Primary Psychiatry. 2008;15(9):44-50

Depression in the Physically Ill

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ABSTRACT

As depression is strongly associated with physical illness, it can be a complex and challenging condition for the medically ill. Approximately 33% of physically ill patients have depressive symptoms, many of which are regarded as understandable responses or reactions to the physical illness. Depressive illness is often underdiagnosed and under-treated, particularly in those with coexisting physical illnesses. The assessment of both conditions and the interaction between them is critical in managing these patients. Studies have clearly established that these depressive disorders are amenable to psychological or pharmacologic treatments.

FOCUS POINTS

- Depression should not be discounted as an inevitable natural consequence to a serious medical illness.
- The utility of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, in diagnosing depression in the medially ill is limited.
- Aggressive treatment of depression utilizing all available modalities along with the treatment of comorbid medical illnesses is important as it affects not only the patient's improved participation in the treatment but also decreased morbidity.
- The overall effect on the course of the disease itself and mortality needs to be further studied.

INTRODUCTION

Depressed patients are more likely than non-depressed patients to have longer hospital stays and more outpatient visits, suffer greater disability, suffer from poorer quality of life, and experience suicidal thoughts and even commit suicide.

Major depression is at least twice as common in hospitalized medical patients compared to depression in the general population. The prevalence of major depressive disorder (MDD) in patients with comorbid medical illness can be as high as 30% in the hospital setting.[1] Presence of comorbid depression is predictive of worse outcomes of medical illness and increased mortality.[2] It may be better to risk over diagnosing depression than to leave depression untreated. Studies have shown that treatment of even minor or sub-syndromal depression has beneficial effects on the overall functioning of the physically ill individual and enhances treatment compliance for the co-existing medical illness and the recovery and rehabilitation process. It has been well established that in patients with type-2 diabetes, MDD is both a precursor as well as a comorbid illness. This is also the case in cerebrovascular and cardiovascular diseases.

THE ASSOCIATION OF DEPRESSION AND PHYSICAL ILLNESS

The association of depression and physical illness can be best understood as follows. First, depression can be caused by an underlying physical illness or be an exacerbated

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Disclosures: Dr. Rao is on the speaker's bureau of Forest.

Acknowledgments: The author thanks Maria Theodorou for her assistance in compiling the references used in this manuscript.

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response[3] or a reaction to the illness. Second, depression can be a consequence of treatment of physical illness with medications (eg, antihypertensives, corticosteroids, and other immunosuppressants) or cancer treatments, especially with interferons.[4] Third, depression may be a consequence of various medical illnesses. Depression occurs in approximately 30% to 40% of patients with acute stroke or myocardial infarction, and has been linked to poorer cognitive and physical recovery. Fourth, depression can be a complication.[3] Depression should be considered a new strong risk factor among other pre-existing risk factors, especially anxiety or panic states, through increased sympathetic activity; mobilization of free fatty acid from adipose tissue; thrombogenicity and platelet activation, agglutination; thrombus formation; and inflammation, particularly in coronary and cerebrovascular disorders; and possibly in other conditions. Fifth, depression may be a co-existant, pre-existant, or coincidental association[3] to a physical illness. Sixth, depression can be contextual; it may be an effect of illness and its impact on life situations (eg, personal, job, relationships, finances) or in the context of metabolic disturbances (eg, hypoactive delirium presenting as depression). Seventh, depression may be a cue or clue to an underlying illness or a prelude to yet to be diagnosed major illness, especially in those who have the first onset of depression in mid-life or later. Approximately 33% of Alzheimer's patients experience depression in the prodromal and early stages of dementia.[5] Last, depression may be a contributing factor to the prolongation of the distress of a physical illness.

DETECTION OF DEPRESSION

Detection of depression in the medically ill can be difficult for the following reasons.[6] First, it may be regarded as a "normal: reaction to physical illness. Second, common vegetative symptoms include weight loss, fatigue, weakness, and anorexia often due to the medical illness. Third, it is difficult to distinguish onset of a depressive syndrome from psychological reactions to life-threatening illness. Last, the effects of impaired cognitive functioning secondary to the medical illness itself may detract from the detection of depression. As a result, the symptom pattern cannot be relied upon to a make a definitive diagnosis.[7]

To quote Dr. Elizabeth Scott[8]:

