Depression and Medication Adherence in Outpatients With Coronary Heart Disease

Findings From the Heart and Soul Study

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Background: Depression leads to adverse outcomes in patients with coronary heart disease (CHD). Medication nonadherence is a potential mechanism for the increased risk of CHD events associated with depression, but it is not known whether depression is associated with medication nonadherence in outpatients with stable CHD.

Methods: We examined the association between current major depression (assessed using the Diagnostic Interview Schedule) and self-reported medication adherence in a cross-sectional study of 940 outpatients with stable CHD.

Results: A total of 204 participants (22%) had major depression. Twenty-eight (14%) of 204 depressed participants reported not taking their medications as prescribed compared with 40 (5%) of 736 nondepressed participants (odds ratio [OR], 2.8; 95% confidence interval [CI], 1.7-4.7; *P*<.001). Twice as many depressed participants as nondepressed participants (18% vs 9%) reported forgetting to take their medications (OR, 2.4; 95% CI, 1.6-3.8; *P*<.001). Nine percent of depressed participants and 4% of nondepressed participants reported deciding to skip their medications (OR, 2.2; 95% CI, 1.2-4.2; *P*=.01). The relationship between depression and nonadherence persisted after adjustment for potential confounding variables, including age, ethnicity, education, social support, and measures of cardiac disease severity (OR, 2.2; 95% CI, 1.2-3.9; *P*=.009 for not taking medications as prescribed).

Conclusions: Depression is associated with medication nonadherence in outpatients with CHD. Medication nonadherence may contribute to adverse cardiovascular outcomes in depressed patients.

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MAJOR DEPRESSION IS AN established risk factor for morbidity and mortality in patients with coronary heart disease (CHD).[1-11] Recently, psychosocial factors, such as depression, have been identified as 1 of 9 modifiable risk factors, along with diabetes mellitus, smoking, and hypertension, that account for more than 90% of the risk of myocardial infarction worldwide.[12] Several biological factors have been considered as potential mechanisms by which depression may lead to cardiac events, including increased sympathetic tone,[13,14] increased catecholamine levels,[15] increased cortisol levels,[16] increased platelet activation, increased levels of inflammatory mediators,[17] and antidepressant drug reactions.[18] However, nonadherence to important cardiac prevention and treatment recommendations may also be associated with depression and could contribute to the increased risk of CHD events in depressed patients.[19]

Depression has been associated with medication nonadherence in the general population[20] and in patients with human immunodeficiency virus,[21,22] kidney transplants,[23] hypertension,[24,25] diabetes mellitus,[26-30] and hyperlipidemia.[31,32] Nonadherence to cardiac treatment recommendations

See also page 2497

has been linked to worse outcomes in cardiac patients.[33] However, only 1 small study[34] of 10 depressed and 45 nondepressed patients has examined the association between depression and medication adherence in patients with stable CHD, and no study, to our knowledge, has evaluated the relationship between depressive symptom severity and medication adherence.

To determine whether poor adherence is a mediator in the relationship between depression and CHD outcomes, we must first examine whether depression is associated with poor adherence in patients with stable CHD and whether this

relationship differs by severity of depressive symptoms. We evaluated the association between depression and medication nonadherence in 940 outpatients with stable CHD from the Heart and Soul Study.

METHODS

PARTICIPANTS

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in patients with CHD. Details regarding recruitment procedures have been published previously.[35] Briefly, we used administrative databases to identify outpatients with documented CHD at 2 Veterans Affairs Medical Centers (San Francisco and Palo Alto, Calif), 1 university medical center (University of California at San Francisco), and 9 community health clinics in northern California. Patients were eligible to participate if they had at least 1 of the following: a history of myocardial infarction, angiographic evidence of at least 50% stenosis in 1 or more coronary vessels, previous evidence of exercise-induced ischemia by treadmill or nuclear testing, a history of coronary artery revascularization, or a diagnosis of CHD by an internist or a cardiologist. Patients were excluded only if they could not walk 1 block or were planning to move from the local area within 3 years.

Of 1024 individuals enrolled between September 11, 2000, and December 31, 2002, 84 were excluded from the present analysis because they were not taking a cardiac medication (β-blocker, renin-angiotensin system inhibitor, aspirin, or statin), leaving 940 participants for this cross-sectional study. All the participants completed a daylong study examination that included a comprehensive health interview, blood sample collection, an exercise treadmill test with stress echocardiography, a 6-minute walk, 24-hour Holter monitoring, and 24-hour urine sample collection. The protocol was approved by the appropriate institutional review boards, and all the participants provided written informed consent.

