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DEPRESSION AND THE MEDICALLY ILL

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The lifetime prevalence of depression in the general U.S. population has been reported to be as high as 17% (1). The rates of depression in healthy persons are significantly lower than those among the medically ill. The rates of depression among medically ill patients range as high as 20% to 40%. Depression in the presence of medical illness, in comparison with depression in the absence of medical illness, is associated with more severely impaired physical or cognitive function. Untreated, depression can persist for many months and may complicate recovery from the medical illness.

Each year, approximately $44 billion is spent in the treatment of depression (2). Although depression associated with medical illness has been shown to increase mortality (3), the benefits of treating depression on medical morbidity and mortality have not yet been established. In this chapter, we review the relationship between depression and medical illness, with cerebrovascular and cardiovascular disease used as a prototype of medical illness.

PREVALENCE OF DEPRESSION AFTER MYOCARDIAL INFARCTION OR STROKE

The prevalence of major depression in patients after myocardial infarction (MI) has been estimated to be about 20% (3–8). Depressive symptoms following an acute MI have been reported in 60% of patients (9–10). Even in patients with only angiographically proven coronary artery disease, the prevalence of depression is approximately 18% (11).

The prevalence of depression after stroke has been studied in numerous countries of the world (12–14). These studies have found a mean prevalence of major depression of 20% among hospitalized and outpatient victims of stroke, and a prevalence of 13% has been found in community surveys (14). The mean prevalence of minor depression, defined as a subsyndromal form of major depression or the symptoms of dysthymia without the 2-year duration, has been found to be 19% in hospital and 10% in community samples (15) (Fig. 81.1).

DIAGNOSIS OF DEPRESSION IN PATIENTS WITH MYOCARDIAL INFARCTION OR STROKE

The problem of diagnosing depression in patients with medical illness has been a focus of research and a source of controversy among consultation and liaison psychiatrists for many years. Cohen-Cole and Stoudemire (16) reported that four approaches have been used to deal with this problem in the medically ill. In the "inclusive approach," depressive diagnostic symptoms are counted whether or not they are related to physical illness. In the "etiologic approach" of Rifkin et al. (17), a symptom is counted only if the diagnostician feels it is not caused by the physical illness. Rapp and Varna (18) use the "substitutive approach" of Endicott (19), in which the psychological symptoms of depression are substituted for the vegetative symptoms, which tend to be nonspecific in a physically ill population, and the "exclusive approach" of Bukberg et al. (20), in which symptoms are removed from the diagnostic criteria if they are not found to be more frequent in depressed than in nondepressed patients.

The utility of these methods in the diagnosis of poststroke depression was examined in a study that included 142 patients with acute stroke who were reexamined at 3, 6, 12, and 24 months after their stroke. Of the 142 patients, 60 (42%) reported a depressed mood during their acute hospitalization, and the remaining 82 patients denied a depressed mood. No significant differences in background characteristics were found between the depressed and nondepressed groups except that the depressed group was significantly younger ($p = .006$) and the frequency of personal

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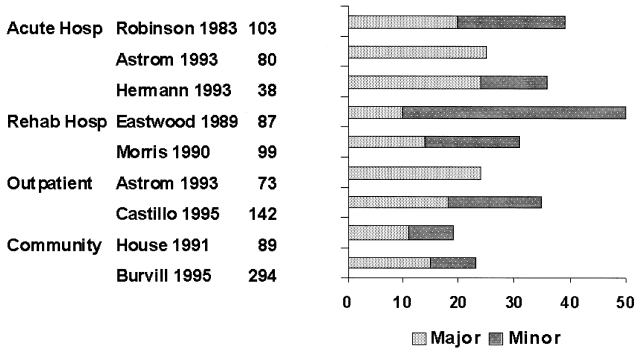

FIGURE 81.1. The percentage of patients found to be depressed after stroke based on the setting in which they were evaluated. Note that hospitalized patients and those in outpatient clinics generally show higher rates of depression than those studied in the community. This finding probably reflects the fact that the strokes of patients who seek medical service are more severe than those of patients in community surveys, in which persons with very mild or no impairment are studied. These studies represent findings from the United States, Canada, England, Sweden, Germany, and Australia.

