Journal of Affective Disorders Reports 1 (2020) 100001

Contents lists available at ScienceDirect

Journal of Affective Disorders Reports

journal homepage: www.elsevier.com/locate/jadr

Clinical correlates of high burden of general medical comorbidities in patients with bipolar disorder

Fabiano A. Gomes[a,b,e,*], Pedro V. Magalhães[c,d], Taylor Magee[a,b], Elisa Brietzke[a,b,e], Maurício Kunz[c,d], Flávio Kapczinski[c,f]

[a] Department of Psychiatry, Queen's University School of Medicine, Kingston, ON, Canada
[b] Kingston Health Sciences Centre, Kingston, ON, Canada
[c] Departmento de Psiquiatria e Medicina Legal, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
[d] Hospital de Clinicas de Porto Alegre, Porto Alegre, RS, Brazil
[e] Centre for Neuroscience Studies, Kingston, ON, Canada
[f] Department of Psychiatry and Behavioral Sciences, McMaster University, Hamilton, ON, Canada

ARTICLE INFO

Keywords:
Bipolar disorder
General medical comorbidity
Cirs

ABSTRACT

Background: Bipolar disorder is associated with an increased burden of general medical conditions that might be related to a more severe illness course.

Methods: This is a cross-sectional study that evaluated clinical correlates of general medical comorbidities in outpatients with bipolar disorder (BD) involving 203 adult patients with a DSM-IV diagnosis of BD, consecutively recruited from the Bipolar Research Program (PROTAHBI) in Porto Alegre, Brazil. Clinical, demographic and anthropometrical variables were systematically assessed, and general medical comorbidity was measured using the Cumulative Illness Rating Scale (CIRS).

Results: The prevalence of one or more medical comorbidities was 90.1%. The most common were those from endocrine/metabolic/breast, neurologic and vascular categories. A high burden of general medical comorbidities (defined as CIRS total score ≥ 4) was related to increasing age and body mass index and longer duration of illness after controlling for confounding factors.

Limitations: The cross-sectional design limits our ability to make causal conclusions. Also, our sample consisted of patients with longer illness duration from a tertiary clinic and may not generalize to the whole spectrum of bipolar disorder.

Conclusions: BD was associated with a high burden of general medical conditions related to age, obesity and longer duration of illness. Medical comorbidities must be incorporated as a core feature in the development of effective treatment strategies for bipolar disorder.

1. Introduction

Bipolar disorder (BD) is a chronic and complex clinical entity associated with significant illness burden and deleterious effects on general functioning (Grande et al, 2016). In addition to mood and cognitive symptoms, patients with BD usually present a wide range of psychiatric and medical comorbidities that are associated with worse prognosis (Mansur et al, 2015).

Several studies have highlighted the increased prevalence of general medical conditions associated with BD and its relationships with premature death, morbidity, treatment costs and functional impairment (Li et al, 2019). Although most clinical conditions are overrepresented in BD populations, cardiovascular and metabolic problems are of particular concern since they are usually related to unhealthy lifestyles and psychopharmacological treatment (Brietzke et al, 2017). Recently, there has been a renovated interest in which factors – particularly those related to BD itself – may be associated with a common underlying pathophysiology (Mansur et al, 2013; Lin et al, 2020). The present study aims to evaluate the prevalence and clinical correlates of general medical comorbidities in a sample of Brazilian outpatients with BD. We hypoth-

* Corresponding author: Fabiano Alves Gomes MD, MSc, PhD, 76 Stuart Street, Kingston Health Sciences Centre, Kingston General Hospital Site, Burr 4, Kingston, ON, K7L 2V7, Tel: 613 549 6666 ext. 7887
E-mail address: fabiano.alvesgomes@queensu.ca (F.A. Gomes).

https://doi.org/10.1016/j.jadr.2020.100001
Received 13 August 2020; Accepted 18 August 2020
Available online 24 August 2020

Table 1
Clinical and demographic variables of the sample.