PREDICTOR VARIABLES

Our primary predictor variable was current (past month) major depression, defined according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria.[36] To assess major depression, we used the Computerized Diagnostic Interview Schedule-IV, a validated computerized version of the National Institute of Mental Health Diagnostic Interview Schedule.[37-40] Trained research assistants administered the computerized interview. Participants found to have current depression were informed that they were experiencing depression, were instructed to discuss these symptoms with their primary care provider, and were provided with a list of local resources available for further evaluation and treatment.

Our secondary predictor variable was severity of depressive symptoms. To assess severity, we administered the 9-item Patient Health Questionnaire (PHQ).[41,42] Based on this score, we categorized participants as having no symptoms to minimal depressive symptoms (PHQ score of 0-3), mild-to-moderate depressive symptoms (PHQ score of 4-9), or severe depressive symptoms (PHQ score ≥10).[42]

OUTCOME VARIABLES

We assessed overall medication adherence (not adherence to specific medications) using 3 questionnaire items based on those used in the CARDIA (Coronary Artery Risk Development in Young Adults) study[43]:

1. "In the past month, how often did you take your medications as the doctor prescribed?" Possible responses were all of the time (100%), nearly all of the time (90%), most of the time (75%), about half the time (50%), or less than half the time (<50%). Nonadherence was defined as 75% of the time or less.

2. "In the past month, how often did you forget to take 1 or more of your prescribed medications?" Possible responses were never, once in the past month, 2 to 3 times in the past month, once per week, several times per week, and nearly every day. We defined nonadherence as forgetting to take prescribed medications once per week or more.

3. "In the past month, how often did you decide to skip 1 or more of your prescribed medications?" Possible responses were the same as for question 2. We defined nonadherence as deciding to skip medications once per week or more.

We chose to measure self-reported medication adherence for several reasons. First, self-reported medication adherence has been validated as a reliable predictor of health outcomes, including blood pressure control,[44] hospitalization for heart failure,[45] serum drug concentrations,[46] and response to antiretroviral therapy.[47] Second, in a study of hypertensive patients taking hydrochlorothiazide, self-reported medication adherence was more strongly correlated with qualitative urinary hydrochlorothiazide levels, changes in serum potassium levels, and decreases in blood pressure than was pill count adherence.[48] Third, other methods of assessing adherence were not appropriate for our study. For example, pharmacy refills are often given for 90 days, so pharmacy data would not allow us to assess the association between current (past month) depression and current (past month) adherence. Finally, Medication Event Monitoring System caps are expensive and have their own limitations.[49] For example, the number of cap openings does not necessarily reflect the number of pills ingested by the patient.

OTHER VARIABLES

Age, sex, ethnicity, education, income, marital status, living situation, medical history, smoking status, and alcohol use were determined by questionnaire. We assessed social support by asking participants, "Do you have as much contact as you would like with someone you feel close to, someone in whom you can trust and confide? (yes/no)."[50]

We determined angina frequency by asking participants, "During the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina?"[51] We measured weight and height and calculated body mass index. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Patients were instructed not to take aspirin for 1 week before the examination to complete another part of the study protocol. We assessed left ventricular ejection fraction using a resting echocardiogram. Exercise capacity (metabolic equivalents achieved) was measured using a symptom-limited, graded exercise treadmill test according to a standard Bruce protocol.

STATISTICAL ANALYSIS

Our goal was to examine the association between current depression and current medication adherence. Differences in characteristics between participants with and without current depression were compared using a standard 2-tailed *t* test for continuous variables and a χ^2 test for dichotomous variables. We then used logistic regression to examine the association between current depression and medication adherence. To obtain adjusted risk estimates, we entered all **Table 1** variables

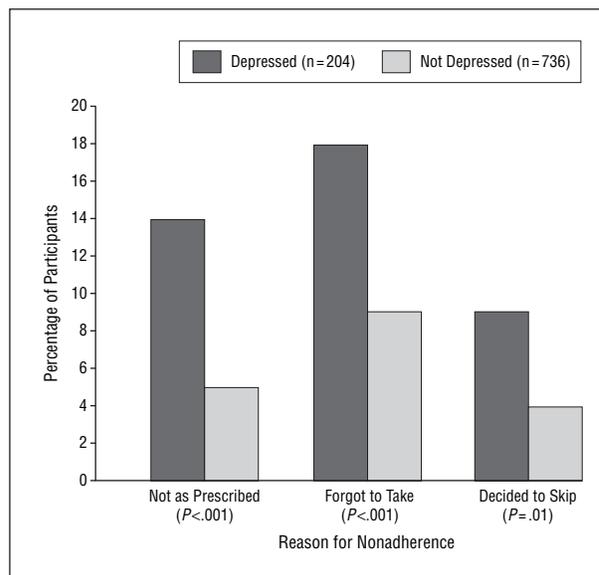**Table 1. Characteristics of 940 Participants With Coronary Heart Disease by Depression Status***

