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# General Medical Conditions Are Associated With Delay to Treatment in Patients with Bipolar Disorder

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## Abstract

### Background

Bipolar disorder (BPD) is associated with worse physical health. Indeed patients with BPD more frequently suffer from medical conditions such as cardiovascular illness, hypertension, diabetes, hypothyroidism, respiratory disease, liver disease, peptic ulcer, and arthritis. Since some clinical characteristics have been associated with worse course and outcome of BPD, it is possible that they might also bring to an increased medical burden in patients with BPD. The aim of the present report is to assess the prevalence of medical conditions in patients with BPD, and to determine the clinical variables associated with the presence of a medical condition.

### Methods

Charts of patients with BPD I and II were reviewed: socio-demographic and clinical information were collected. Medical conditions were classified by the ICD-10 and grouped according to the Cumulative Illness Rating Scales in: cardiac, vascular, hematopoietic, respiratory, ear/nose/throat, upper and lower gastrointestinal, hepatic, renal, genitourinary, musculoskeletal, neurologic, endocrine/metabolic. The associations between the presence of medical conditions and demographic/clinical variables of BPD were then analyzed.

### Results

Charts of 309 patients were included in the study. 170 (55%) patients had at least one medical condition. The most common were endocrine/metabolic disease (23%), and vascular disease (21%). Having a medical condition was associated with longer duration of untreated illness and female gender.

### Conclusions

Patients with BPD have high rates of medical conditions, especially hypertension and metabolic disorders. A longer duration of untreated illness is associated with having a medical condition, probably due to the long-lasting adoption on unhealthy lifestyles not counterbalanced by treatment and psychoeducation.

## Keywords

Bipolar disorder

general medical conditions

cardiovascular disease

duration of untreated illness

## Introduction

Bipolar disorder (BPD) is a chronic mental illness that has been associated with significant disability, low levels of educational attainment, unemployment, and extensive utilization of health care services.

A growing body of evidence demonstrates that people with BPD also display worse physical health and a reduction in life expectancy of approximately 30% compared with the general population.<sup>1-3</sup>

Several studies have evaluated the prevalence of general medical conditions (GMC) in patients with BPD, finding that these patients more frequently suffer from medical conditions (such as cardiovascular illness, hypertension, diabetes, hypothyroidism, respiratory disease, liver disease, peptic ulcer, and arthritis).<sup>4-8</sup> Few studies have reported how the presence of medical conditions adversely affects the course of BPD. For example, Ruzickova and colleagues<sup>9</sup> found that patients with BPD and diabetes were more chronically ill, had rapid cycling course, and had lower global functioning. In other studies, obese patients with BPD had more and also more severe mood episodes, treatment resistance, and lifetime suicide attempts.<sup>10,11</sup> A recent report found that a higher medical burden was associated with a diagnosis of BPD and a history of attempted suicide.<sup>12</sup>

Several reports also highlighted that an earlier age at onset, a higher duration of illness, and a longer duration of untreated illness predicted a worse course of BPD as defined by more manic and depressive episodes, a higher proportion of rapid cyclers, substance abuse, and more suicide attempts.<sup>13-19</sup> However, patients with these characteristics may be more at risk to develop unhealthy lifestyles (such as poor diet, sedentary life), and reduced access to care that may eventually determine the occurrence of medical conditions. If this statement proves true, a longer duration of illness and of untreated illness might also predict a worse general health in terms of increased medical burden.

The aim of the present report is to assess the prevalence of GMC in patients with BPD, and to determine the clinical variables associated with the presence of a GMC, which have been understudied in past research but may help in the early recognition of patients at risk for medical comorbidity. In particular, we hypothesize that the presence of a GMC might be correlated with a longer duration of illness and duration of untreated illness.

## Method

The study had a naturalistic design and involved patients consecutively admitted to the Psychiatric Inpatient Unit and to the Mood and Anxiety Disorders Outpatient Unit of the University of Turin, Italy, from April 2003 to October 2011. Chart Of patients with a diagnosis of BPD type I and II (DSM-IV) were reviewed. Patients had the aims and study procedures explained and had to give their written consent to disclose data from their clinical charts. Exclusion criteria included age  $\leq 18$  years, and refusal to consent to participation in the study. All subjects were of Caucasian Italian origin.

## Assessments and Procedures

All diagnoses were confirmed by means of the Structured Clinical Interview for DSM Axis I Disorders (SCID-I).<sup>20</sup> At the time of assessment, general sociodemographic and clinical information were collected for each subject.

