Antidepressant Treatment in Major Depressive Disorder Comorbid with Medical Illness
Dan V. Iosifescu, MD, and Renerio Fraguas Jr, MD, PhD

Needs Assessment: Major depressive disorder (MDD) is highly prevalent in medically ill subjects and is associated with increased morbidity and mortality in that population. Although many antidepressants have established efficacy and tolerability in depression associated with medical conditions, current research shows that physicians prescribe antidepressants less frequently and in lower doses for medically ill MDD subjects compared to other depressed patients. However, treatment nonresponse and depressive relapse are more common in medically ill MDD subjects than in depressed individuals with no medical illness. Physicians treating depression in the medically ill should be prepared to use common strategies utilized for treatment-resistant depression (eg, dose increases, augmentation, or switching of antidepressants).

Learning Objectives:
• Understand the concept of depression comorbid with a general medical condition, and the higher morbidity and mortality reported in this population.
• Recognize the higher rates of treatment nonresponse and depressive relapse in medically ill depressed subjects compared to depressed individuals with no medical illness.
• Describe strategies for treating depression associated with comorbid medical illness.

Target Audience: Primary care physicians and psychiatrists.

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Abstract

Medically ill subjects experience high rates of depression. This is a significant association that impacts the prognosis of both medical and psychiatric treatments. This article reviews studies comparing the outcome of antidepressant treatment in subjects with major depressive disorder (MDD) with and without comorbid medical illness. MDD subjects with medical illness tend to have lower improvement of depressive symptoms and higher rates of depressive relapse with antidepressant treatment compared to MDD subjects without medical illness. In addition, this article reviews the limited data for specific antidepressant treatment strategies for MDD subjects with medical illness. It concludes with clinical strategies recommended in light of the literature reviewed: an increased index of suspicion for depression in medically ill subjects, and more aggressive antidepressant treatment in depressed subjects with medical comorbidity.

Introduction

For decades, there has been a controversy over whether depression in medically ill individuals is a distinct diagnostic entity from major depressive disorder (MDD). In the 1970s, depression associated with medical illness was considered “secondary” or “reactive” (ie, a psychological consequence of having an illness), and considered to have a less severe clinical course.1 However, at that time,

Dr. Iosifescu is director of neurophysiology studies in the Depression Clinical and Research Program at Massachusetts General Hospital, and assistant professor of psychiatry at Harvard Medical School, both in Boston, Massachusetts.

Dr. Fraguas is a research fellow in psychiatry at Massachusetts General Hospital and Harvard Medical School, and chief of the consultation group of the Institute of Psychiatry at the Hospital das Clinicas of the University of Sao Paulo School of Medicine in Brazil.

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Please direct all correspondence to: Dan V. Iosifescu, MD, Massachusetts General Hospital, 50 Staniford St, Ste 401, Boston, MA 02114; Tel: 617-724-7741; Fax: 617-724-3028; E-mail: diosifescu@partners.org.
several investigators also found few and inconsistent differences in clinical presentation between primary and secondary depression, especially when considering depression associated with medical illness, and found no support for this category as a distinct subtype of MDD. Currently, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR), diagnostic category of “mood disorder due to a general medical condition” is restricted to cases where the clinician can establish that the mood disturbance is “etiologically related to the general medical condition through a physiological mechanism.” Therefore, in most cases, depression associated with comorbid medical illness is not considered a different diagnostic entity, but as MDD.

Multiple studies have reported a significantly higher prevalence of depression in the medically ill compared to the general population. This article will review studies reporting a high incidence of depression in patients with a variety of medical illnesses. However, the importance of this comorbidity is related to the negative impact that the presence of one condition has on the course of the other condition. In a number of studies, the presence of depression was predictive of poor medical outcome and of increased mortality. Such results were reported with cardiovascular disease, stroke, diabetes, and cancer. Similar increases in mortality were reported in studies of depression associated with the overall burden of comorbid medical illness. Conversely, this article will then review a series of studies in which the outcome of medical illness was also predictive of poor outcome of antidepressant treatment.