Characteristic	Not Depressed (n = 736)	Depressed (n = 204)	P Value
Demographics			
Age, mean ± SD, y	69 ± 10	62 ± 10	<.001
Female sex	97 (13)	55 (27)	<.001
White race	442 (60)	124 (61)	.87
High school graduate	641 (87)	180 (88)	.73
Married	347 (47)	66 (33)	<.001
Annual income <$20 000	324 (44)	129 (63)	<.001
Psychosocial and behavioral factors			
Live alone	242 (33)	81 (40)	.06
Poor social support	193 (26)	111 (55)	<.001
Current smoking	117 (16)	62 (31)	<.001
Regular alcohol use	206 (28)	63 (31)	.45
BMI, mean ± SD	28 ± 5	29 ± 6	.01
Medical history			
Hypertension	542 (74)	149 (73)	.86
Diabetes mellitus	194 (26)	67 (33)	.07
Myocardial infarction	416 (57)	106 (52)	.25
Congestive heart failure	134 (18)	39 (19)	.77
Stroke	109 (15)	29 (14)	.83
Revascularization	476 (65)	110 (54)	.005
Renal insufficiency (≤60 mL/min)	233 (29)	59 (26)	.41
Angina weekly or more	119 (16)	57 (28)	<.001
Medication use			
Cardiovascular medications, mean ± SD, No.	2.8 ± 1.0	2.6 ± 1.0	.18
β-Blocker	469 (64)	125 (61)	.52
Renin-angiotensin system blocker	413 (56)	110 (54)	.58
Diuretic	235 (32)	58 (28)	.34
Statin	525 (71)	130 (64)	.04
Aspirin	617 (84)	175 (86)	.49
Antidepressant	76 (10)	100 (49)	<.001
Cardiac function			
Left ventricular ejection fraction <50%	93 (13)	15 (7)	.03
Poor exercise capacity (metabolic equivalents <5)	166 (24)	44 (24)	.93

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
*Data are given as number (percentage) except where indicated otherwise. Denominators may vary because of missing data.

Figure 1. Proportion of participants with and without depression who were medication nonadherent.

into backward-elimination logistic regression models. Variables that were associated with medication nonadherence (at P<.05) were retained in these models. To determine whether the association between depression and medication nonadherence differed by the use of specific medications, we tested for interactions between depression and the use of antidepressants, β-blockers, aspirin, statins, and renin-angiotensin system blockers. For these analyses, we report adjusted odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were performed using statistical analysis software (SAS version 8; SAS Institute Inc, Cary, NC).

RESULTS

Of the 940 participants, 204 (22%) had current depression based on the computerized version of the Diagnostic Interview Schedule. Compared with nondepressed participants, depressed participants were more likely to be younger, to be female, to be unmarried, and to have an annual income of less than $20 000 (Table 1). Depressed participants were more likely to have poor social support, to be current smokers, and to have a higher body mass index. They were less likely to have a history of coronary revascularization and more likely to report weekly angina. Participants with depression were less likely to be using statins and more likely to be using antidepressants. Compared with nondepressed participants, those with depression had worse cognitive function and higher ejection fractions. We observed no difference in the number of current cardiovascular medications between depressed and nondepressed participants.

Overall, 7% (68/940) of the participants reported not taking their medications as prescribed. Participants with depression were more likely than those without depression to report not taking their medications as prescribed, forgetting to take their medications, and deciding to skip their medications (**Figure 1**). After adjusting for potential confounding variables, depression remained associated with all 3 measures of medication nonadherence, although the association of depression with forgetting to take medications was no longer significant at the P<.05 level (**Table 2**).

A total of 5% (24/483) of the participants with no symptoms to minimal depressive symptoms (PHQ score of 0-3) reported not taking medications as prescribed compared with 7% (19/278) of the participants with mild-to-moderate symptoms of depression (PHQ score of 4-9) and 14% (25/177) with severe symptoms of depression (PHQ score ≥10) (**Figure 2**). Compared with participants who had no symptoms to minimal depressive symptoms, those with severe depressive symptoms had 3-fold odds of not taking medications as prescribed (OR, 3.1; 95% CI, 1.7-5.7; P<.001). This association remained strong after adjustment for potential confounding variables (OR, 2.2; 95% CI, 1.1-4.2; P=.02).