history of a psychiatric disorder was significantly higher in the depressed group ($p = .04$). Throughout the 2 years of follow-up, the depressed patients reported a significantly higher frequency of both vegetative and psychological symptoms of depression than did the patients who were not depressed. The vegetative symptoms that were examined included anxiety, anxious foreboding, morning depression, weight loss, delayed sleep, subjective anergia, early morning awakening, and loss of libido (21). The only vegetative symptoms that were not more frequent in the depressed than in the nondepressed group were weight loss and early morning awakening at the initial evaluation; weight loss, delayed sleep, and early morning awakening at 3 months; weight loss and early morning awakening at 6 months; weight loss, early morning awakening, anxious foreboding, and loss of libido at 1 year; and weight loss and loss of libido at 2 years. Most psychological symptoms were more frequent in the depressed patients throughout the 2-year period. The psychological symptoms assessed included worrying, brooding, loss of interest, hopelessness, suicidal plans, social withdrawal, self-deprecation, lack of self-confidence, simple ideas of reference, guilty ideas of reference, pathologic guilt, and irritability. The only psychological symptoms that were not significantly more frequent in the depressed than in the nondepressed group were suicidal plans, simple ideas of reference, and pathologic guilt at 3 months; pathologic guilt at 6 months; pathologic guilt, suicidal plans, guilty ideas of reference, and irritability at 1 year; and pathologic guilt and self-deprecation at 2 years.

The effect of using each of the proposed alternative diagnostic methods for post-stroke depression based on DSM-IV criteria was examined (22). Symptoms were assessed with the inclusive approach (i.e., a symptom was included if acknowledged, even if it was suspected that the symptom was related to the physical illness). Thus, the initial diagnoses were based on inclusive criteria during the in-hospital evaluation. When this approach was used, 26 patients (18%) met the DSM-IV diagnostic criteria for major depression. The DSM-IV diagnostic criteria were then modified by imposing a requirement for five or more specific symptoms (weight loss and early morning awakening were excluded as criteria for major depression because they were not significantly more frequent in the depressed than in the nondepressed patients). Of the 27 patients with major depression, three were excluded in comparison with the diagnosis based on inclusive criteria. The diagnoses based on unmodified symptoms had a specificity of 98% and a sensitivity of 100% in comparison with use of the "exclusive" criteria as the "gold standard."

Next, the DSM-IV criteria were modified to examine the substitutive approach (i.e., all vegetative symptoms were eliminated and the presence of four psychological symptoms plus depressed mood was required for the diagnosis of major depression). When this approach was used, none of the original 27 patients in whom major depression had been diagnosed with the inclusive approach was excluded.

At the 3-month follow-up, use of the exclusive approach, which requires only specific symptoms (i.e., weight loss, insomnia, and suicidal ideation were eliminated), resulted in the exclusion of 1 of 12 patients (16%) with major depression. When a diagnosis based on specific symptoms was used as the gold standard, the unmodified DSM-IV criteria and inclusive approach had a sensitivity of 100% and a specificity of 97%. If the substitutive approach, which requires depression plus four psychological symptoms, had been used, none of the 12 patients would have been excluded.

At the 6-month follow-up, when the exclusive approach (i.e., weight loss and insomnia were excluded) was used, 3 of 15 patients no longer met the criteria for major depression. When specific symptoms were used as the gold standard, the unmodified inclusive DSM-IV criteria had a sensitivity of 100% and a specificity of 95%. If the substitutive approach had been used, none of the 15 patients with major depression would have been excluded. At the 1-year follow-up, when the exclusive approach (i.e., weight loss, difficulty concentrating, and suicidal ideation were excluded) was used, 3 of 7 patients no longer met the diagnostic criteria, and the unmodified inclusive DSM-IV criteria had a sensitivity of 100% and a specificity of 95%. With use of the substitutive approach, none of the 7 patients was excluded. At the 2-year follow-up, when the exclusive approach (i.e., weight loss was excluded) was used, 2 of 16 patients with major depression were excluded. With use of the unmodified inclusive DSM-IV criteria, the sensitivity was 100% and the specificity was 96% in comparison with the exclusive approach. The substitutive approach excluded none of the 16 patients.

