

Review article

## Impact of major depression on chronic medical illness

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### Introduction

Due to the aging of the U.S. population, healthcare providers will be called upon to diagnose and treat patients with chronic medical illness with increasing frequency. This paper will review the epidemiology of depression in patients with chronic illness and the impact of comorbid depression on increased use of medical resources and costs, amplification of physical symptoms, additive functional impairment, decreased ability to adhere to medications, important lifestyle changes (i.e., increasing exercise, changing dietary patterns, quitting smoking), and increased mortality.

### Epidemiology of depression and chronic medical illness

The prevalence rates of major depression have been shown to increase from 2–5% in community settings [1] to 5–10% in primary care [2] to 6–14% in medical/surgical inpatients [3–5]. A large study of community respondents found that people suffering from one of eight medical disorders had a 41% increase in the relative risk of having any recent psychiatric disorder compared to people without chronic medical disorders [6]. Anxiety, affective, and substance abuse disorders were each more prevalent in patients with these chronic medical disorders compared to patients without medical illness. In a prospective study of nondepressed elderly living in the community, the most common stressful life event that was associated with the new onset of major depression was the development of a life-threatening medical illness in the respondent or his/her spouse [7]. Most studies of patient samples with common medical illnesses, such as diabetes, heart disease, or chronic obstructive pulmonary disease (COPD), have also demonstrated an increased prevalence of affective illness. For instance, in a review of 10 controlled studies of the prevalence of major

depression or depressive symptoms in patients with diabetes, depression was significantly more common among diabetics compared to controls in all but one study [8]. Current major depression was observed in 10–15% (a mean of 14%) of diabetics with similar prevalence rates for Types 1 and 2 cases [8].

### Medical utilization of costs

Recent data from both elderly and mixed-age samples of primary care patients have found significantly higher medical costs in patients with either depressive symptoms or major depression compared to patients without depression [9–11]. This increase in costs is seen in every category that was measured, including primary care visits, medical specialty visits, lab tests, pharmacy costs, inpatient medical costs, and mental health visits.

Simon et al. [9] recently showed that 6256 mixed-age primary care health maintenance organization (HMO) patients with a visit diagnosis of depression had healthcare costs of approximately US\$4246 per year compared with costs of US\$2371 in a comparison group of 6257 patients with no depression diagnosis. After adjustment for chronic medical illness, the mean costs were still significantly higher in the depressed patients (US\$4246 vs. US\$2880). In two studies [10,11] of elderly primary care patients, patients with depression were found to also have significantly higher costs than nondepressed elderly. Callahan et al. [10] found that patients with depression had mean total outpatient charges of US\$1210 over a 9-month period compared with US\$752 in a nondepressed control group after controlling for medical diagnoses. Unützer et al. [11], in an elderly cohort of 2588 patients from a large HMO, found that patients with depression had total median medical costs over a 1-year period of US\$2147 compared to US\$1461 in nondepressed controls after adjustment for chronic medical illness. Unützer et al. [11] also showed that the increase in costs in depressed elderly was seen in every level of increasing medical comorbidity. In one of the few studies of primary care patients with one chronic medical illness,

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Ciechanowski et al. [12] demonstrated that patients with diabetes mellitus with higher levels of depressive symptoms had significantly higher costs than patients without depressive symptoms. In this study, he divided a primary care population of 367 diabetics into low-, medium-, and high-depression tertile categories based on depression scores on the Hopkins Symptom Checklist [13]. The total costs of the high tertile group were US\$3654 vs. US\$2653 in the medium-depression tertile and US\$2094 in the low tertile groups after adjusting for diabetes severity and medical comorbidity [12].

Several primary care studies have also found that patients with major depression are disproportionately represented among high utilizers of care [14,15]. In two large primary care clinics of Group Health Cooperative, we found that 10% of patients use more outpatient visits, specialty medical visits, and in-hospital days than the 50% of lowest utilizers of these clinics [14]. To put this in perspective, a typical primary care doctor has approximately 2000 patients in his or her panel; 10% or 200 patients were found to have significantly more medical visits and in-hospital days than the 1000 patients with the lowest utilization. We found that more than one-half of these high utilizers had significant psychological distress, and among the distressed high utilizers, more than two-thirds had recurrent major depressive episodes and approximately one-third had dysthymia [14]. Approximately two-thirds of high utilizers has also had one or more chronic medical illnesses, showing the very high rate of psychiatric and medical comorbidity in these populations. McFarland et al. [15] have also shown that high-utilizing elderly patients from a large HMO populations suffer from high rates of major depression and chronic medical illness. Lubert et al. [16] found that elder primary care patients with depression utilized significantly more primary care appointments and medications after controlling for severity of medical illness compared to nondepressed elderly controls.