> The reason for these disorders largely being unrecognized is fairly complex. But, certainly the conventional classification systems that we use in psychiatry contribute to this. Those classification systems are often not helpful in patients with physical illness. That's because these systems largely depend on vegetative symptoms, as part of their diagnostic criteria. Symptoms such as sleep or appetite disturbance, changes in weight, changes in neuro-cognitive status, short-term memory or concentration, or changes in energy level also are symptoms of the underlying physical illness itself and then it becomes hard to tease out what's the underlying physical illness or the disease process and what's the contribution of depression or anxiety and also it makes it hard to gauge the severity of depressive or anxiety symptoms. Psychiatrists generally have a lack of agreement or consensus about the appropriate diagnostic criteria or classification systems to use in these patients...Physicians and patients themselves often assume that these symptoms are a reaction to the underlying physical illness, or...part of the disease process itself, so they often feel that they don't merit separate identification assessment or intervention.

Screening instruments such as the Beck Depression Inventory cannot replace clinical assessment. When usual resilience to illness is replaced by pervasive low mood, depression characterized by lack of interest in life should be strongly suspected; empirical trial of treatment should be considered, especially in view of newer, safer antidepressants and psychological treatments.[4] Although depression associated with medical illness has been shown to increase mortality, the benefits of treating depression on medical morbidity and mortality have yet to be established.[9]

ALTERNATIVE APPROACHES TO HELP DETECT COMORBID DEPRESSION

The Inclusive Approach

Instead of excluding symptoms appearing to be caused by a medical condition (eg, fatigue), the inclusive approach considers all symptoms describing depression. The inclusive approach is easy to use and sensitive to functional impairment.[10]

Substituting the "Classic" Vegetative Symptoms

Classic vegetative symptoms include change in appetite and sleep, fatigue and loss of energy, diminished ability to think or concentrate, indecisiveness, psychomotor slowing, tearfulness, depressed appearance, social withdrawal and decreased talkativeness, brooding, self-pity, pessimism, lack of reactivity to environmental events, and latency in responses.[11]

Modifying *DSM-IV* Criteria

One alternative approach to help detect comorbid depression is to modify the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[12] to include the criteria in Table 1.[13]

Eliciting Positive Answers

Eliciting positive answers to the questions in Table 2 should raise awareness of the possibility of depression.

Asking Useful Questions

It is important to ask prime medical questions eliciting emotion and cognitive symptoms (Table 3).[14] For example, during the past month, has the patient been frequently bothered by feeling down, depressed, or hopeless? During the past month, has he or she held little interest or experienced meager pleasure from certain activities? More simply, the patient could be directly asked if he or she felt sad or depressed, which seems to be the simplest and most yielding research question.

TABLE 1
MODIFYING *DSM-IV* CRITERIA

- Hopelessness, helplessness, not caring anymore
- Loss of interest particularly in people
- Feeling bad about oneself, not one's situation; feeling that illness is a punishment for wrongdoing
- Diminished ability to think or concentrate not easily explained by delirium, dementia, physical illness, or treatments
- Recurrent thoughts of death – not related to wishing to be dead to end physical suffering, but temporally related to affective and cognitive symptoms of depression
- Vegetative changes (significant weight/sleep/appetite changes; anergia) not easily explained by physical illness, treatments, or hospital environment
- Psychomotor agitation or retardation not easily explained by delirium, dementia, physical illness, or treatments
- Assessment of the patient's sphere of functioning extended to include participation in medical care. The point is not participating in medical care in spite of his or her ability to do so, not progressing despite improved medical condition, and/or is functioning at a lower level than the medical condition warrants.

Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

TABLE 2
ELICITING POSITIVE ANSWERS

1. Does the person's distress appear to be very severe?
2. Is the mood change persistent? (ie, lasting >2 weeks)
3. Is there evidence of a failure to adjust to the illness?
4. Is the person expressing suicidal ideas?
5. Is the person's physical function poorer than expected?
6. Is the person's recovery from illness slower than expected, or has the rehabilitation been particularly difficult?
7. Is there poor social interaction? eg, the patient does not respond to family visits and the family members are acknowledging or expressing the concern over this change.

Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

PREVALENCE RATES OF DEPRESSION IN VARIOUS MEDICAL CONDITIONS

As per the United States Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, the prevalence rates of depression in various medical conditions are listed in Table 4 and Figure 1.[15-27]

CARDIOVASCULAR SYSTEM

According to Ginzburg, "the damage to the heart, with its symbolic meaning as the essence of the human being may shatter the patient's sense of wholeness and safety."[28]

TABLE 3
ASKING USEFUL QUESTIONS

Low mood:	How are you feeling, how is your mood?
Tearfulness:	Do you become tearful easily? Are you more weepy than normal?
Anhedonia:	Have you lost interest in things that are pleasurable? Are you still enjoying the things you used to?
Loss of interest:	Are you able to keep your interest going?
Poor concentration:	How is your concentration? Can you read the paper or watch TV and take it in?
Irritability:	Are you more snappy than usual?
Panic attacks:	Do you get easily anxious and panicky?
Diurnal change in moods:	Is your mood worse at any particular time of day? How do you feel when you wake up?
Guilt, self-blame:	Do you find yourself blaming yourself or regretting things? Do you ever feel like a burden on others?
Worthlessness:	How do you view yourself, in comparison to others?
Low self-esteem:	Do you ever feel very unsure of yourself or feel you have little to offer compared to others?
Pessimism and hopelessness:	How do you feel about the future?
Thoughts of dying:	Are there ever times when you feel you just want to go to sleep and never wake up? Do you sometimes feel life is not worth living?

Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

Figure 2 shows cumulative mortality for depressed and nondepressed patients following a heart attack.[29]

As first reported by Frasure-Smith and colleagues,[29] MDD in patients hospitalized following a myocardial infarction is an independent risk factor for mortality at 6 months and increases mortality 3–5 fold. Its impact is at least equivalent to that of left ventricular dysfunction and history of previous myocardial infarction.

A prospective cohort study by Surtees and colleagues[30] found that MDD was associated with an increased risk of ischemic heart disease mortality. This association was independent of established risk factors for ischemic heart disease and remained undiminished several years after the original assessment.

One study[31] has shown that, after acute coronary syndromes, depressed patients have elevated levels of inflammatory markers, thus suggesting chronic endothelial activation among these patients.

TABLE 4

PREVALENCE RATES OF DEPRESSION IN VARIOUS MEDICAL CONDITIONS[22-25]

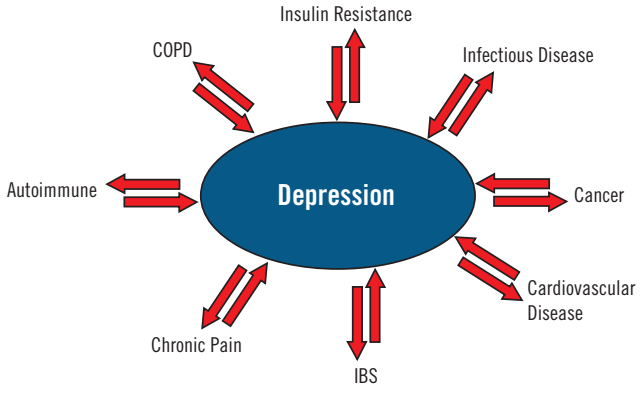
Older cancer patients	25%
Post-stroke patients	5% to 50%
Post-MI Patients	30%
Alzheimer's patients	33%
Parkinson's patients	50%

MI=myocardial infarction.

Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

FIGURE 1

A FEW MEDICAL CONDITIONS AND THEIR ASSOCIATION WITH CLINICAL DEPRESSION[15-21]



COPD=chronic obstructive pulmonary disease; IBS=irritable bowel syndrome.

Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

Depression may itself predispose to vascular disease. Mechanisms proposed for the linkage between depression and cardiovascular disease include the effects of hypercortisolemia (glucocorticoids inhibiting inflammation processes[38] or by reducing glucocorticoid signaling leading to abnormal brain functioning[32-24]), immune activation, depression-related platelet aggregation leading to increased thrombosis, depression-induced impairment of arterial endothelial functioning, and abnormal folate or homocysteine metabolism. Although these mechanisms have been proposed to relate depression to cardiovascular diseases, depression could also be linked to cerebrovascular disease.[32]

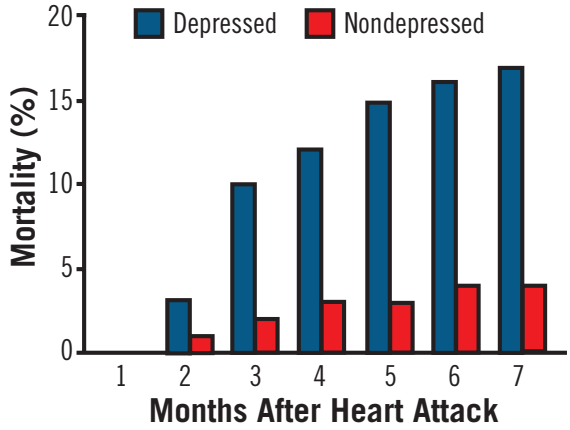
CEREBROVASCULAR SYSTEM

Depression occurs in approximately 40% of patients with acute stroke and has been linked to poorer cognitive and physical recovery. An association between depressive symptoms and stroke mortality was reported by Morris and colleagues,[35] who found that stroke patients with in-hospital depression were 3.5 times more likely to die during 10 years of follow up than patients without depression.