Although Kathol et al. (23) concluded that the substitutive approach is the best one given our current knowledge, the inclusive approach previously described for patients with stroke during the first 2 years of follow-up had a sensitivity of 100% and specificity of more than 95% in comparison with the exclusive approach. Weight loss was the only symptom that was not significantly more frequent among depressed than among nondepressed patients during the entire 2-year period. Given that the unmodified DSM-IV criteria consistently showed a sensitivity of 100% and a specificity that ranged from 95% to 98% in comparison with "exclusive" criteria that counted only specific symptoms, one could reasonably conclude that the use of unmodified DSM-IV criteria and the inclusive approach is the most rational way to diagnose depression in patients with vascular disease.

DEPRESSION AS A RISK FACTOR FOR CARDIAC DISEASE

It has been suggested that depression may play a role in the development of cardiac disease (24–29). For example, data from a study of 2,832 U.S. adults found that persons with symptoms of depression are at 50% greater risk of fatal ischemic heart disease (relative risk, 1.5; 95% confidence interval, 1.0 to 2.3) than are persons without depression (24). A notable exception, however, is a study of more than 2,500 persons followed for 15 years in which an association between depression and increased cardiovascular mortality or ischemic heart disease was not observed (30). The relationship of depression to the development of stroke has not been studied systematically. Although a significant number of patients in whom acute stroke develops have a preexisting depressive disorder (31), a causal relationship of depression and stroke has not been established.

IMPACT OF DEPRESSION IN MYOCARDIAL INFARCTION

A higher cardiovascular mortality among patients with major depression has been reported by numerous investigators (24,26,27,32–43). Large, controlled studies have confirmed an increased cardiovascular risk in persons in whom depression develops following an ischemic event (3,7,26, 44–46). Frasure-Smith and colleagues (3) studied 222 patients who had experienced an acute MI. Patients were screened with the Beck Depression Inventory and interviewed after their MI with a modified version of the National Institute of Mental Health Diagnostic Interview Schedule to determine if criteria for depression were met. Even after corrections were made for relevant variables that determine outcome, including previous MI and Killip class, major depression was a significant independent predictor of adverse outcome (adjusted hazard ratio, 4.29; 95% confidence interval, 3.14 to 5.44; $p = .013$). The same results were found for patients with modest depressive symptoms (i.e., Beck Depression Inventory > 10).During a subsequent 18-month follow-up, the risk persisted. The underlying pathophysiology and the effects of antidepressant treatment on mortality are the focus of ongoing clinical investigations.

An increased risk for mortality among patients with depression following stroke has been reported in two studies utilizing different patient populations (47–48). One study examined the 10-year follow-up of 91 of 103 patients evaluated following acute stroke. Among the 48 patients who had died, it was found that those with major or minor depression while in the hospital were 3.4 times more likely to have died (confidence interval, 1.4 to 8.4; $p = .007$) than were those who were not depressed while in the hospital, even when other variables (e.g., lesion volume) related to mortality were controlled (47,48) (Fig. 81.2).

A 15-month follow-up of 84 Australian patients who were initially examined in a rehabilitation hospital found that 23% of the patients with major depression at initial evaluation had died, in comparison with 10% of those with minor depression and 2% of those without depression. Patients with major or minor depression were 8.1 times more likely to have died during the 15-month follow-up (confidence interval, 0.9 to 72.9; $p = .06$) than were nondepressed patients (47,48). However, Astrom et al. (49) found that in 21 of 80 patients who had initially been examined within the first 2 weeks following an acute stroke and had died during 3 years of follow-up, mortality was associated

