ORIGINAL ARTICLE

Cardiovascular risk factors in outpatients with bipolar disorder: a report from the Brazilian Research Network in Bipolar Disorder

Fabiano A. Gomes,[1] Karla M. Almeida,[2] Pedro V. Magalhães,[1] Sheila C. Caetano,[2] Márcia Kauer-Sant'Anna,[1] Beny Lafer,[2] Flávio Kapczinski[1]

[1]Bipolar Disorder Program (PROTAHBI) and National Science and Technology Institute for Translational Medicine (INCT-TM), Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. [2]Bipolar Disorder Research Program (PROMAN), Institute of Psychiatry, Universidade de São Paulo (USP), São Paulo, SP, Brazil.

Objective: Bipolar disorder (BD) is associated with significant morbidity and mortality due to comorbid general medical conditions, particularly cardiovascular disease. This study is the first report of the Brazilian Research Network in Bipolar Disorder (BRN-BD) that aims to evaluate the prevalence and clinical correlates of cardiovascular risk factors among Brazilian patients with BD.
Methods: A cross-sectional study of 159 patients with DSM-IV BD, 18 years or older, consecutively recruited from the Bipolar Research Program (PROMAN) in São Paulo and the Bipolar Disorder Program (PROTAHBI) in Porto Alegre. Clinical, demographic, anthropometric, and metabolic variables were systematically assessed.
Results: High rates of smoking (27%), physical inactivity (64.9%), alcohol use disorders (20.8%), elevated fasting glucose (26.4%), diabetes (13.2%), hypertension (38.4%), hypertriglyceridemia (25.8%), low HDL-cholesterol (27.7%), general (38.4%) and abdominal obesity (59.1%) were found in the sample. Male patients were more likely to have alcohol use disorders, diabetes, and hypertriglyceridemia, whereas female patients showed higher prevalence of abdominal obesity. Variables such as medication use pattern, alcohol use disorder, and physical activity were associated with selected cardiovascular risk factors in the multivariable analysis.
Conclusion: This report of the BRN-BD provides new data regarding prevalence rates and associated cardiovascular risk factors in Brazilian outpatients with BD. There is a need for increasing both awareness and recognition about metabolic and cardiovascular diseases in this patient population.

Keywords: Bipolar disorder; cardiovascular risk factors; comorbidity

Introduction

Bipolar disorder (BD) is a chronic and disabling illness associated with significant morbidity and mortality.[1] Patients with BD are subject to premature death from all causes when compared to the general population[2] and usually have several comorbid general medical conditions associated with worse outcomes and higher burden of disease.[3-5]

Increased rates of obesity,[6,7] diabetes,[8] hypertension,[9] dyslipidemia,[10] and metabolic syndrome[11-13] have been reported in recent clinical and epidemiological studies.[14,15] In addition to being exposed to the weight gain effects of the pharmacological treatment, BD patients are more likely to have sedentary lifestyles and poor dietary habits,[16] which are well-established cardiovascular risk factors.[17]

Most of the abovementioned data come from developed countries, which have somewhat distinct realities from the developing world. In Brazil, together with an increase in the absolute prevalence of obesity and metabolic syndrome, the trend is shifting toward the lower income population.[18] This is of particular interest for the field of BD since most patients are treated by the public health system and prescription patterns may be different from the rest of the world, particularly regarding the use of atypical antipsychotics.[19]

Despite being a leader in psychiatric research among developing countries,[20] one of the shortcomings that may constrain the progress of clinical research in Brazil is the relatively limited number of patients enrolled in most studies, and a natural step to overcome this limitation is to establish research networks.[21] In 2005, the Brazilian Association for Bipolar Disorder (ABTB) created the Brazilian Research Network in Bipolar Disorder (BRN-BD) as a means to promote the integration of BD research centers and to develop collaborative studies. The BRN-BD comprises BD urban university-affiliated treatment and research centers of São Paulo, Porto

Alegre, Salvador, and Fortaleza, and some studies from this initiative have already been published.[22-25]

In this context, the present study is a report of the BRN-BD that aims to evaluate the prevalence and clinical correlates of cardiovascular risk factors among patients with BD from two research centers in São Paulo (PROMAN) and Porto Alegre (PROTAHBI), Brazil.