Treatment with fluoxetine or nortriptyline for 12 weeks during the first 6 months poststroke significantly increased the survival of both depressed and nondepressed patients. This finding suggests that the pathophysiologic processes determining the increased mortality risk associated with poststroke depression last longer than the depression itself and can be modified by antidepressants.[36]

FIGURE 2

CUMULATIVE MORTALITY FOR DEPRESSED AND NONDEPRESSED PATIENTS FOLLOWING A HEART ATTACK[29]



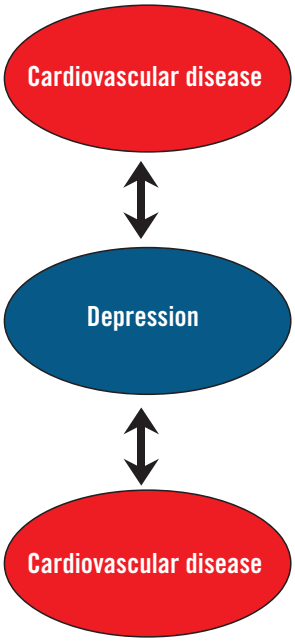
Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

Based on the above, one could wonder if depression is a "contributor or a consequence" of both cardiovascular and cerebrovasular pathologies (Figure 3).[37,38] It remains possible that the high rate of depression in both conditions represents a common vascular mechanism.[39]

CANCER

The prevalence of depression among cancer patients ranges between 23% and 60%. Acute stress and anxiety and/or dysphoric states following discovery of cancer (a traumatic life event) are poorly understood in traditional medical settings. Pain and depression are the most common neuropsychiatric presentations, and they are followed by fatigue, distress, and various disabilities. As the disease progresses, immunologic changes and the effect of treatment could be an additional burden contributing to MDD. Increased levels of cytokines, (eg, interleukin) secreted by the immune system to fight cancer or infections could also result in "sickness behavior syndrome," characterized by a depressed mood, sleepiness, and poor concentration (Figure 4).[40] Higher than normal plasma IL-6 concentrations were associated with a diagnosis of MDD in cancer patients. IL-6 may contribute to sickness behavior that has overlapping symptoms with MDD.[41]

FIGURE 3
CONTRIBUTOR, CONSEQUENCE, OR BOTH?[37,38]



Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

While helping to bolster the immunologic response, it is equally important to acknowledge the patient's symptoms and treat them vigorously with cognitive-behavioral therapy, stress management, and antidepressant drug therapy.

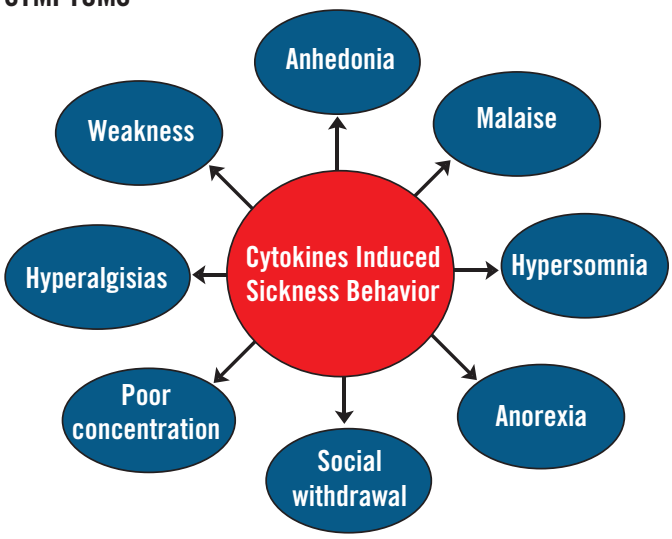
DIABETES MELLITUS

Depression as a precursor and as a consequence to type 2 diabetes has been studied. Prevalence of depression in adult diabetics is 3–5 times compared to prevalence in general population. Fourteen percent to 15% of patients diagnosed with type-2 diabetes have MDD. Thirty-three percent of all patients with neuropathy, retinopathy, and nephropathy are depressed. MDD in diabetes indicates poorer prognosis, worse glucose control, increased symptoms, decreased adherence to prescription plans, increased complications, decreased overall functional well being, and occasionally suicidality with complications.