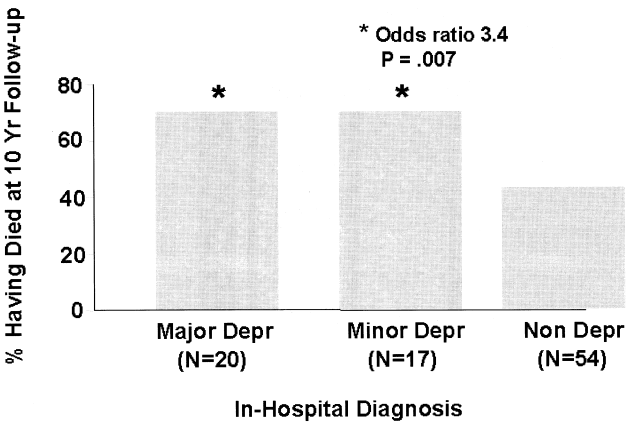

FIGURE 81.2. Survival curves during 10 years for 37 patients with major or minor depression at the time of in-hospital post-stroke evaluation and for 54 patients without in-hospital depression. By 10-year follow-up, 14 of 20 patients with major depression and 12 of 17 with minor depression had died, in comparison with only 22 of 54 nondepressed patients. (Data extracted from Morris PLP, Robinson RG, Andrezejewski P, et al. Association of depression with 10 year post-stroke mortality. *Am J Psychiatry* 1993;150: 124–129, with permission.)

with older age, disorientation during the hospitalization, greater impairment in activities of daily living, and a greater degree of cortical atrophy, but not with depression. Despite this negative finding, numerous studies have found that depression associated with stroke or MI increases the risk for death during the first 3 to 5 years after the vascular illness.

Concurrent depression also increases the risk for poor outcome among patients with MI, unstable angina, and heart failure. Unpublished data from Duke University suggest a twofold increase in mortality in depressed patients with heart failure. Besides the increase in mortality, a substantial effect on morbidity has been noted. Post-MI patients who are depressed take longer to return to work than those without depression (10,50,51). The most parsimonious explanation is that patients who are depressed following an MI are more likely to drop out of cardiac rehabilitation and exercise programs than are patients who are not depressed (52). For example, depressed smokers are 40% less likely to stop smoking than nondepressed smokers (relative risk, 0.6) (53), and depressed patients with coronary artery disease are less likely to comply with low-dose aspirin therapy than are nondepressed patients (54). These findings would suggest that all depressed patients with coronary artery disease should be treated, but data indicating the efficacy and safety of treatments for depression associated with heart disease are very limited.

Numerous studies have documented the adverse effect of depression on physical recovery from stroke (55–57). In a study of 25 patients with major or minor depression after stroke and some impairment in their activities of daily living versus a comparable group of 38 nondepressed patients, the degree of recovery in activities of daily living was significantly greater in the nondepressed than in the depressed patients at 2-year follow-up ($p < .01$), even when other factors that influence outcome (e.g., baseline deficits, early intervention, specialized stroke and rehabilitation care, nature and size of the lesion) were controlled (57). This delayed recovery was evident as early as 3 to 6 months following stroke (57,58) (Fig. 81.3).

In addition to the adverse effects of depression on activities of daily living, numerous studies have demonstrated the adverse effects of major depression after stroke on cognitive function (59–62). In a study of 275 patients with acute stroke, the mean Mini-Mental State Examination (MMSE) score for patients with major depression ($n = 56$) was 20.0 $\pm$ 6.2; for those with minor depression ($n = 49$), it was 22.9 $\pm$ 6.3; and for those without depression ($n = 170$), it was 23.3 $\pm$ 5.3 ($p = .001$) (63) (Fig. 81.4). To control for the possibility that the location of lesions, which has been correlated with affect during acute stroke, might have influenced these findings, patients with and without major depression were matched for size and location of stroke lesion (64). Patients with major depression had significantly lower MMSE scores than did their lesion-matched counterparts. Furthermore, on a battery of detailed neuropsychological tests, patients with major depression after stroke showed significantly greater impairment in orientation, language, visual–spatial skills, and executive motor and frontal lobe tasks than did nondepressed patients with lesions in similar locations (59). These findings indicate that major depression following stroke leads to a dementia of depression. Furthermore, this adverse effect of major depression on cognitive function lasts for the first year following stroke (63).