Methods

Subjects

The study is a cross-sectional analysis of outpatients with BD, 18 years or older, consecutively recruited from the Bipolar Research Program (PROMAN) at the University of São Paulo Medical School, São Paulo, Brazil, and the Bipolar Disorder Program (PROTAHBI) at the Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. Because these institutions are tertiary treatment facilities, patients are usually referred from primary care units and secondary hospitals for specialized treatment. As part of the research protocols of both sites, BD and comorbid conditions are diagnosed with the Structured Clinical Interview for DSM-IV® Axis I Disorders (SCID-I). Exclusion criteria were schizophrenia or other psychotic disorders, schizoaffective disorders, and organic mental disorders. The study was approved by the Institutional Review Boards (FMUSP 1326/06 and GPPG-HCPA 06-245) of both research sites, and all participants gave written informed consent before entering the study.

Clinical and laboratory data

Patient assessment was similar in both institutions. Clinical, demographic, anthropometrical, and metabolic measures were assessed at the first visit. These included height and weight, body mass index (BMI), waist circumference, and blood pressure (measured twice at different times during the interview with calibrated manual sphygmomanometers at a seated position after at least a 5-minute rest). All patients were wearing light clothes and no shoes, and there was no need of fasting for anthropometric evaluation. Mood symptoms were assessed with the 17-item Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale (YMRS). Patients were requested to have a fasting blood sample drawn the next day to evaluate fasting serum glucose, high-density cholesterol (HDL), and triglycerides levels. Patients from the PROTAHBI site also had total cholesterol data available. A second study visit was scheduled to provide test results and counseling. Those patients who needed to be treated were referred for treatment.

Determination of cardiovascular risk factors

Cardiovascular risk factors were diagnosed according to recent Brazilian guidelines for diabetes, hypertension, and dyslipidemia.[26-28] High glucose was defined as fasting glucose $\geq$ 100 mg/dL; high total cholesterol as fasting total cholesterol $\geq$ 240 mg/dL; low HDL cholesterol as fasting HDL cholesterol $<$ 40 mg/dL (men) or $<$ 50 mg/dL (women); diabetes as fasting glucose $\geq$ 126 mg/dL or previous diagnosis of diabetes and current use of hypoglycemic medication; hypertriglyceridemia as fasting triglycerides $\geq$ 200 mg/dL; hypertension as blood pressure $\geq$ 140/90 mmHg or previous diagnosis of arterial hypertension and current use of antihypertensive drugs; overweight as BMI between 25-29.9 kg/m^2; obesity as BMI $\geq$ 30; abdominal obesity as waist circumference $\geq$ 102 cm (men) and $\geq$ 88 cm (women); physical inactivity as self-report of no regular exercise; and smoking as self-report of current use of cigarettes, cigars or pipes.

Statistical analysis

Differences between patients from the two research sites as well as differences in clinical variables associated with each cardiovascular risk factor were compared using chi-squared tests for dichotomous variables, whereas Student's t tests or Mann-Whitney tests were used for parametric and non-parametric continuous data. Multilevel logistic regression analyses were used in order to control for confounding factors associated with cardiovascular risk factors. Age, gender, and research site were included in the first level, whereas other related variables such as smoking, physical activity, alcohol use disorders, and medication use (lithium, valproate, other anticonvulsants, antidepressants, typical and atypical antipsychotics) were included in the second level. All tests were two-tailed.

Results

A total of 159 outpatients were enrolled in the study, 84 from the PROMAN site and 75 from the PROTAHBI site. Demographic and clinical characteristics of the sample are shown in Table 1. Patients from the PROMAN site were more likely to be younger (p = 0.031), single (p = 0.018), and have more years of formal education (p $<$ 0.001). There were significant differences in prescription patterns between the sites, such as more use of atypical antipsychotics (p = 0.001), antidepressants (p = 0.002), and lamotrigine (p = 0.005) at the PROMAN site, whereas we found more use of lithium (p = 0.001) and valproate (p = 0.013) at the PROTAHBI site. Patients from the PROTAHBI site also had more depressive (p = 0.001) and manic (p = 0.001) symptoms.

The prevalence of the selected cardiovascular risk factors is presented in Table 2. In addition to the high rates of the different risk factors, we found significant gender differences. Male patients were more likely to have alcohol use disorders (p = 0.001), diabetes (p = 0.037), and hypertriglyceridemia (p $<$ 0.001); female patients showed increased rates of abdominal obesity (p = 0.007).

