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Mood Disorder Symptoms and Elevated Cardiovascular Disease Risk in Patients with Bipolar Disorder

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Abstract

Objectives—We examined the association between mood symptoms and 10-year CVD risk estimated by Framingham risk score in a cohort of patients with bipolar disorder.

Methods—Veterans with bipolar disorder and CVD risk factors (N=118) were recruited from outpatient VA clinics. CVD risk factor data were collected from electronic medical records and patient surveys, and used to calculate patient Framingham Scores. The relationship between mood symptoms (depressive, manic) and Framingham scores was examined, as was the relationship between mental health symptoms and individual CVD risk factors (lipids, blood pressure, weight, smoking, and fasting glucose).

Results—Mean sample age was 53 years (SD=9.9), 17% were female, and 5% were African-American. Almost 70% were obese (BMI ≥30), 84% had hyperlipidemia, 70% were hypertensive, and 25% had diabetes. Nineteen percent had a Framingham score of >20%, indicative of elevated 10-year risk of developing CVD. After adjusting for age, gender, diabetes diagnosis, smoking status, and mood symptoms, patients with clinically significant depressive symptoms had a 6-fold increased odds of having a Framingham score of >20% (OR=6.1, p=0.03) while clinically significant manic symptoms were not associated with the Framingham score (OR=0.6, p=0.36). Depressive symptoms were also associated with elevated BMI, fasting glucose, and blood pressure.

Limitations—Single-site study reliant on cross-sectional and self-reported mood measures.

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AMK designed the study, managed data collection and analysis, and contributed to the writing of this manuscript. JMS conducted the literature review, contributed to the analyses, and wrote the manuscript. ZL conducted the statistical analyses. JP, SK, and EPP contributed to the study methods and contributed to the writing of the manuscript. DEG contributed to the final editing of this manuscript. All authors contributed to and have approved the final manuscript.

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None of the authors have conflicts of interest- financial or non-financial, regarding the content described in this paper.

Declaration of conflicting interests
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Conclusion—After controlling for physiologic correlates, depressive symptoms were associated with greater relative 10-year risk for CVD mortality among patients with bipolar disorder. Interventions that address self-management of depressive symptoms may help persons with bipolar disorder decrease CVD risk.

Keywords

cardiovascular disease; bipolar disorder; preventive screening; heart disease; risk factors

1. INTRODUCTION

Persons with mental disorders are disproportionately burdened by medical comorbidity compared to age-matched controls, notably from cardiovascular disease (CVD) (Fagiolini and Goracci, 2009). The causes for increased CVD risk are multi-factorial and include unhealthy lifestyles exacerbated by psychiatric symptoms, smoking, and side effects of psychotropic medications. Efforts to reduce these risk factors are often hindered by the fragmentation of physical and mental health services (Kilbourne et al., 2008).

These integrated care issues are exemplified by bipolar disorder, a common mental disorder not only associated substantial functional impairment (Judd and Akiskal, 2003) but also medical costs (Peele et al., 2003) for treatment of CVD, the leading cause of mortality (Roshanaei-Moghaddam and Katon, 2009). Episodic mood episodes unique to bipolar disorder may accelerate the pathophysiology of CVD via an “allostatic load” (McEwen, 2003). Hence, improved CVD risk detection is warranted because the cost to treat CVD alone is anticipated to triple in the United States by 2030 (Heidenreich et al., 2011).

Relatively little research has explored the role of bipolar symptoms and long-term risk for CVD. Prior studies of patients with bipolar disorder have focused on specific CVD risk factors, such as elevated cholesterol levels and weight gain or, the receipt of CVD-related risk factor assessment (Fagiolini et al., 2002). However, the evidence is unclear whether depressive or manic symptoms are more salient to CVD outcomes (Goldstein et al., 2009; Ramsey et al., 2010). The objective of this study was to determine the association between manic and depressive symptoms and long-term CVD risk factors among a cohort of patients with bipolar disorder.

2. METHODS

2.1. Participants and recruitment

Data were obtained from the baseline assessment of participants enrolled in the Self-Management Addressing Heart Risk Trial (SMAHRT), a randomized controlled trial determining whether an integrated health behavior intervention (Life Goals Collaborative Care [LGCC]), improves physical and mental health outcomes for Veterans with bipolar disorder. Details of this trial are described elsewhere (Goodrich et al., 2012). Briefly, eligible patients had 1 ≥ CVD risk factors and an active diagnosis of bipolar disorder (I, II, or NOS) as confirmed by their psychiatrist. This study was reviewed and approved by the local medical center Institutional Review Board.