The presence of GMC was also investigated. A trained physician reviewed the charts of all patients included in the present report, classified the illnesses according to ICD-10 diagnoses, and grouped them according to the Cumulative Illness Rating Scales (CIRS)<sup>21</sup> as follows: cardiac, vascular, hematopoietic, respiratory, ear/nose/throat, upper and lower gastrointestinal, hepatic, renal, genitourinary, musculoskeletal, neurologic, and endocrine/metabolic. Although the scale was originally meant by the authors to be completed during clinical assessment, other studies have used the CIRS based on chart reviews, showing good reliability.<sup>22,23</sup>

## Statistical Analysis

The demographic variables analyzed in this study included gender, age, and marital status. The clinical variables included age at onset, duration of illness, duration of untreated illness (DUI), defined as time from onset of the disorder to first correct treatment received, psychiatric comorbidity (Axis I and II), presence of any lifetime suicide attempt, number of lifetime suicide attempts, age at first suicide attempt, and family history of psychiatric disorders. Demographic and clinical measures were summarized as means and standard deviations or percentages. GMCs according to CIRS systems were summarized as percentages.

The associations between the presence of a GMC and the demographic and clinical variables of BPD were analyzed using  $\chi^2$  tests for categorical variables and *t*-tests for continuous variables. Subsequently, we performed a logistic regression with presence of a GMC serving as the primary dependent variable, and the previously found significantly associated variables as the independent variables.

## Results

We assessed the clinical charts of 429 patients with BPD. Of these, 87 lacked medical comorbidity information, and 33 patients could not give their consent either because they could not be contacted or because they refused to disclose the information in their charts; 309 clinical charts had complete information and were thus utilized for the present study.

Patients had a mean age of  $52.2 \pm 15.3$  years; 195 (63.1%) were females. Mean age at onset of first mood episode was  $30.5 \pm 12.1$  years, with a mean duration of illness of  $21.7 \pm 14.1$  years. Mean age at first contact with a mental health professional was  $39.3 \pm 15.4$  years, whereas age at the correct diagnosis and treatment was  $44.6 \pm 15.8$  years; the mean DUI was  $14.1 \pm 13.7$  years. All sociodemographic and clinical variables are reported in Table 1.

A total of 170 (55%) patients had at least one comorbid GMC. The most common medical conditions were endocrine/metabolic disease (23%, of which 64% was metabolic syndrome), and vascular disease (21%, of which 92% was hypertension). All medical conditions according to CIRS systems are presented in Table 2.

When we correlated the presence of at least one GMC with clinical variables such as gender, age, diagnosis (type I or II), age at onset, duration of illness, and DUI. Patients with a GMC were more frequently females (63.6% vs. 40.4%), were older (56.2 vs. 42.3 years), had a later age at onset (32.4 vs. 28.2 years), higher DUI (18.1 vs. 9.3 years), and had attempted suicide at least once in their lifetime (18.1% vs. 10.1%) (Table 3). When

we entered the significant variables in a stepwise logistic regression model with the presence/absence of GMC as the dependent variable, we found only female gender and DUI remained as significant predictors of GMC (Table 4).

## Discussion

Fifty-five percent of our sample was affected by at least one GMC. Studies evaluating medical comorbidity in patients with BPD showed great variability, with figures of prevalence of having at least one medical condition ranging from 23% to 100%. This variability is likely due to difference in study design; for example, the low 23% reported in the Kilbourne et al. study<sup>24</sup> might be explained by the source data coming from administrative datasets and not from direct assessment or chart review. On the other hand, the 100% prevalence of any GMC reported by Kemp and colleagues<sup>12</sup> is likely related with the selection of a very severe group of patients with rapid cycling and comorbid substance use disorders. Our result correlates with the STEP-BD study, where 58% of respondents had at least one GMC<sup>24</sup>; both studies have ascertained medical comorbidity by reviewing clinical charts of patients with BPD naturalistically recruited in a clinical setting.

The most prevalent medical conditions in our sample were endocrine/metabolic disorders and vascular disorders, in particular hypertension, with 23% and 21% prevalence rates, respectively. Our results are in line with the studies investigating medical burden in patients with BPD, with rates of endocrine/metabolic disorders ranging from 23% to 50%,<sup>4,23</sup> and rates of hypertension and vascular disorders ranging from 18 to 47%.<sup>5,23</sup> Although we could not perform any direct comparison, these figures of prevalence are clearly higher than what has been observed in the Italian general population, where prevalence rates of endocrine/metabolic disorders and hypertension are 10% and 16%, respectively (ISTAT, 2005).

The prevalence of metabolic disorders (such as diabetes or hyperlipidemia) and hypertension is consistently higher in patients with BPD than in the general population. Patients with BPD exhibit at-risk behaviors (such as unhealthy diet, limited physical exercise, poorer self-care), and reduced access to healthcare, particularly during depressive episodes. Moreover, patients with BPD are often exposed to medications (such as antipsychotics or mood stabilizers) for a lifetime; these treatments may contribute to the development of obesity, metabolic syndrome, and eventually cardiovascular illness and diabetes.<sup>25,26</sup> Furthermore, the characteristic fluctuating course with the disruption of circadian rhythms might lead to the vulnerability to medical disorders. Pathways of illness found to be altered in patients with BPD, such as oxidative stress, inflammation, or HPA axis dysregulation, might also contribute to mediate the development of medical disorders (such as cardiovascular disease, diabetes, and osteoporosis).<sup>24</sup>

Only 3% in our sample had hepatic disease vs. the 6%–17% reported in similar studies.<sup>4,12,23</sup> The most reported hepatic disease was alcoholic hepatitis or viral hepatitis B or C, typically caused by drug intravenous administration; high rates of these disorders have indeed been found in patients with BPD and with comorbid substance use disorders.<sup>12,27,28</sup> The most likely explanation of this discrepancy, then, is the low comorbidity with alcohol or substance use disorders in our sample (10%) compared with the US samples (25%–63%).

