' perceptions of improvement. A recent study conducted by Doraiswamy et al.[30] attempted to examine patterns of improvement in quality of life (QOL) in elderly patients with recurrent major depression following acute treatment. After treating 100 patients (60–88 years old) with recurrent depression using either bupropion sustained-release (100–300 mg/day) or paroxetine (10–40 mg/day) for 6 weeks, researchers determined that remitters showed significantly greater improvement than both partial responders and nonresponders on numerous quality of life measures. The researchers concluded it is imperative that patients achieve full remission to maximize impact on both physical and emotional quality of life.

Another problematic consequence from failure to achieve full remission is patients' extensive use of depression-related and general medical services. Patients who achieve only partial remission use more medical resources than those who are not depressed at all and more than those who were depressed but achieved remission. According to a naturalistic, retrospective analysis[31] that reviewed the characteristics and health care utilization of patients with treatment-resistant depression, treatment resistance was associated with use of 1.4 to 3 times more psychotropic medications, and patients were twice as likely to be hospitalized, having over 6 times the mean total medical costs compared with non–treatment resistant depressed patients. These findings underscore the need for early identification, adequate treatment, and true remission with effective long-term maintenance treatment to sustain it.

FUTURE GOALS AND UNMET RESEARCH NEEDS

The shared goals of all clinicians should ideally be achieving remission and sustaining it. There are various measures that psychiatrists and primary care physicians can take toward achieving those goals.

Early detection involving better screening with a greater emphasis on physical symptoms and more effective interventions designed to achieve remission could aid psychiatrists and primary care physicians in attaining remission for patients with major depressive disorder. Because an obvious pattern of multiple episodes and/or a family history of depression is generally apparent in the profiles of patients that are most vulnerable to recurrence, a preventable chronic disease model comparable to models used for cardiovascular disease should be employed in treating patients with major depressive disorder and the physical symptoms that accompany it. One instrument that is conventionally used to assess depression severity is the HAM-D-17; however, only about one third of the items on this scale specifically pertain to physical symptomatology. As a result, even in sophisticated depression clinics where screening tools like the HAM-D are used, there is a tendency to prioritize the emotional symptom portfolio over the physical symptom portfolio. Better screening methods that address naturalistic clinical realities could greatly improve early detection and precipitate higher remission rates and should be developed.

The effective use of antidepressants in treating the physical symptoms and chronic pain that are associated with depression has enormous potential for reducing health care utilization in affected patients and improving their overall qualities of life. Improved antidepressant treatments need to be developed. Various strategies should be pursued, including further testing of dual reuptake inhibitors that alter both serotonin and norepinephrine. Physicians and psychiatrists should focus on ways to enhance patient adherence (compliance) with their recommended treatments. Personalized, confidential electronic monitoring tools such as personal digital assistants (PDAs) and computerized monitoring systems for medication are being tested to determine if they aid monitoring medication adherence. These tools initially appear to improve patient adherence among some, and further testing is indicated.

In the primary care setting, where the vast majority of patients with depression and concomitant physical symptoms present for evaluation, screening barriers such as time limitations, negative stereotypes, and inadequate reimbursements need to be overcome. More focus should be directed toward effectively screening and treating adolescents, students, women of childbearing age, and high-risk medical populations, by both primary care physicians and psychiatrists. Psychiatrists and primary care physi-

cians together must form collaborative alliances through which they evaluate and deliver care side-by-side. This approach should also help alleviate negative stigmas associated with depression and other psychiatric disorders.

In essence, a paradigm shift appears required. An international network of comprehensive depression centers comparable to the network of cancer centers that exist in the United States and other countries may be necessary to catalyze the multidisciplinary screening, research, education, translation, and public policy changes that are warranted. Such centers would also reduce many of the negative stigmas that are frequently associated with psychiatric illness and chronic pain.

These are selected strategies to address many of the unmet needs concerning the burden of major depressive disorder and the debilitating, life-altering physical and emotional symptoms that frequently accompany it. Depression's burdens are great, so the research emphasis on achieving even better approaches should be concomitantly great. Combination approaches and collaborative partnerships will be required, but when used and improved, considerable progress will be made.

SUMMARY

The burden of depression is huge. Evidence indicates that there is a high correlation between physical symptoms, pain, and depression. Physical symptoms, including pain, interfere with accurate diagnosis and appropriate onset of treatment, which impairs achievement of full remission. Those with residual physical and emotional symptoms following acute antidepressant treatment for depression appear to be at a higher risk of relapse. Therefore, physical symptoms and pain can serve not only as early indicators that depression is present but as signals that a patient may not have achieved complete remission.

Complex genetic vulnerabilities appear to underlie the depressive diathesis, with stress apparently accentuating the gene expression that sets off or worsens episodes of depression. Stress is unavoidable, so for some, maintenance treatments that sustain wellness may be required. Without maintenance therapy, these patients may develop patterns of episodic recurrence, cycle acceleration, increased severity, and treatment resistance.

Serotonin and norepinephrine together may occupy a shared neurochemical link tying depression and physical symptoms together. This hypothesis has led some researchers to test whether antidepressants that incorporate both serotonin and norepinephrine reuptake inhibition might be the most efficacious treatment approach for patients with physical symptoms and depression. Initial results among patients with chronic pain appear to support this. There are many feasible solutions that can be incorporated into the daily practices of psychiatrists and primary care physicians that would lessen the burden of major depressive disorder and the debilitating life-altering physical and emotional symptoms that accompany it.

Drug names: bupropion (Wellbutrin and others), paroxetine (Paxil).

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.

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