2.2. Data collection and measures

After providing informed consent, participants completed a survey and a clinical assessment (height, weight, waist circumference, and a blood draw). Height and weight were used to calculate body mass index (BMI). Non-fasting blood draws were collected and analyzed for total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and non-

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fasting plasma glucose. Hypertension was defined as an average systolic reading of 140 mmHg and/or an average diastolic reading of 90 mmHg on two occasions. Framingham risk scores (FRS) were calculated using the algorithm from the original Framingham Heart Study (Wilson et al., 1998). The FRS is an established diagnostic tool based on population studies that incorporates CVD risk factors into a formula to estimate the 10-year relative risk for a serious CVD event to inform evidence-based decisions about treatment intensity and therapy selection. The scoring algorithm includes gender, age, total cholesterol, HDL, systolic/diastolic blood pressure, diabetes, and current smoking status. Bipolar mood symptoms were assessed with the Internal State Scale (ISS), a valid self-report measure (Bauer et al., 2000). The 8-item ISS was used to create measures of manic and depressive symptoms ("depression" and "activation" as well as measures of "well-being" and "perceived conflict").

2.3. Analyses

All analyses were conducted using SAS Version 9.2 (SAS Inc., Cary, NC). Univariate analyses examined mean values for bipolar symptom scales, individual CVD risk factors, and the FRS. T-tests were used to compare values for overall mood symptoms, blood pressure, blood glucose, BMI, cholesterol, and waist circumference across subgroups. Clinically significant depressive and manic symptoms were defined based on previously established criteria. Specifically, a cutoff of >15.5 for manic symptoms indicated an active manic episode and a score of <12.5 on the depression scale, indicated clinical depression (Bauer et al., 2000).

A series of nested logistic regression models were fit to determine the association between clinically significant depressive and manic symptoms and measures of patient CVD risk (FRS and individual physiologic measures). The outcome for the models was a binary indicator for FRS >20%. Initial analyses controlled only for psychiatric symptoms and demographic covariates. Subsequent models also controlled for diabetes, age and gender.

3. RESULTS

A total of 118 patients were enrolled in the SMAHRT study. Participants averaged 53 years in age (SD=9.9), 17% were female, and 5% were African-American. At baseline, 70% of the sample met criteria for clinical obesity while 84% of participants were diagnosed with hyperlipidemia, 70% with hypertension, and 25% with type 2 diabetes. Moreover, 19% had a FRS >20%, indicative of elevated (1 in 5) risk of developing CVD within 10 years (Table 1). Approximately 60% of SMAHRT participants had a moderate to high 10-year risk of experiencing an acute cardiovascular event based on FRS predictions. Overall, trial participants reported a mean depression score of 6.9 (SD=5.3) consistent with clinically significant depression. The mean activation score was 17.2 (SD=11.9), consistent with a current manic episode. A third of patients (33%) met criteria for significant manic symptoms at baseline assessment, while 17% met criteria for clinical depression.

After adjusting for age, gender, diabetes, and smoking status, participants with significant depressive symptoms had a 6-fold increased odds of having a FRS of >20% (adjusted OR=6.1; 95% CI=1.2, 30.8; p=0.03). Clinically significant manic symptoms were *not* associated with an elevated FRS (adjusted OR=0.6; 95% CI=0.2, 3.0; p=0.36). Depressive symptoms were also associated with elevated BMI (OR=4.7; 95% CI=0.3, 9.1; p=0.04), fasting glucose (OR=38.8; 95% CI, 17.5-60.2; p=0.0005), and diastolic blood pressure (OR=11.1; 95% CI=4.2, 18.1; p=0.002), while manic symptoms were associated with elevated fasting glucose only (OR=0.6; 95% CI=0.2, 3.0; p=0.39)(Table 2).

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4. DISCUSSION

This study found that depressive symptoms, but not manic symptoms, were strongly associated with increased odds of long-term CVD risk among patients with bipolar disorder after adjustment. Depressive symptoms were also significantly associated with elevated blood pressure, glucose and BMI. In contrast, manic symptoms had little association with CVD risk factors after controlling for depressive symptoms. Results support previous studies that found that depression and not mania was associated with reduced quality of life and overall outcomes (Kilbourne et al., 2009; Maina et al., 2007). While mania was initially associated with elevated CVD risk, the association largely disappeared after adjusting for depressive symptoms and other patient factors.

Strikingly, 70% of SMAHRT participants were obese at baseline assessment. In contrast, the estimated population prevalence of obesity among U.S. adults is 34% (Flegal et al., 2010). Findings appear representative of the VA patients at this location with 1≥ CVD risk factors because 74% of these patients were recruited and 70% reporting *3* > CVD risk factors (Goodrich et al., 2012). Obesity is strongly associated with CVD risk (Whitlock et al., 2009) and current findings underscore the need for health promotion efforts for patients with bipolar disorder in order to reduce weight and the onset of CVD morbidity. For example, one prospective study of patients with bipolar disorder found obese patients prescribed psychotropic drugs associated with weight gain received more exercise counseling and/or dietary consultations, yet overweight patients were less likely to receive preventive counseling (Goodrich et al., 2010).

SMAHRT baseline findings also suggest that bipolar disorder is associated with substantial long-term CVD risk based on FRS criteria. Depressive and not manic symptoms were associated with greater relative 10-year risk for CVD mortality. Furthermore, depressive symptoms are the predominant mood experienced in bipolar disorder whereas manic symptoms occur infrequently (Bauer et al., 2001). Hence, longitudinal research that examines the pairing of simple diagnostic tools like the FRS with interventional mood management strategies, may provide practical insight into mitigating this CVD disease pathway.