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, sponsored by the National Heart, Lung, and Blood Institute, is currently under way (65). Psychosocial interventions in post-MI patients with depression or a high level of perceived social isolation are being evaluated in this multicenter mortality trial of 3,000 patients. Results should be available by the end of 2001 and should provide

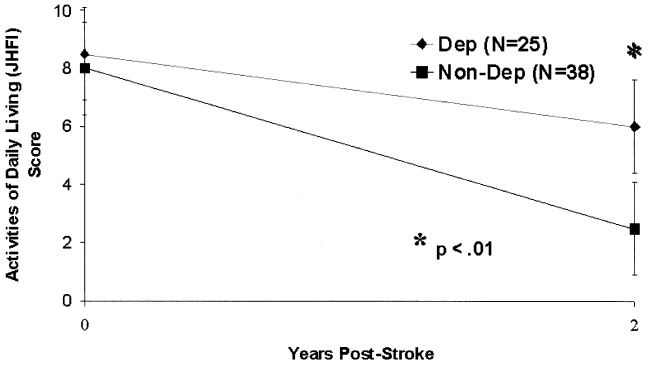

FIGURE 81.3. Changes in activities-of-daily-living scores for depressed (major or minor) patients and nondepressed patients at the time of in-hospital evaluation and 2 years later. Depressed patients show less recovery than nondepressed patients. (Reprinted from Parikh RM, Robinson RG, Lipsey JR, et al. The impact of post-stroke depression on recovery in activities of daily living over two-year follow-up. *Arch Neurol* 1990;47:785–789, with permission.)

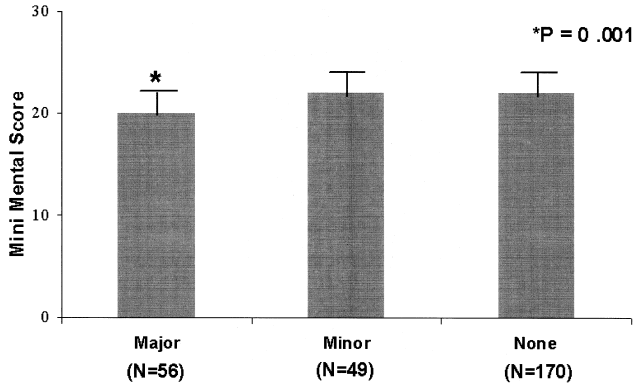

FIGURE 81.4. Mini-Mental State Examination scores in patients with major and minor depression and patients without depression.

answers to the question of whether psychosocial treatments should be initiated in patients with post-MI depression.

TREATMENT WITH ANTIDEPRESSANTS

The evidence for antidepressant use is also limited. Tricyclic antidepressants are known to cause adverse cardiovascular effects, including orthostatic hypotension and slowed intraventricular conduction (66,67); therefore, it would not be prudent to use these agents in a population at risk.

Pilot studies suggest that the selective serotonin reuptake inhibitors are safe and effective in persons with ischemic heart disease and depression (68,69). The only study of an antidepressant in post-MI patients is that of Shapiro et al. (70). In this study, sertraline (Zoloft) was well tolerated, and no unexpected cardiac effects were noted. Large, randomized, controlled trials are necessary to assess the effects of long-term antidepressant treatment on morbidity and mortality. A multicenter study of sertraline is under way in post-MI patients with major depression (SADHART).

Currently, at least four double-blinded, placebo-controlled studies have examined the efficacy of antidepressant medication in the treatment of post-stroke depression (71–74). In the first study, reported in 1984, 11 patients given nortriptyline showed a significantly greater improvement on the Hamilton Depression Scale (HAM-D), the Zung Self-Rating Depression Scale, and the profile of depressive symptoms assessed by the Present State Examination than did 14 placebo-treated controls (71). It is worth noting that three of the original 14 patients treated with nortriptyline dropped out of the study. Two patients became delirious, and one had a sudden syncopal episode of unknown cause.