The fact that subjects with BPD had a rate of respiratory disease as low as 3% was unexpected; patients with BPD usually smoke more than those in the general population,<sup>29</sup> and rates of respiratory disease around 10%–13% have been reported in previous studies.<sup>4,5,30</sup> However, this is difficult to ascertain since cigarette smoking was properly assessed only in a minority of our sample. Clearly, this finding should be confirmed in future research.

The impact of medical comorbidity associated with BPD is intuitively relevant for reasons such as a worsened quality of life, higher utilization of medical services, and mortality. However, the very few studies that tried to define the clinical features associated with comorbid medical conditions found that patients with BPD and a GMC also exhibited worse mental and social functioning<sup>6</sup> or suicide attempts<sup>12</sup> than patients without a GMC. Among the clinical characteristics more strongly associated with having at least one GMC, we also found advancing age and lifetime suicide attempts; however, with the help of the logistic regression we found that these characteristics were mediated by a longer duration of untreated illness. Although this issue has been adequately studied in patients with schizophrenia, only three studies have recently examined the impact of DUI on the outcome of BPD. Goldberg and Ernst pointed out that delay to correct treatment was associated with higher risk for suicide attempts;<sup>13</sup> Altamura and colleagues have highlighted that a longer DUI predicts more depressive episodes, a higher number of hospitalizations, a rapid cycling course, and lifetime suicide attempts.<sup>16</sup> Drancourt and colleagues also found that an extended DUI was associated with more suicide attempts and mood episodes in a large sample of 501 patients with BPD.<sup>19</sup> Nevertheless, this is the first study to find an association between DUI and medical conditions in patients with BPD, confirming the previous observations of worse outcome in bipolar patients with a longer DUI.

The etiology of the association between longer DUI and increased medical burden might be explained by several factors. It may be hypothesized that patients who have been undertreated for years are keener to adopt unhealthy lifestyles (such as poor diet, sedentary life, cigarette smoking), and reduced access to care, which may heighten the risk to develop medical conditions, especially endocrine and cardiovascular conditions. As a further explanation, more severely ill patients display higher levels of stress, and this might eventually lead to an increase in cortisol levels, thus leading to poor glucose tolerance, diabetes, and hypertension. Other hypotheses may involve brain-derived neurotrophic factor (BDNF) levels as the bridging element: a longer duration of untreated illness has been associated with low BDNF levels in patients with schizophrenia.<sup>31</sup> On the other hand, low BDNF levels have been associated with increased prevalence of type II diabetes.<sup>32</sup> Clearly, these hypotheses deserve proper investigation in patients with BPD.

The relationship between GMCs and the severity of BPD is likely bidirectional: on one hand, having a chronic illness may lead to depressed mood and perhaps destabilization of BPD *via* psychological and physiological factors; on the other hand, having a severe, poorly-controlled mental disorder might bring about the adoption of unhealthy lifestyles and a reduced access to healthcare, eventually leading to increased incidence of disease. Our study has a relevant clinical implication. Since the risk of medical illness (especially vascular and metabolic illness) seems to increase with a longer DUI, an early diagnosis and eventually treatment is further needed in order to prevent the development of adverse medical outcomes.

A point of strength in our study is that medical diagnoses do not rely merely on administrative claims like previous reports.<sup>4,5,30</sup> Instead, they were collected by looking at clinical charts filled in by hospital physicians. Some limitations must also be acknowledged. The fact that data were completed retrospectively may account for the loss of some important information compared with the direct interview methodology. Nonetheless, this method has previously been adopted in similar studies<sup>12,23</sup> and has shown a good reliability.<sup>22</sup> Another limitation is the lack of a control group from the general population. However, our objective was to look for significant correlations between the presence of GMCs and clinical variables, and for such an aim, a control group was not needed.

In conclusion, we confirmed significant chronic medical comorbidity in patients with BPD, especially conditions previously described, such as endocrine/metabolic disease and hypertension. Given the strong association with DUI, we further strive for improving the early diagnosis of BPD in order to avoid not only psychiatric but also general medical complications in later years.

Our results further stress the importance of thorough assessment of medical conditions in BPD, in particular endocrine/metabolic and vascular illness. A better dissemination of integrated medical and psychiatric care might help accomplishing secondary prevention of potentially severe medical conditions, possibly increasing the expectancy of life in patients with BPD.

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