In the multilevel logistic regression - after controlling for site, age, and gender -, valproate (odds ratio [OR] = 2.11; confidence interval [CI] = 1.03-4.35) was associated with obesity. Older age (OR = 1.09; CI = 1.03-1.15) and male gender (OR = 5.15; CI = 1.45-18.29) remained associated with diabetes; recruitment from the PROTAHBI site (OR = 2.18; CI = 1.04-4.60) and older age (OR = 1.09; CI

Table 1 Sociodemographic and clinical variables of bipolar disorder outpatients

Variable	Total sample (n=159) n (%)	PROMAN (n=84) n (%)	PROTAHBI (n=75) n (%)	p-value
Age*	43.5±12.0	41.5±11.5	45.8±12.1	0.031
Years of formal education*	10.4±4.0	11.6±3.6	9.1±4.0	< 0.001
Gender				
Male	52 (32.7)	29 (34.5)	23 (30.7)	
Female	107 (67.3)	55 (65.5)	52 (69.3)	0.61
Marital status				
Single	58 (36.5)	39 (46.4)	19 (25.3)	
Living with partner	60 (37.7)	27 (32.1)	33 (44.0)	
Separated/divorced	29 (18.2)	15 (17.9)	14 (18.7)	
Widowed	12 (7.5)	3 (3.6)	9 (12.0)	0.018
Bipolar disorder				
Type I	150 (94.3)	78 (92.9)	72 (96.0)	
Type II	9 (5.7)	6 (7.1)	3 (4.0)	0.50
Current medication				
Any mood stabilizer	140 (88.1)	71 (84.5)	69 (92.0)	0.22
Lithium	84 (52.8)	34 (40.5)	50 (66.7)	0.001
Valproate	56 (35.2)	22 (26.2)	34 (45.3)	0.013
Carbamazepine/oxcarbazepine	42 (26.4)	31 (36.9)	11 (14.7)	0.002
Typical antipsychotics	30 (18.9)	13 (15.5)	17 (22.7)	0.31
Atypical antipsychotics	63 (39.6)	44 (52.4)	19 (25.3)	0.001
Risperidone	21 (13.2)	6 (7.1)	15 (20.0)	0.02
Quetiapine	17 (10.7)	17 (20.2)	0 (0.0)	< 0.001
Olanzapine	19 (11.9)	16 (19.0)	3 (4.0)	0.003
Clozapine	6 (3.8)	2 (2.4)	4 (5.3)	0.42
Ziprasidone/aripiprazole	12 (7.5)	11 (13.1)	1 (1.3)	0.005
Antidepressants	46 (28.9)	32 (38.1)	12 (16.0)	0.002
Other				
Lamotrigine	24 (15.1)	19 (22.6)	5 (6.7)	0.005
Topiramate	13 (8.2)	13 (15.5)	0 (0.0)	< 0.001
Gabapentin	6 (3.8)	5 (6.0)	1 (1.3)	0.21
Benzodiazepines	49 (30.8)	27 (32.1)	22 (29.3)	0.73
Number of current medications[†]	3 (1)	3 (2)	2 (1)	0.003
HAM-D score[†]	5.5 (10)	4 (6)	8 (10)	0.001
YMRS score[†]	1 (4)	0 (2)	2 (5)	0.001

HAM-D = Hamilton Depression Rating Scale; PROMAN = Bipolar Research Program; PROTAHBI = Bipolar Disorder Program; YMRS = Young Mania Rating Scale.
* Mean ± standard deviation.
[†] Median (interquartile distance).

Table 2 Prevalence of cardiovascular risk factors in bipolar disorder outpatients

Variable	Total sample (n=159) n (%)	Males (n=52) n (%)	Females (n=107) n (%)	χ^2	p-value
Age (men ⩾ 45; women ⩾ 55)	36 (22.6)	12 (23.1)	24 (22.4)	0.008	0.539
Smoking	43 (27.0)*	18 (35.3)*	25 (23.6)	2.374	0.090
Physical inactivity	103 (64.9)[†]	30 (60.0)[†]	73 (70.2)	1.584	0.141
Alcohol use disorders	33 (20.8)[†]	19 (36.5)[†]	14 (13.7)	10.646	0.001
High glucose	42 (26.4)	15 (28.8)	27 (25.2)	0.235	0.381
Diabetes	21 (13.2)	11 (21.2)	10 (9.3)	4.256	0.037
Hypertension	61 (38.4)	23 (44.2)	38 (35.5)	1.124	0.187
Hypertriglyceridemia	41 (25.8)	23 (44.2)	18 (16.2)	13.737	< 0.001
High total cholesterol[‡]	34 (45.3)	08 (34.8)	26 (50.0)	1.490	0.166
Low HDL cholesterol	44 (27.7)	13 (25.0)	31 (29.0)	0.276	0.372
Overweight	52 (32.7)	21 (40.4)	31 (29.0)	2.071	0.105
Obesity	61 (38.4)	18 (34.6)	43 (40.2)	0.459	0.309
High waist circumference	94 (59.1)	23 (44.2)	71 (66.4)	7.087	0.007

χ^2 = chi-square test; HDL = high-density cholesterol.
* Data unavailable for 2 PROMAN patients.
[†] Data unavailable for 5 PROMAN patients.
[‡] Data unavailable for PROMAN patients.