Variable	Total Sample (n=203)	CIRS total score ≤ 3 (low to moderate burden of clinical comorbidity) (n=88)	CIRS total score ≥ 4 (high burden of clinical comorbidity) (n=115)	*P*- value
Age in years, mean (DS)	41.9 (11.8)	36.2 (10.6)	46.3 (10.7)	< 0.001
Sex Female (%)	70.9	63.6	76.5	0.045
Ethnicity (%)				
Caucasian	83.7	84.1	83.3	0.885
Marital status				
Married/living with partner (%)	39.4	35.2	43.0	0.264
Education in years, mean (SD)	9.6 (4.16)	10.4 (3.8)	8.9 (4.3)	0.013
Age at onset in years, mean (SD)	25.4 (11.8)	24.1 (11.4)	26.4 (12.1)	0.183
Duration of illness in years, mean (SD)	16.4 (11.6)	12.1 (10.5)	19.7 (11.5)	< 0.001
Number of hospitalizations, mean (SD)	3.21 (4.50)	2.53 (3.73)	3.73 (4.97)	0.060
Diagnosis				
Bipolar disorder type I (%)	87.6	86.2	88.7	0.595
Rapid cycling (%)	28.7	30.7	27.2	0.587
Lifetime psychiatric comorbidities				
Anxiety disorders (%)	63.2	56.3	68.4	0.078
Alcohol abuse/dependence (%)	28.7	32.2	26.1	0.343
Drug abuse/dependence (%)	21.3	28.7	15.7	0.024
BMI classification				
Normal weight (%)	32.6	48.6	21.9	< 0.001
Overweight (%)	34.9	34.3	35.2	
Obesity (%)	32.6	17.1	42.9	

esized that patients with a high burden of medical comorbidities would present with more severe BD clinical features.

2. Methods

Two hundred and three patients, aged 18 years or older, with a diagnosis of bipolar disorder type I or II were consecutively recruited from the Bipolar Disorder Program at the Hospital de Clínicas de Porto Alegre, Brazil. This research project has received approval from the local ethics committee and written informed consent was obtained from all patients before their inclusion. Psychiatric diagnosis of BD and psychiatric comorbidities were confirmed with the Structured Clinical Interview for DSM-IV-axis I (SCID I). Socio-demographic and clinical variables were collected as part of a structured standard protocol (Gazalle et al, 2005). Anthropometrical variables included height and weight. Body mass index (BMI) was calculated as [weight in kilograms/(height in meters)^2]. Patients were classified as normal weight (BMI < 25.0), overweight (BMI ranging 25.0-29.9) or obese (BMI ≥ 30) (WHO, 1997).

Data regarding medical comorbidities was obtained from the best available information including interviews with patients and relatives, and a review of medical records. For each patient, the first author (FAG) generated a score on the Cumulative Illness Rating Scale (CIRS) which was used as an index for the burden of general medical conditions. The CIRS is a valid and reliable instrument developed to assess chronic medical burden (Linn et al, 1968) and has been used in studies with psychiatric populations (Miller et al, 1992; Mistry et al, 2004), including BD (Soreca et al, 2008; Kemp et al, 2009).

The CIRS includes 13 organ systems plus a psychiatric illness category that was excluded for the purpose of this analysis. For each organ system, a score ranging from 0 to 4 is graded. A score of 0 represents “no problem”; a score of 1 is a “current mild or past significant problem”; a score of 2 is “moderate disability requiring first line treatment”, a score of 3 is “uncontrollable chronic problems or significant disability” and a score of 4 is “end organ failure requiring immediate treatment”. No patient received a score of 4 in any of the 13 categories since all study subjects were outpatients. Two indices were obtained: the CIRS count, which is the number of categories endorsed by the patient, and the CIRS total score, which is the sum of each of the 13 individual system scores. Patients were divided according to the magnitude of general medical comorbidity burden into two groups (Kemp et al, 2009): low to moderate (CIRS total score ≤ 3) and high burden (CIRS total score ≥ 4).

Table 2
Prevalence rates of comorbidity in each organ systems (CIRS category) among BD outpatients

Category	Patients with at least one comorbidity (%)
Endocrine/Metabolic/Breast	50.2
Neurologic	35.5
Vascular	29.1
Musculoskeletal/Integumentary	25.6
Respiratory	21.2
Genitourinary	13.3
Hepatic/Pancreatic	10.8
Cardiac	7.4
Renal	7.4
Head and neck	6.4
Upper gastrointestinal	6.4
Lower gastrointestinal	3.9
Hematological	2.0

Bivariate analyses were performed for differences in demographic and clinical variables associated with each medical comorbidity group using chi-squared tests for dichotomous variables and student t-tests or Mann-Whitney tests for parametric and non-parametric continuous data, respectively. Logistic regression was used to control for confounding factors associated with high burden of general medical comorbidity. All tests were two-tailed.