In inpatient medical/surgical populations, researchers have found that those patients with comorbid affective illness have significantly longer lengths of stay after controlling for severity of medical illness compared with nondepressed controls [17–19].

### **Amplification of symptoms**

Patients with both psychiatric disorders as well as sub-syndromal psychological distress report significantly more physical symptoms on medical review of systems than nondistressed populations when controlling for severity of medical illness [20,21]. Many patients with chronic medical illness must learn to live and adapt to chronic medical symptoms caused by their medical illness. For instance, patients with osteoarthritis often live with chronic pain symptoms, patients with COPD have to adapt to symptoms of dyspnea and fatigue. Most patients with chronic medical

illnesses habituate to these chronic aversive symptoms quite well until they reach severe levels that start to markedly affect functioning [22]. However, there is now extensive data to suggest that having comorbid anxiety and depressive illnesses in patients with chronic medical illness interferes with this adaptation process and is associated with amplification of both symptoms from that physical illness as well as physical symptoms associated with other body organ systems [23–27].

Dwight et al. [25] recently reported that patients with hepatitis C with higher depressive severity complained of significantly more impairment from the symptom of fatigue (which is the main symptom associated with hepatitis C) compared with nondepressed hepatitis C patients when controlling for severity of liver pathologic changes found on biopsy or by liver enzyme changes. Lustman et al. [26] have described in patients with diabetes that depression was significantly correlated with patient reports of 9 of 11 symptoms commonly associated with poor glucose control (i.e., polyuria, polydipsia), whereas a physiologic measure of glycemic control, hemoglobin A<sub>1C</sub>, was poorly correlated with these nine symptoms. Walker et al. [23] have also shown that patients with inflammatory bowel disease and major depression or anxiety disorder complain of significantly more gastrointestinal and nongastrointestinal physical symptoms compared to patients with inflammable bowel disease without affective and anxiety disorders when controlling for severity of gastrointestinal illness. Fann et al. [24] has shown that head injury patients with current DSM-IV or depressive or anxiety disorders suffer from more postconcussive symptoms associated with head injury (i.e., dizziness, irritability) than head injury patients without psychiatric disorders. This study actually showed that head injury patients with psychiatric disorders had significantly milder head injuries compared to those without these diagnoses despite complaining of more postconcussive symptoms. Sullivan et al. [27] has also demonstrated that in patients with coronary heart disease, depression, and anxiety symptoms were significantly associated with more symptomatic reports of chest pain and fatigue 5 years later, even after carefully controlling for the number of coronary vessels occluded and ventricular output at baseline.

Since comorbidity with depressive and chronic medical illness is often associated with increased symptom reporting and amplification of chronic medical illness symptoms, physicians are apt to order more testing and do more work-ups in these patients. This may explain findings by Ciechanowski et al. [12], which showed that diabetics with more severe depressive symptoms have significantly higher medical costs compared to nondepressed diabetics, even when controlling for severity of diabetes and other medical illness. There is a need for more studies to determine the effect on symptom amplification of treating comorbid depression in patients with chronic medical illness. Two such studies have shown that when major depression was effectively treated in patients with either chronic tinnitus

and hearing impairment [28] or COPD [29], patients reported they were able to cope more effectively with their illness and their symptoms of medical illness were less distressing despite little change in objective measures of their medical disorder.

### **Depression and functional disability**

Wells et al. [30] have shown in the Medical Outcomes Study that patients with major depression perceive their social and vocational functioning and general health as more impaired than patients with one of seven other medical disorders. Moreover, when major depression was comorbid with one of these medical disorders, there was additive functional impairment [30]. Subsyndromal depressive symptoms have also been found to be associated with additive disability in patients with chronic medical illness [30]. Unützer et al. [31] compared 2558 primary care patients aged 65 and older with clinically significant depressive symptoms to individuals with 1 of 8 chronic medical illnesses and found that depressed elderly had significantly more decrements in quality-adjusted life years (QALYs) over the 4-year study period than did nondepressed subjects, even after adjusting for differences in age, gender, and chronic medical disorders. In terms of the entire population, only arthritis and heart disease were more strongly associated with decrements in QALYs than depression. In addition, Unützer et al. [31] showed that patients with comorbid depression and one of these chronic medical illnesses had additive decrements in QALYs.