The Prevalence of MDD in Subjects with Medical Illness

Increased rates of MDD have been reported in the medically ill. Of patients hospitalized for acute myocardial infarction (MI), 18% were diagnosed with MDD and 45% with major as well as minor depression. The prevalence of MDD was 25% to 32% in patients in the first year post-MI and 18% in subjects with coronary artery disease documented by coronary angiography, and 17% in subjects during their first year after heart transplantation. The prevalence of MDD was also increased in subjects with chronic heart failure. Among 452 psychiatric outpatients, the prevalence of MDD was increased 3-fold in subjects with hypertension. The prevalence of MDD was 20% to 30% in the first 6 months poststroke, and remained at 38% after 1 year and 29% after 3 years poststroke. In a meta-analysis of 20 studies, Gavard and colleagues reported that depression was 3-4 times more prevalent in patients with diabetes than in the general population. In a meta-analysis of 42 studies, the odds of depression in the diabetes group were twice that of the nondiabetes group. The mean prevalence of depression in these studies was 14% (range: 9% to 27%). High prevalence of depression was also described in cancer patients (for a review, see Spiegel and Giese-Davis). Other studies have analyzed the impact of overall medical illness on the prevalence of MDD. Koenig and colleagues identified the presence of severe medical illness as a risk factor for depression. In a study of 2,554 subjects, Wells and colleagues found the 6-month prevalence of depression increased from 6% to 9% when comorbid medical illness was present, and the lifetime prevalence increased from 9% to 13%. In a sample of 17,626 Canadians from the Canadian National Population Health Survey, several chronic medical conditions (eg, asthma, chronic obstructive pulmonary disease, gastrointestinal ulcers, cancer, migraine, and back pain), as well as the total burden of medical disease, were associated with an elevated prevalence of MDD. In a study of 2,481 post-MI patients, the rates of major and minor depression were significantly higher in patients with greater levels of medical comorbidity.

Antidepressant Treatment in the Medically Ill

In some studies, antidepressant drugs have been reported to be more efficacious than placebo in patients with MDD and comorbid medical illness, while in other studies the antidepressant treatment did not separate from placebo. Such mixed results have been reported in randomized, placebo-controlled studies of antidepressants in subjects with MDD and a variety of comorbid medical illnesses (eg, MI, stroke, diabetes, and cancer). These mixed efficacy results are consistent with the following reports showing that depression with comorbid medical illness is more refractory to antidepressant treatment. Earlier studies of tricyclic antidepressants (TCAs) reported low rates of improvement of depressive symptoms in MDD subjects with comorbid medical illness. However, most of these studies used open designs with subtherapeutic doses of TCAs due to the side effects and contraindications of TCAs in these severely ill populations. Several studies have been published in the last decade comparing the outcome of antidepressant treatment in MDD subjects with and without medical illness. These studies differ in design, diagnosis of depression, ratings of medical illness, and antidepressant treatment utilized. Out of nine studies on the outcome of acute antidepressant treatment, the study population included MDD and other depressive disorders in two studies, MDD only in five studies, and treatment-resistant MDD in two studies. The ratings of the medical illness were done by merely noting the presence of medical illness, by number of comorbid medical illnesses, by a severity rating (mild, moderate, severe) of comorbid medical illness, or by organ systems affected by medical illness. Three studies used the Cumulative Illness Rating Scale (CIRS), a validated scale rating the number and the severity of comorbid medical illnesses. As for the study design, four studies had randomized and controlled designs, and two studies had an open-label prospective design with one single antidepressant being utilized, and three other studies had naturalistic designs with a variety of antidepressants. Comparing the results is difficult given the differences among studies. Six out of the nine studies reported lower treatment response in MDD subjects with comorbid medical illness (Figure 1). The three other studies reported no difference in treatment outcome in subjects with and without medical comorbidity. Of these, two studies included only treatment-resistant MDD patients and had a small population (N=92 and N=101, respectively).
respectively), thus having small power to detect a difference.

Only two studies\textsuperscript{52,58} compared antidepressant treatment for prevention of MDD relapse in subjects with and without comorbid medical illness. Both studies included subjects with MDD in remission after acute antidepressant treatment, and both studies used the CIRS to rate the severity and the total burden of all comorbid illnesses. One study used nortriptyline\textsuperscript{52} and the other used fluoxetine\textsuperscript{58} for prevention of depressive relapse. In the study by Iosifescu and colleagues,\textsuperscript{39} higher medical comorbidity (measured by the CIRS score) was predictive of higher rates of relapse (Figure 2), as well as increases in self-reported symptoms of depression, anxiety, and anger. Alexopoulos and colleagues\textsuperscript{52} reported no significant relationship between medical comorbidity (CIRS score) and MDD relapse or recurrence. However, this study sample was smaller (N=58 versus N=128 for Iosifescu and colleagues\textsuperscript{39}), thus having smaller statistical power to detect a difference.\textsuperscript{32}

In conclusion, MDD subjects with comorbid medical illness achieve lower rates of antidepressant treatment response and remission in the acute phase of MDD treatment, and higher rates of depressive relapse in the continuation phase, compared to MDD without medical illness.