3. Results

A total of 203 individuals with BD were included. Clinical and demographic variables are summarized in Table 1. The prevalence of at least one medical comorbidity was 90.1% and the most common categories of comorbidities were endocrine-metabolic-breast, neurologic and vascular (table 2). The mean number of CIRS categories in our sample of patients (CIRS count) was 2.18 ± 1.27 and the mean CIRS total score of the sample was 4.02 ± 2.54.

Age, female gender, education, duration of illness and BMI were associated with a CIRS total score ≥ 4 in the bivariate analyses compared with patients with a CIRS total score of 3 or less. Age, BMI and illness duration remained associated with a high burden of general medical comorbidities in the regression analysis (Table 3).

Table 3
Binomial logistic regression analysis of the association of clinical variables with high burden of general medical comorbidity in BD patients.

Variable	B	Standard Error	Wald χ^2	*P* value	Odds Ratio	CI (95%)
Age	0.053	0.021	6.472	0.011	1.06	1.01 - 1.10
Married/Living with partner	0.026	0.405	0.004	0.949	1.03	0.46 - 2.27
Female gender	-0.741	0.449	2.729	0.099	0.48	0.20 - 1.15
Education, years	-0.017	0.051	0.107	0.744	0.98	0.89 - 1.09
Duration of illness, years	0.047	0.021	4.773	0.029	1.05	1.01 - 1.09
Number of hospitalizations	0.001	0.047	0.000	0.986	1.00	0.91 - 1.10
Smoking	0.295	0.441	0.446	0.504	1.34	0.57 - 3.19
Alcohol use disorders	-0.077	0.457	0.029	0.866	0.91	0.38 - 2.27
Substance use disorders	-0.683	0.495	1.909	0.167	0.51	0.19- 1.33
Anxiety disorders	0.215	0.417	0.266	0.606	1.24	0.55 - 2.81
BMI	0.122	0.040	9.168	0.002	1.13	1.04 - 1.22

4. Discussion

Our sample of BD outpatients presented with a high level of general medical comorbidities with approximately 90% of the sample presenting at least one comorbid condition. We also found that after controlling for confounders, age, BMI and illness duration were associated with a higher burden of general medical comorbidities.

These results are consistent with previous reports indicating a high level of medical comorbidity in BD, usually greater than patients with unipolar depression (Iosifescu et al, 2004; Gildengers et al, 2008) and at a similar level to geriatric patients (Miller et al, 1992). Endocrine/metabolic, neurological and vascular diseases are also commonly reported comorbidities associated with BD. (Sinha et al, 2018).

There is an increasing body of evidence that medical disease is correlated with several indicators of poorer prognosis in BD (Grande et al, 2016). The relationships among the burden of general medical conditions, BD chronicity and worse outcomes are probably mediated by significant factors not only related to demographic variables such as age, gender and ethnic background, but particularly to illness-related factors (Grande et al, 2012). Previous studies have shown that high levels of medical comorbidity are associated with treatment response and clinical correlates of severity such as BD subtype, obesity, suicidality, history of physical abuse, early onset and longer duration of illness (Thompson et al, 2006; Soreca et al, 2008; Kemp et al, 2009; Kemp et al, 2010, Magalhães et al, 2012). In our sample, age, BMI and illness duration were independently associated with a high burden of medical disease, supporting the hypothesis of a process of accelerated aging in BD related to the cumulative incidence of mood episodes and disease neuroprogression. (Kapczinski et al, 2017).

The changing view that BD is a chronic and disabling condition rather than a benign episodic illness is endorsed by data regarding the interplay between psychiatric symptoms and medical comorbidities. Illness severity is crucially bonded with medical problems in terms of reciprocal interactions (Kupfer et al, 2015). Notwithstanding potentially shared genetic diathesis, overload of regulatory systems such as endocrine, immunological and inflammatory networks associated with mood symptomatology have a definite impact on health status and medical disease incidence and progression (Berk et al, 2011). On the other hand, despite direct influences on the underlying pathophysiology of BD, general health status is an important variable concerning quality of life and functioning.