Functional impairment in aging patients itself predicts the development of depression and, conversely, depressive symptoms have been found to be a risk factor for the progression of disability [32–34]. Multiple studies have also shown that depression and disability measures change synchronously over time: as depression improves, so do measures of functional impairment [35,36]. Sullivan et al. [27,37] demonstrated that symptoms of depression and anxiety at initial diagnosis of coronary artery disease by angiogram were more highly correlated with functional impairment at both 1- and 5-year follow-ups compared to the number of vessels occluded 70% or more at baseline. Two studies have demonstrated that effective treatment of depression in patients with chronic tinnitus and hearing impairment and COPD have been shown to be associated with significant improvement in functional impairment that the patient had perceived as due to their medical illness [28,29].

### **Poor self-care and adherence**

Self-management of chronic illness includes working effectively with healthcare providers, self-monitoring (i.e., checking blood glucose), implementing medication regimens, following prescribed diet and exercise regimens,

quitting smoking and minimizing drinking as well as minimizing impact of medical illness on social role functioning. Depression has been shown to adversely impact self-management of chronic illness by its adverse effect on memory, energy, sense of self-efficacy, and interpersonal interactions [38]. Depression also adversely affects satisfaction with care [39], which itself predicts poor adherence to medical regimens [40]. Specific studies in chronic illnesses have shown that depression has been associated with poor adherence to diet and exercise regimens in patients with diabetes [12,41], to impaired ability to participate in exercise rehabilitation in patients with heart disease, [42], and to significantly reduce the likelihood of quitting smoking over a 9-year period [43]. Patients with depression and diabetes have also been shown to have more lapses in filling their prescriptions for oral hypoglycemic medications [12]. A recent meta-analysis of the effect of depression on patient adherence by Dimatteo et al. [44] showed that compared to nondepressed patients, the odds were three times greater that depressive patients would be nonadherent with medical treatment recommendations.

### **Depression and chronic medical illness relationship to mortality**

Several large epidemiologic studies in recent years have suggested that prior episodes of major depression may be an important risk factor for the development of coronary artery disease [45] and diabetes mellitus [46,47], two illnesses that are associated with decreased longevity in our aging populations. Pratt et al. [45] have shown that the risk of development of myocardial infarction in 1551 community respondents followed up 13 years after initial assessment was significantly higher in patients with a history of dysphoria (odds ratio 2.07, 95% CI 1.16–3.71) and major depression (odds ratio 4.54, 95% CI 1.65–12.44) even after controlling for cardiac risk factors. Controlling for multiple risk factors, Eaton et al. [46] have shown that community respondents with major depression had an estimated relative risk of 2.23 of developing adult onset of diabetes mellitus over a 13-year period. Kawakami et al. [47] also demonstrated in a sample of 2764 male employees of an electrical company in Japan that significant depressive symptoms over an 8-year period were associated with a 2.3 times increased risk of developing Type 2 diabetes compared to nondepressed employees after controlling for known risk factors.

Several large-scale studies have reported an increase in cardiovascular mortality compared to nondepressed. For instance, Ferketich et al. [48] analyzed results from a study of 5007 women and 2886 men enrolled in a 10-year national health and nutrition survey and found that men with depression had a 71% greater risk of developing heart disease and were 2.34 times more likely to die from this condition compared to nondepressed men. On the other hand, depressed women faced a 73% higher risk of devel-

oping heart disease but were not more likely to die as a result [48]. Bruce and Leaf [49] reported in a prospective study of 3007 adults, age 50 years and older, that there were 4.3 times more non-suicide-related deaths in patients with major depression over the 15-month follow-up period. The major cause of death was cardiovascular in approximately two-thirds of the respondents. A nationally representative survey of 8000 community Finnish respondents also showed in a 6.6-year follow-up that the risk of coronary death was increased in depressed persons both with and without cardiovascular disease at entry [50].

A recent systematic review of 57 studies in the world's literature on the risk of increased mortality rates in patients with depression found that 29 (51%) were positive, 13 (23%) were negative, and 15 (26%) were mixed [51]. The summary of this systematic analysis suggested that depression seemed to increase the risk of death by cardiovascular disease, especially in men but future studies needed to control for multiple risk factors such as smoking, obesity, and chronic poor health that were not controlled for in many studies [51].

Researchers have also shown that negative emotions such as hostility and depression are associated with increased mortality after myocardial infarction even when controlling for heart disease severity [52]. Frasure-Smith et al. [53] found a fourfold increase in mortality among post myocardial infarction patients with major depression compared to those without affective illness, controlling for severity of coronary artery disease.

## Conclusion

Major depression has been shown in multiple studies in patients with chronic medical illness to increase symptom burden, lead to additive function impairment, increase medical costs and to impair self-care and adherence. There is also provocative evidence, particularly in male patients with heart disease, that depression may be associated with increased mortality. There is a need for large treatment trials aimed at improving outcomes of depression in medical illness to study the effects on medical costs, symptom burden, functioning and quality of life, and morbidity and mortality.

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