Following a large population-based study in Norway, Engum and colleagues[21] concluded that diabetes did not predict symptoms of depression or anxiety. Rather, symptoms of depression and anxiety emerged as significant risk factors for onset of type-2 diabetes independent of established risk factors for diabetes, such as socioeconomic factors, lifestyle factors, and markers of the metabolic syndrome.

The studies, presented at the meeting of the European Association for the Study of Diabetes,[42] add to a growing body of evidence linking depression and other mental disor-

FIGURE 4
EFFECTS OF IMMUNE ACTIVATION RESEMBLE DEPRESSIVE SYMPTOMS[40]



Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

ders to diabetes risk. Symptoms of depression or psychological stress were associated with increased risk of type-2 diabetes in men, but not in women, as per Swedish researchers.[42] "People with diabetes had a higher prevalence of all mental illnesses compared with people without diabetes," according to researchers from Canada.[43] In particular, they noted that the rate of affective and anxiety disorders was >30% higher in people with diabetes who were <50 years of age. Other researchers have found hippocampal changes in patients with juvenile onset diabetes.

NEUROLOGIC ILLNESSES

Table 5 provides the rates of depression in neurologic illnesses.[44]

AGING, FRAILTY, AND ALZHEIMER'S DISEASE

Physical frailty and need for assistance in daily living often causes dysphoria. However, depression should not be accepted as a normal part of aging, as untreated depression in the elderly causes needless suffering. Depression can render mild cognitive impairment to appear like dementia, thus confounding diagnosis and prognostication. A history of early onset depression increases the risk for Alzheimer's disease compared to those with no history.[45]

HIV/AIDS

In addition to social stigma in the early stages, even when physically well, drug issues, HIV's later physical effects of nausea and fatigue with anti-retro virals, HIV-related apathy, mood disorders, and cognitive impairments are seldom recognized early in the course of the disease. The cerebral events may remain compartmentalized and not necessarily reflected in the routine assessment of peripheral markers such as viral loads or T-cell counts.

TABLE 5
DEPRESSION IN NEUROLOGIC ILLNESSES[44]

Alzheimer's disease	0% to 57%
Parkinson's disease	25% to 50%
Post stroke (within first 2 years after initial stroke)	30% to 60%
Huntington's disease	50%
Multiple sclerosis (Goldman Consensus Group 2005)[44]	50%

Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

MUSCULOSKELETAL REHABILITATION

See Table 6 for the prevalence of psychiatric disorders in musculoskeletal rehabilitation.[46]

CONCLUSION

In addition to the knowledge that depression contributes both to disability and diminished survival among medically ill, it is increasingly evident that MDD is a multi-systemic disorder that affects both brain and bodily functions.[40]

The inter-relationship between the two is rather complex. Inflammation could be the common link through neuro-immuno-endocrine mechanisms contributing to both psychological and somatic symptoms such as depression and cardiovascular diseases.[27,47,48] As more evidence accumulates, it seems clear that late-onset depression in particular is not just a mood disorder but could be a warning signal of an impending major or catastrophic physical illness. It is well known that depression is a heralding symptom of undiagnosed medical conditions including multiple sclerosis, Parkinson's disease, hypo- or hyperthyroidism, Cushing's disease, and pancreatic cancer. The assessment of both conditions and the interaction between them is critical in managing these patients.[1] When the medical illness is treated, the depression often gets better. While the importance of recognition and treatment of comorbid depression in helping reduce disability and suffering is very clear, the effect of treatment on the course of the comorbid illnesses themselves and the overall effect on survival need to be further studied. Also in need of further investigation are yet-to-be-discovered, non-antidepressant, disease-modifying effects of selective serotonin reuptake inhibitors or other newer agents on diabetes, stroke, multiple sclerosis, and Alzheimer's disease (among other diseases).

Considering the available evidence, it is clearly prudent to include aggressive treatment of comorbid depression, utilizing all available modalities—including psychopharmacologic agents—in the management of all physical illnesses. ***PP***

TABLE 6
PREVALENCE OF PSYCHIATRIC DISORDERS IN MUSCULOSKELETAL REHABILITATION[46]

31% for 4-week period
47% for 12-month period
65% for lifetime period

Rao M. *Primary Psychiatry.* Vol 15, No 9. 2008.

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