= 1.05-1.13) were positively associated with hypertension, whereas physical activity (OR = 0.35; CI = 0.14-0.87) and lithium use (OR = 0.18; CI = 0.07-0.46) were negatively associated with this disease. Recruitment from the PROTAHBI site (OR = 2.34; CI = 1.09-5.03) was positively associated with reduced HDL-cholesterol, while alcohol use disorder (OR = 0.30; CI = 0.09-0.99) was negatively associated with this cardiovascular risk factor; and male gender (OR = 4.09; CI = 1.92-8.70) remained associated with hypertriglyceridemia.

Discussion

Our study investigated the prevalence and clinical correlates of well-established cardiovascular risk factors in two samples of outpatients with BD. In line with previous studies, we found elevated prevalence rates of obesity, smoking, physical inactivity, diabetes, hypertension, and dyslipidemia in Brazilian BD outpatients. We also found statistically significant gender differences regarding alcohol use disorders, diabetes, hypertriglyceridemia, and abdominal obesity.

BD is associated with substantial morbidity and increased rates of all-cause mortality,[29,30] and there has been increasing awareness and recognition about the contribution of cardiovascular risk factors to the medical burden of this illness.[31,32] In addition to general medical conditions such as cardiovascular, endocrine, and metabolic diseases,[8,33] patients with BD usually have a wide range of modifiable cardiovascular risk factors such as obesity, smoking, physical inactivity, and poor eating habits.[17]

As expected and in line with recent studies from other countries, patients with BD had higher prevalence of the selected cardiovascular risk factors when compared with data regarding the Brazilian population, in which recent studies have shown rates of 5-10% for diabetes and around 30% for hypertension and high cholesterol.[26-28] Previous findings on the prevalence of comorbid general medical conditions in BD have reported alarming high rates of cardiovascular risk factors such as obesity (20-32%),[34] hypertension (34-60%),[10,35] diabetes (2-26%),[9] and dyslipidemia (23-41%).[8] Furthermore, studies investigating the prevalence of the metabolic syndrome in BD patients have reported varying rates as low as 18-25.3% in Belgium[36] and Italy,[37] 33.9% in Taiwan,[38] and as high as 40-49% in the United States.[39,40] A recent report on cardiovascular risk factors in BD patients[41] has also pointed out differences between prevalence rates not only among different countries, but also according to the cardiovascular risk estimation method used. In addition to these findings, our results underscore the relevance of considering regional differences when studying cardiovascular risk factors in psychiatric patients. Differences in lifestyle, socioeconomic level, and unequal access to psychotropic medication are probably related to the distinctive results between sites.[19]

There may be a wide range of confounding factors when studying cardiovascular risk factors in patients with severe mental illnesses.[42,43] Despite individual variables such as age and gender, patients with BD are particularly at risk due to both disease and treatment-related factors.[39] Clinical and biological features such as depression with atypical features, anxiety, hypercortisolism, disruption of the adipocytokine levels and pro-inflammatory states, increased oxidative stress and DNA damage,[44] as well as treatment with weight gaining medication and polipharmacy, are related to increased medical burden in BD.[45] The interplay among these factors may have a cumulative effect on morbidity and mortality resulting from a hazardous combination of intrinsic and exogenous pathophysiological mediators.

In this context, differences in cardiovascular risk factors prevalence rates seen in our study may be explained not only by distinct genetic, lifestyle, and dietary backgrounds, but also by varying prescription patterns. In order to control for potential confounders (age, gender, and treatment site), we used multivariable analysis to explore other associated risk factors. Some variables such as medication use pattern, alcohol use disorder, and physical activity were associated with selected cardiovascular risk factors and may represent a possible target for intervention. The multivariable analysis approach is relevant in this study since most of the variables studied are highly correlated.[46]

Our results must be interpreted in the light of some of limitations. In addition to the relatively small size, our samples came from tertiary treatment settings, and most of the participants were difficult-to-treat patients, which may limit the generalization of our results to the whole spectrum of BD. Due to the cross-sectional nature of our study, we cannot offer mechanistic causal explanations, and longitudinal studies are necessary to further clarify the abovementioned associations.

Despite these limitations, this report of the BRN-BD provides a significant amount of new data regarding prevalence rates and associated cardiovascular risk factors in Brazilian outpatients with BD. This information may be useful for increasing both awareness and recognition of comorbid metabolic and cardiovascular diseases in this patient population, which may potentially lead to changes in clinical practice resulting in a reduction in the increased medical burden of BD.

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Disclosure

a consultant for Servier. The other authors report no conflicts of interest.

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