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Research report

General medical conditions in 347 bipolar disorder patients: Clinical correlates of metabolic and autoimmune-allergic diseases

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ABSTRACT

Background: Patients with bipolar disorder (BD) suffer from greater physical morbidity and mortality than the general population. The aim of the present study is to explore the prevalence and clinical correlates of General Medical Conditions (GMC) in a large consecutive sample of patients with BD.
Method: The study sample comprised of 347 patients who met *DSM-IV*-TR criteria for BD I ($n=207$, 59.7%), BD II or Cyclothymic Disorder ($n=140$, 40.3). Diagnostic information was collected by means of the Structured Clinical Interview for DSM-IV Axis I Disorders– *Clinical Version* (SCID-I), and information about personal and family history were collected by the Semi-Structured Interview for Mood Disorder-Revised (SIMD-R). Standardized procedure was used to assess the diagnosis of GMC, which was considered present only if a specific therapy to treat the condition was prescribed by a specialist or a general practitioner. In order to explore possible relationships between physical comorbidity and clinical features of BD, we compared patients with (MD) and without (No-MD) Metabolic Diseases (MD) and patients with (AAD) and without (No-AAD) Autoimmune-Allergic Diseases (AAD).
Results: The most commonly reported GMCs were: Headache, Hypercholesterolemia (> 200 mg/dl), Chronic Constipation, Obesity, Arterial Hypertension (BP > 140/90 mmHg), Hypothyroidism, Allergic Rhino-Conjunctivitis, Irritable Bowel Syndrome, Hypertriglyceridemia (> 150 mg/dl), Metabolic Syndrome, Hiatus Hernia, Dysmenorrhea, Urticaria, Atopic Dermatitis, Psoriasis, Seborrheic Dermatitis, Diabetes Mellitus, Bronchial Asthma, Cardiac Arrhythmias, Biliary Lithiasis, and COPD. In our sample, MD ($n=148$, 42.7%) and AAD ($n=167$, 48.1%) were the most common categories of GMCs. Interestingly, the lifetime prevalence of cancer and neoplastic diseases was very low: 1 patient (.3%) reported Lung Adenocarcinoma and 2 (.6%) patients Bowel Cancer. In the group comparisons, length of pharmacological treatment (OR=1.054; 95% CI=1.030–1.078), age at onset of first major episode (OR=1.043; 95% CI=1.019–1.067), length of the current episode (OR=1.025; 95% CI=1.020–1.533) and absence of lifetime comorbid substance abuse (OR=.373; 95% CI=.141–.989) were statistically associated with the presence of comorbid MD; while only AD-induced hypomania (OR=1.62; 95% CI=1.011–2.597), and cyclothymic temperament (OR=1.051; 95% CI=1.016–1.087) were statistically associated with the presence of comorbid AAD.
Limitations: Possible referral and selection bias; retrospective, non-blind, cross-sectional evaluation.
Conclusion: MD and AAD were highly represented in our sample, while cancer and neoplastic diseases were uncommon. The clinical correlates of different sub-groups of GMC suggest different interpretations. The presence of MD seems to be correlated with the progression of BD and the chronic medication exposure, while comorbid AAD seems to correlate with a specific clinical subtype of BD, characterized by mood reactivity and temperamental mood instability. If the link with autoimmune-allergic diathesis will be confirmed, it could provide an interesting new paradigm for the study of the "systemic" nature of mood disorders and a promising target for future treatment options.

1. Introduction

Patients with bipolar disorder (BD) were reported to present higher physical morbidity and mortality than the general population (McIntyre et al., 2006). The relationship between affective

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disorders and General Medical Conditions (GMC) is bidirectional: many chronic physical illnesses are associated with mood disorders and, on the other hand, affective symptoms forerun many chronic diseases and worsen/impact their outcome (Kisely and Goldberg, 1993; Kupfer, 2005).

BD is associated with a large number of GMC which includes illnesses affecting cardiovascular (e.g. hypertension, heart disease, stroke), metabolic and endocrine (e.g. diabetes, Metabolic Syndrome), respiratory (e.g. asthma, chronic obstructive pulmonary disease), gastrointestinal (e.g. peptic ulcer, liver disease, inflammatory bowel diseases) system, nephropathies, cancer, rheumatoid arthritis, migraine, HIV/AIDS, psoriasis, etc. (Cassidy et al., 1999; Kemp et al., 2010; Kilbourne et al., 2004) (Cruess et al., 2003; Sokal et al., 2004).

It is unclear whether GMCs among individuals with BD is a comorbidity, a consequence of treatment, or a combination of both (Krishnan, 2005). The association between affective disorders and high prevalence of physical morbidity and mortality can be partially explained by unhealthy behaviors (e.g. smoking, physical inactivity, poor diet), psychosocial functioning and chronic medication exposure (Kupfer, 2005; Leboyer et al., 2012). However, the association remains significant after controlling for the above mentioned confounding factors, which suggests additional and specific mechanisms (Goldstein et al., 2009; Leboyer et al., 2012).