Table 2. Multivariable Association of Depression With Medication Nonadherence

Reason for Nonadherence	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)*	P Value
Not taking medications as prescribed	2.8 (1.7-4.7)	<.001	2.2 (1.2-3.9)	.009
Forgot to take medications	2.4 (1.6-3.8)	<.001	1.6 (1.0-2.7)	.06
Decided to skip medications	2.2 (1.2-4.2)	.01	2.1 (1.1-4.0)	.03

Abbreviations: CI, confidence interval; OR, odds ratio.

*All the variables from Table 1 were entered into a backward-elimination logistic regression model, with $P<.05$ for retention in the model. Other variables associated with not taking medications as prescribed were white race (OR, 0.4; 95% CI, 0.2-0.7), high school education (OR, 0.5; 95% CI, 0.3-0.9), weekly angina (OR, 2.1; 95% CI, 1.1-3.8), and number of cardiac medications (OR, 0.7; 95% CI, 0.5-0.9). Other variables associated with forgetting to take medications were Hispanic race (OR, 2.1; 95% CI, 1.1-4.1), poor social support (OR, 2.0; 95% CI, 1.2-3.2), weekly angina (OR, 2.3; 95% CI, 1.4-3.8), and use of a renin-angiotensin system blocker (OR, 0.5, 95% CI, 0.3-0.8). Other variables associated with deciding to skip medications were history of congestive heart failure (OR, 4.0; 95% CI, 1.9-8.4), history of myocardial infarction (OR, 0.5; 95% CI, 0.4-0.8), taking aspirin (OR, 15.3, 95% CI, 2.0-118), and number of cardiac medications (OR, 0.6, 95% CI, 0.4-0.8).

We observed no difference in the association of depression with medication nonadherence in users and nonusers of antidepressants, aspirin, statins, or renin-angiotensin system blockers (all $P>.20$ for interaction). However, the association between depression and medication nonadherence differed in users and nonusers of β-blockers ($P<.001$ for interaction). Among the 594 users of β-blockers, depression was associated with increased odds of not taking medications as prescribed (adjusted OR, 6.3; 95% CI, 2.9-13.7; $P<.001$), forgetting to take medications (OR, 2.0; 95% CI, 1.1-3.7; $P=.02$), and deciding to skip medications (OR, 2.5; 95% CI, 1.0-5.8; $P=.03$). Among the 346 nonusers of β-blockers, depression was not associated with not taking medications as prescribed (OR, 0.6; 95% CI, 0.2-1.5; $P=.25$), forgetting to take medications (OR, 1.5; 0.7-3.2; $P=.35$), or deciding to skip medications (OR, 1.7; 95% CI, 0.7-4.8; $P=.26$).

COMMENT

We found that depression was associated with medication nonadherence in 940 outpatients with CHD. Although our study participants reported high adherence overall, those with depression were more likely to report not taking their medications as prescribed, forgetting to take their medications, and deciding to skip their medications. In addition, participants with more severe depression were more likely to be nonadherent. This association between depression and nonadherence persisted after adjusting for other factors that may affect medication adherence, such as age, ethnicity, education, social support, and measures of cardiac disease severity.

These findings confirm those from Carney et al,[34] who found that depression was associated with nonadherence to prescribed aspirin in 10 depressed and 45 nondepressed patients. Our results also support a study by Ziegelstein et al[32] that found decreased adherence to recommended behavior and lifestyle changes, including stopping smoking, exercising regularly, and following a low-fat diet, in 31 depressed vs 173 nondepressed patients after acute myocardial infarction. Ziegelstein et al[32] reported that depression was associated with taking less prescription medication, but it was unclear whether the frequency of "taking prescription medication" was measuring adherence or the number and frequency of medi-
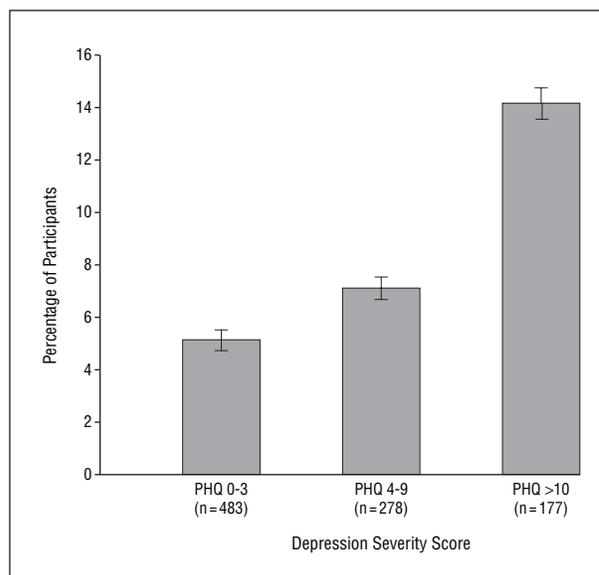
Figure 2. Proportion of participants who were medication nonadherent according to the depression severity score on the Patient Health Questionnaire (PHQ) ($P=.003$ for trend). Error bars represent SD.

cations prescribed. To our knowledge, ours is the first large study to examine the association between depression and medication nonadherence in patients with stable CHD and to demonstrate that more severe depression is associated with greater nonadherence.