**Are There Specific Antidepressant Treatments for the Medically Ill?**

The efficacy of psychostimulants as a treatment of depression in medically ill subjects is supported by retrospective analyses\textsuperscript{59-62} and by open-design prospective studies with very few patients.\textsuperscript{63,64} The few double-blind controlled studies on psychostimulant treatment for depression associated with medical conditions are varied in their design. Three of these studies were placebo controlled,\textsuperscript{65-67} while another study used desipramine as an active comparator.\textsuperscript{68} The study population was also very different, ranging from elderly patients with a variety of medical illnesses,\textsuperscript{65} to poststroke patients,\textsuperscript{66} to patients with human immunodeficiency virus.\textsuperscript{67,68} Although these double-blind studies indicated an antidepressant effect of psychostimulants, the number of subjects enrolled was significantly small, varying from 16–23.\textsuperscript{65-67} Due to these methodological limitations, it is very difficult to assess the true efficacy of stimulants in depressed, medically ill subjects. It appears that stimulants can quickly improve certain depressive symptoms (eg, lethargy) in short-term treatments.\textsuperscript{69,70} Contrasting with these data, almost all of the studies with depression not associated with medical disorders have reported no antidepressant effect of stimulants.\textsuperscript{71,72}

Interestingly, psychostimulants have not shown antidepressant efficacy in depression subjects with Parkinson's disease. In one study,\textsuperscript{73} depressive patients with Parkinson's disease failed to experience a euphoric reaction to methylphenidate, which was present in nonparkinsonian depressive patients, in normal controls, and even in subjects with Parkinson's but without depression. Since stimulants act by releasing dopamine from dopaminergic neurons, it is possible that the lack of psychostimulant efficacy in depression due to Parkinson's disease is a consequence of the degeneration of dopaminergic connections with the limbic system.

Specific antidepressant treatments have also been proposed for depressed subjects with chronic pain. TCAs have been shown to be effective in a variety of conditions associated with chronic pain, including diabetic neuropathy, fibromyalgia, chronic fatigue, postherpetic neuralgia, trigeminal neuralgia, migraine, and tension headache prophylaxis.\textsuperscript{74-76} Compared to TCAs, selective serotonin reuptake inhibitors (SSRIs) appear to be less efficacious in pain control.\textsuperscript{77} In a large meta-analysis\textsuperscript{78} of 94 randomized placebo-controlled trials, both TCAs and SSRIs showed a substantial benefit in achieving pain control in a variety of conditions (eg, headache, fibromyalgia, gastrointestinal pain, and idiopathic pain), although TCAs had a significantly greater likelihood of efficacy than SSRIs.

Medications with dual serotonin and norepinephrine reuptake inhibition appear to have good activity in pain. Sindrup and Jensen\textsuperscript{79} found that TCAs with both norepinephrine and serotonin activity (eg, amitriptyline) are more effective than noradrenergic TCAs (eg, desipramine) in providing pain relief, and concluded that pain control requires a combination of serotoninergic and noradrenergic reuptake inhibition. This is consistent with data\textsuperscript{80,81} indicating that both serotonin and norepinephrine exert analgesic effects via descending pain pathways. More recently, the serotonin norepinephrine reuptake inhibitors venlafaxine\textsuperscript{82} and duloxetine\textsuperscript{83,84} have also shown efficacy in the treatment of both depression and painful physical symptoms in subjects with MDD.

**Conclusion**

The studies reviewed here suggest that although usual antidepressant treatments are effective in subjects with MDD and comorbid medical illness, this comorbidity is associated with lower rates of recovery and
remission of depressive symptoms, as well as higher rates of relapse during continued treatment, compared with depressed subjects with no medical comorbidity. The impact of comorbidity of medical illness on treatment outcome in MDD has been attributed to a variety of factors, including poor self-care, nutrition, and lack of adherence to treatment; a generalized stress reaction mediated by hypothalamic-pituitary-adrenal axis activation; chronic inflammation and increased cytokines, present in a variety of medical illnesses; or to changes in pharmacokinetic or pharmacodynamic properties of antidepressants in the presence of comorbid medical illness.

In conclusion, MDD with comorbid medical illness represents a more treatment-resistant form of depression. As such, treatment of depression in the medically ill should include common strategies utilized for treatment-resistant depression: dose increases, augmentation, or switching of antidepressants. This approach would represent a significant improvement over the current practice, where depressed medically ill patients tend to receive lower doses of antidepressants than subjects with MDD and no medical illness. The efficacy of antidepressant treatment combined with cognitive-behavioral therapy was proven in large studies of depressed subjects after MI; this combination should be recommended for most depressed subjects with comorbid medical illness. Two clinical strategies appeared warranted in light of the studies presented here: (1) an increased index of suspicion for depression in medically ill subjects, and (2) more aggressive antidepressant treatment in depressed subjects with medical comorbidity.

References