The findings from this study are not without limitations. First, this was a cross-sectional study and no longitudinal data were available to determine changes in CVD risk over time. Depressive symptoms, health behaviors, and CVD physiologic risk factors likely have multi-directional relationships (Katon et al., 2004), therefore, causality cannot inferred and the influence of other covariates affecting CVD risk cannot be ruled out. Second, there was no clinician assessment of bipolar disorder symptoms, and the lack of identified associations may reflect measurement error in mood symptom self-report measure. Finally, results may not generalize to non-VA settings were integrated treatment services are less common. Current findings suggest that there is a positive association between depressive symptoms in patients with bipolar disorder and elevated CVD risk. Developing cost-effective programs that focus on management of mood symptoms as well as CVD risk factors are needed in order to improve outcomes and reduce preventable mortality in this group. Providers are increasingly recognizing the need for medical care management, particularly for CVD risk factors among patients with chronic mental disorders. SMAHRT results may inform intervention strategies for a number of initiatives being employed in the VA and community settings to address gaps in management of CVD risk factors in patients with bipolar and other chronic mental disorders.

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Table 1

Bipolar Disorder Symptoms and CVD Risk Factors

Symptom Scores	**Overall Mean (+SD)**
ISS Depression (0-20)*	6.9 (5.3)
ISS Activation (manic) (0-50)	17.2 (11.9)
ISS Well-being (range: 0-30)	15.8 (7.2)
ISS Perceived conflict (0-50)	13.4 (9.8)
Clinically Significant Symptoms	**Percent**
Depression	17%
Mania	33%
CVD Risk Factors	
Systolic BP, mmHg	132.8 (16.9)
Diastolic BP, mmHg	82.3 (12.9)
Total cholesterol, mg/dL	186.4 (41.8)
LDL, mg/dL	110.8 (35.2)
HDL, mg/dL	36.8 (12.3)
BMI, kg/m^2	33.0 (7.9)
Waist circumference, inches	43.9 (5.9)
Glucose mg/dL	111.5 (48.1)
Framingham Score (10-Year CVD risk)	13.7 (10.0)
Framingham Risk Category	**Percent**
<10 %	40.7%
10-20%	40.7%
>20%	18.6%

* ISS=Internal States Scale.

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Table 2

Symptoms and CVD risk: Multivariable Regression Results for Clinically Significant Mood Symptoms for Each CVD-related Outcome[†]

	Clinically Significant Depressive Symptoms		**Clinically Significant Manic Symptoms***	
	Unadjusted Odds Ratio (95% CI)	**Adjusted Odds Ratio (95% CI)**	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
Framingham Score ≥ 20%	2.7(p=0.05) (0.9, 7.2)	6.1* (p=0.03) (1.2, 30.8)	0.4* (p=0.02) (0.2, 0.9)	0.6(p=0.39) (0.2, 3.0)
Individual CVD Risk Factors	**Unadjusted Beta (95% CI)**	**Adjusted Beta (95% CI)**	**Unadjusted Beta (95% CI)**	**Adjusted Beta (95% CI)**
Systolic BP, mmHg	3.1 (-4.9, 11.3)	5.9 (-3.5, 15.4)	0.9 (-5.2, 7.1)	4.6 (-2.7, 11.9)
Diastolic BP, mmHg	8.4* (2.4, 14.4)	11.1* (p=0.002) (4.2, 18.1)	-0.5 (-5.1, 4.2)	3.7 (-0.16, 9.0)
Total cholesterol, mg/dL	19.5 (-0.4, 39.3)	10.9 (-12.4, 34.3)	-3.6 (-18.7, 11.6)	-4.9 (-22.9, 13.0)
LDL, mg/dL	4.1 (-12.9, 21.2)	-2.2 (-22.3, 17.9)	2.8 (-10.1, 15.7)	-2.9 (-18.6, 12.8)
HDL, mg/dL	5.6 (-0.3, 11.5)	4.1 (-2.6, 10.8)	-0.9 (-5.5, 3.5)	0.2 (-4.9, 6.3)
BMI, kg/m^2	39* (0.2, 7.6)	4.7* (p=0.04) (.3, 9.1)	-1.2 (-4.0, 1.7)	0.4 (-2.9, 3.8)
Waist circumference, inches	0.9 (-1.9, 3.8)	2.4 (-.9, 5.6)	-0.2 (-2.4, 1.9)	0.9 (-1.6, 3.4)
Glucose mg/dL	14.7 (-8.4, 37.8)	38.8* (p=0.0005) (17.5, 60.2)	-9.2 (-26.6, 8.2)	21.8* (p=0.01) (5.3, 38.3)

[†]Defined as ISS score of ≥15.5 for the manic symptom scale and <12.5 for depressive symptom scale. Models adjusted age, gender, diabetes diagnosis, smoking status, depressive, and manic symptoms.

*p<0.05.