There are several reasons why depression may be associated with medication nonadherence. First, expectations of the benefit of treatment recommendations are an essential component of patient adherence.[20] Depressed patients often have an outlook of hopelessness, which may compromise any confidence in the benefits of therapy. Second, depression can be accompanied by a lack of the energy and focus required to follow through with treatment recommendations. Third, depressed patients may be more sensitive to medication adverse effects and thus more likely to discontinue medication use. Alternatively, it may be that medication nonadherence leads to depression.

Although one might expect that patients with angina symptoms and a history of revascularization would be more cognizant of their cardiac disease and thus more

likely to be adherent to medications, we found that depression was associated with medication nonadherence even after correction for differences in angina frequency and history of revascularization between depressed and nondepressed participants. Because our results are cross-sectional, it is unclear whether medication nonadherence led to greater angina frequency in the depressed participants or whether depressed patients were less likely to take their medications because they felt sicker.

We found that the association between depression and nonadherence differed in users and nonusers of β-blockers. Depression seemed to be associated with medication nonadherence in participants who were using β-blockers but not in those who were not using β-blockers. It is possible that depressed patients taking β-blockers may be less likely to adhere because they believe that the β-blockers are causing depressive symptoms or because they are more sensitive to the adverse effects of β-blockers. However, we did not measure adherence to β-blockers specifically, and given the low overall rate of medication nonadherence in our study, these post hoc observations may also be due to chance.

Previous studies[1-11] have found that patients who are depressed have a 70% increased rate of CHD events, including nonfatal myocardial infarction and CHD death, compared with those who are not depressed. Aspirin, β-blockers, renin-angiotensin system blockers, and lipid-lowering medications reduce mortality in patients who have CHD.[52-54] If our findings are replicated and depression is associated with a 2-fold odds of not taking medications as prescribed, then depressed patients may not be receiving the benefits of these medications.

The participants in this study had a high overall rate of adherence. Because our subjects were health-conscious, motivated volunteers in a clinical research study, their adherence was likely greater than in the general population of patients with CHD. Thus, the 2-fold odds of nonadherence associated with depression would likely have a greater effect in a less adherent population outside of a clinical study. It is possible that interventions aimed at improving medication adherence in patients with heart disease, such as greater use of medication organizers, pharmacist checks, and nurse follow-up, would decrease the adverse cardiovascular events associated with depression.

The strengths of this study include its large sample size, interview diagnosis of depression, and comprehensive measurement of potential confounding variables. Several limitations must also be considered in interpreting our results. First, we measured overall medication adherence rather than adherence to CHD treatment–specific medications. However, it is unlikely that any discrepancy in overall vs CHD treatment adherence would differ by depression status, particularly because the issue of cost is not a concern to participants recruited from the Veterans Affairs system, who represented most of the participants in this study. Moreover, it has been demonstrated that poor adherence to specific cardiac medications is associated with poor adherence in general.[55]

Second, we assessed medication adherence by self-report. However, other methods of adherence, such as electronic monitoring, pill counts, pharmacy refill records, and bio-logical assays, are also fraught with problems.[56] With many of these other measures of adherence, the patient is given previous warning of monitoring, which has a tendency to overestimate adherence.[49,57] In contrast, self-reported adherence provides a current or short-term estimate of medication adherence, which may be more accurate than pill counts or prescription records.[48] Furthermore, self-reported adherence has been validated as a reliable predictor of clinical outcomes[44,47] and serum drug concentrations.[46] Third, the remarkably low prevalence of nonadherence in this study may have limited the power to perform subanalyses of the overall findings. Fourth, the causal direction between depression and medication nonadherence cannot be determined by a cross-sectional study. Finally, most of the participants were older men, so our results may not be generalizable to women.

In summary, we found that depression is associated with medication nonadherence in a large population of outpatients with CHD. Our findings should direct attention toward medication nonadherence as a possible mechanism by which depression may lead to cardiac events and as a potential target for efforts to improve cardiovascular outcomes in depressed patients.

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