Our findings must be interpreted in the light of some limitations. Due to the cross-sectional nature of the study design and tertiary setting, prospective studies with both clinical and community samples are mandatory in order to elucidate the interactions between BD and general medical conditions. Inclusion of neurobiological data such as biomarkers and measures of physiological mediators are also important to clarify the causal nature of this association. It is also important do consider the potential role of medications in association of BD and medical comorbidity. All patients were receiving pharmacological treatment, and we did not find any association, but it may be due to a relatively small sample size. However, our findings may be even more significant if we consider that most patients had several years of illness, consisting in a sample of late-stage bipolar disorder.

Medical comorbidity may be seen as a correlate of illness severity in BD and must be included in patients' global assessment. The notion of disease staging in which more complex patients (e.g.: highly relapsing, comorbid and with longer illness duration) are considered in a later stage of progression is already established in general medicine and is gaining popularity in psychiatry (Salagre et al, 2018). Our finding that patients with longer duration of illness have a higher rate of chronic medical comorbidities corroborates the necessity of a chronic care model for the adequate management of BD. These models of treatment have been suggested as a new paradigm in the treatment of mood disorders and include physical health as a core feature (Kilbourne et al, 2009; Miller et al, 2013) since effectiveness in remission of both psychiatric symptoms and stabilization of medical problems are essential for the successful treatment of bipolar disorder.

Author's Statement

Fabiano A. Gomes, Mauricio Kunz, Pedro V. Magalhães and Flavio Kapczinski designed and conducted the study. Fabiano A. Gomes and Pedro V. Magalhães analyzed the data and wrote the manuscript with support from Taylor Magee, Elisa Brietzke, Maurício Kunz and Flávio Kapczinski. All authors reviewed the manuscript.

Declaration of cmpeting Interest

None.

Acknowledgements

Funding for this study was provided partly by CNPq and by FIPE-HCPA, Brazil; the CNPq and FIPE-HCPA had no further role in the study design, collection, analysis, or interpretation of data, writing of the report, or decision to submit the paper for publication.

References

Berk, M, Kapczinski, F, Andreazza, AC, Dean, OM, Giorlando, F, Maes, M, Yücel, M, Gama, CS, Dodd, S, Dean, B, Magalhães, PV, Amminger, P, McGorry, P, Malhi, GS, 2011. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 35, 804–817.

Brietzke, E, Mansur, RB, McIntyre, RS, 2017. Impact of inequalities in health care on the mortality risk of individuals with severe mental illnesses. Braz J Psychiatry 39, 193–194.

Gazalle, FK, Andreazza, AC, Ceresér, KM, Hallal, PC, Santin, A, Kapczinski, F, 2005. Clinical impact of late diagnose of bipolar disorder. J Affect Disord 86, 313–316.

Gildengers, AG, Whyte, EM, Drayer, RA, Soreca, I, Fagiolini, A, Kilbourne, AM, Houck, PR, 3rd, Reynolds CF, Frank, E, Kupfer, DJ, Mulsant, BH, 2008. Medical burden in late-life bipolar and major depressive disorders. Am J Geriatr Psychiatry 16, 194–200.

Grande, I, Magalhães, PV, Kunz, M, Vieta, E, Kapczinski, F, 2012. Mediators of allostasis and systemic toxicity in bipolar disorder. Physiol Behav 106, 46–50.