In a controlled study by Reding et al. (72), seven patients with abnormal results on the dexamethasone suppression test and post-stroke depression were treated with trazodone for 5 weeks; these patients showed a significantly greater improvement in activities of daily living as measured by the Barthel Activities of Daily Living Scale than did nine patients with positive Problem Solving Therapies (PSTs) who were treated with placebo.

Andersen et al. (73) assessed the efficacy and tolerability of the selective serotonin reuptake inhibitor citalopram in a controlled study of 66 patients with stroke. HAM-D and Melancholia Scale scores were significantly better after 3 and 6 weeks of treatment in the 33 patients given citalopram (under age 65, 20-mg dose; over age 65, 10-mg dose) than in the 33 patients given placebo.

The most recent of the four studies compared nortriptyline ($n = 16$) with fluoxetine ($n = 23$) and placebo ($n = 17$) (74). About half of the patients had major depression, and the other half had minor depression based on DSM-IV diagnostic criteria elicited by the semistructured Present State Examination. The response rate (defined as a reduction of > 50% in the HAM-D score and no longer meeting criteria for depression) of patients treated with nortriptyline who completed the trial was significantly greater (77%) than the response rate of the patients treated with placebo (31%) or fluoxetine (14%). The HAM-D scores of nortriptyline-treated patients were significantly lower after 12 weeks of treatment than the scores of the patients treated with fluoxetine or placebo, which were not significantly different from each other (Fig. 81.5). The dropout rate of the patients treated with fluoxetine in doses that were increased from 10 to 40 mg during 12 weeks (10-mg increase every 3 weeks) was significantly higher (9 of 23) than those of the other two groups (3 of 16 and 4 of 17).

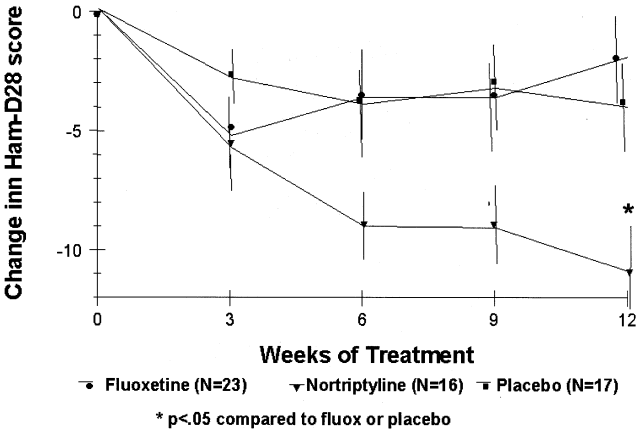

FIGURE 81.5. Change in Hamilton Depression Scale (28 items) scores during 12 weeks of treatment for all patients entered in the study (i.e., intention-to-treat analysis). *Significant group-by-time interaction ($F = 3.45$, $df = 8, 212$, $p = .0035$) and *post hoc* significantly greater change in patients treated with nortriptyline than in those treated with fluoxetine or placebo at 12 weeks.

CONCLUSION

Identifying depression in the medically ill population is difficult. Often, the symptoms that are used to identify depression are confused with the underlying symptoms of the medical illness. One approach is to exclude symptoms (e.g., fatigue) that may arise from the medical condition. Another approach is to replace some of the vegetative symptoms, and a third approach is to include all symptoms. The inclusive approach is favored because of its ease of use and practical applicability, and it appears to be sufficient. It is also more sensitive and relates well to functional impairment (75).

In summary, evidence is increasing that depression in patients with vascular disease can be successfully treated with pharmacologic agents. The effects of antidepressant treatment on the risk for exacerbating medical illness and on improving physical, cognitive, and quality-of-life outcomes remain to be determined. The findings of ongoing pharmacologic treatment studies will be viewed with interest.

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