Grande, I, Berk, M, Birmaher, B, Vieta, E, 2016. Bipolar disorder. Lancet 387, 1561–1572.
Iosifescu, DV, Nierenberg, AA, Alpert, JE, Papakostas, GI, Perlis, RH, Sonawalla, S, Fava, M, 2004. Comorbid medical illness and relapse of major depressive disorder in the continuation phase of treatment. Psychosomatics 45, 419–425.
Kapczinski, NS, Mwangi, B, Cassidy, RM, Librenza-Garcia, L, Bermudez, MB, Kauer-Sant'anna, Kapczinski F, Passos, IC, 2017. Neuroprogression and illness trajectories in bipolar disorder. Expert Rev Neurother 17, 277-285.
Kemp, DE, Gao, K, Ganocy, SJ, Caldes, E, Feldman, K, Chan, PK, Conroy, C, Bilali, S, Findling, RL, Calabrese, JR, 2009. Medical and substance use comorbidity in bipolar disorder. J Affect Disord 116, 64–69.
Kemp, DE, Gao, K, Chan, PK, Ganocy, SJ, Findling, RL, Calabrese, JR, 2010. Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. Bipolar Disord 12, 404–413.
Kilbourne, AM, Biswas, K, Pirraglia, PA, Sajatovic, M, Williford, WO, Bauer, MS, 2009. Is the collaborative chronic care model effective for patients with bipolar disorder and co-occurring conditions? J Affect Disord 112, 256–261.
Kupfer, DJ, Frank, E, Ritchey, FC, 2015. Staging bipolar disorder: what data and what models are needed? Lancet Psychiatry 2, 564-70.
Li, C, Birmaher, B, Rooks, B, Gill, MK, Hower, H, Axelson, DA, Dickstein, DP, Goldstein, TR, Liao, F, Yen, S, Hunt, J, Iyengar, S, Ryan, ND, Strober, MA, Keller, MB, Goldstein, BI, 2019. High Prevalence of Metabolic Syndrome Among Adolescents and Young Adults With Bipolar Disorder. J Clin Psychiatry 80, 18m12422.
Lin, K, Shao, R, Wang, R, Lu, W, Zou, W, Chen, K, Gao, Y, Brietzke, E, McIntyre, RS, Mansur, RB, Zhang, L, Yau, SY, Su, H, Xu, G, So, KF, 2020. Inflammation, brain structure and cognition interrelations among individuals with differential risks for bipolar disorder. Brain Behav Immun 83, 192–199.
Linn, BS, Linn, MW, Gurel, L, 1968. Cummulative illness rating scale. J Am Geriatr Soc 16, 622–626.
Magalhães, PV, Kapczinski, F, Nierenberg, AA, Deckersbach, T, Weisinger, D, Dodd, S, Berk, M, 2012. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand 125, 303–308.
Mansur, RB, Cha, DS, Asevedo, E, McIntyre, RS, Brietzke, E, 2013. Selfish brain and neuroprogression in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 43, 66–71.
Mansur, RB, Brietzke, E, McIntyre, RS, 2015. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. Neurosci Biobehav Rev 52, 89–104.
Miller, CJ, Grogan-Kaylor, A, Perron, BE, Kilbourne, AM, Woltmann, E, Bauer, MS, 2013. Collaborative chronic care models for mental health conditions: cumulative meta–analysis and metaregression to guide future research and implementation. Med Care 51, 922-30.
Miller, MD, Paradis, CF, Houck, PR, Mazumdar, S, Stack, JA, Rifai, AH, Mulsant, B, 3rd, Reynolds CF, 1992. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res 41, 237–248.
Mistry, R, Gokhman, I, Bastani, R, Gould, R, Jimenez, E, Maxwell, A, McDermott, C, Rosansky, J, Van Stone, W, Jarvik, L, Collaborative Group, UPBEAT, 2004. Measuring medical burden using CIRS in older veterans enrolled in UPBEAT, a psychogeriatric treatment program: a pilot study. J Gerontol A Biol Sci Med Sci 59, 1068–1075.
Salagre, E, Dodd, S, Aedo, A, Rosa, A, Amoretti, S, Pinzon, J, Reinares, M, Berk, M, Kapczinski, FP, Vieta, E, Grande, I, 2018. Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0. Front Psychiatry 9, 641.
Sinha, A, Shariq, A, Said, K, Sharma, A, Jeffrey Newport, D, Salloum, IM, 2018. Medical Comorbidities in Bipolar Disorder. Curr Psychiatry Rep 20, 36.
Soreca, I, Fagiolini, A, Frank, E, Houck, PR, Thompson, WK, Kupfer, DJ, 2008. Relationship of general medical burden, duration of illness and age in patients with bipolar I disorder. J Psychiatr Res 42, 956–961.
Thompson, WK, Kupfer, DJ, Fagiolini, A, Scott, JA, Frank, E, 2006. Prevalence and clinical correlates of medical comorbidities in patients with bipolar I disorder: analysis of acute-phase data from a randomized controlled trial. J Clin Psychiatry 67, 783–788.
World Health Organization, 1997. Obesity: Preventing and Managing the Global Epidemic. Publication WHO/NUT/NCS/98.1. World Health Organization, Geneva, Switzerland.