Over the last decades, a growing body of evidence suggests that inflammation may be implicated in the pathophysiology of BD, and represents the link with physical illness (e.g. cardiovascular disease) (Goldstein et al., 2009; Grande et al., 2012; Krishnadas and Cavanagh, 2012; Leboyer et al., 2012). A number of inflammatory markers, such as cytokines, chemokines and acute phase reactant proteins (i.e. C reactive protein, tumour necrosis factor α, interleukin (IL)-6, IL-1, IL-2, IL-4) have been found to be higher in patients with BD than in controls (Hope et al., 2010, 2009; Kim et al., 2007; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007). These inflammatory markers have been detected in patients with BD even in the absence of a comorbid medical condition (Dowlati et al., 2010; Krishnadas and Cavanagh, 2012; Leboyer et al., 2012).

The concept of "allostatic load" has been introduced in order to explain the possible relationship between inflammation and physical and mental illness (Kapczinski et al., 2008), as well as some of their complications. Allostatic load refers to the "cost of chronic exposure to fluctuating or heightened neural or neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful" (McEwen and Stellar, 1993). Allostatic load is associated with oxidative and nitrosative stress, mitochondrial dysfunction, inflammation and lowering of neuroprotective factors, which relates to impaired immunity, atherosclerosis, apoptosis and atrophy of nerve cells in the brain (Grande et al., 2012; Leboyer et al., 2012). Clinically, allostatic load has been correlated with progression of the illness and cognitive decline (Vieta et al., 2013). In fact, preliminary research suggests a correlation between measures of cumulative illness burden, such as a greater chronicity and a higher number of episodes, with the high medical comorbidity in BD (Kapczinski et al., 2008; Vieta et al., 2013).

However, this may not be the whole story. Recent research on inflammation and autoimmune disorders provides additional links between systemic and central nervous system pathophysiology (Rege and Hodgkinson, 2013). Neuroinflammation and peripheral immune dysregulation may play a role in the pathophysiology of BD. This involves a complex interaction between immune cells of the central nervous system and periphery resulting in cellular damage through mechanisms involving excitotoxicity, oxidative stress, and mitochondrial dysfunction (Rege and Hodgkinson, 2013). These pathways are possibly shared between comorbid medical disorders and BD and may reflect common underlying vulnerabilities.

While it is known that the presence of the comorbidities affects the course and severity of BD and its treatment (Black et al., 1989, 1988a, 1988b), only a few studies have systematically examined medical comorbidities in clinical samples, or what impact these problems may have on patient's clinical presentation or course of illness. The aim of the present study is to explore the prevalence and clinical correlates of GMCs in a large consecutive sample of patients with BD.

2. Methods

The study sample was composed of 347 subjects who met *DSM-IV*-TR criteria for Bipolar I ($n=207$, 59.7%), Bipolar II or Cyclothymic Disorder ($n=140$, 40.3%), referred to the outpatient ($n=123$, 35.4%) and inpatient ($n=224$, 64.6%) units of the Department of Psychiatry at the University of Pisa. The mean age was 47.7 (SD=14.3) years, 129 (37.2%) were males and 218 (62.8%) were females. Patients were consecutively included regardless of previous hospitalizations, prior treatment with antidepressants, antipsychotics or mood stabilizers. Subjects, who presented affective symptoms clearly secondary to substance misuse or to general medical condition, were excluded. Each subject was informed about the study procedures and provided written informed consent. The study was approved by the local Ethic Committee.

A face-to-face interview composed of structured and semi-structured parts was used to collect clinical data. The interview lasted for approximately two hours. The interviews were conducted by residents in psychiatry with at least 3 years of post-graduation experience in the diagnosis and treatment of mood disorders. Each interviewer underwent a training program in the use of the interview instruments that included direct observation of experienced interviewers, direct supervision of interviews and inter-rater reliability. Data collection was largely dependent on patient recall of historical information, all clinical variables were reviewed by the senior author (GP) team, with the purpose of consensus agreement. When necessary, patients were re-contacted for further clarification, patients' medical records were reviewed and eventual missing information was obtained from family members and/or previous treating physicians.

Diagnostic information was collected by the means of Structured Clinical Interview for DSM-IV Axis I Disorders– *Clinical Version* (SCID-I) (First et al., 1996). Information about personal and family history was collected by the Semi-Structured Interview for Mood Disorder-Revised (SIMD-R). The instrument systematically explores demographic, anamnestic and clinical information and explores history of previous depressive, hypomanic, manic or mixed episodes, temperamental characteristics and first degree family history for mood and anxiety disorders, schizophrenia, as well as for drug and alcohol abuse. Family history data were collected using the family history method of the Research Diagnostic Criteria, (Andreasen et al., 1977). The SIMD-R was developed as a part of the Pisa-San Diego Collaborative Study on Affective Disorders; in its last version it represents an updated revision of the Structured Interview for Depression (Perugi et al., 2001). Validity and reliability have been examined and discussed in numerous studies, showing a high relevant level (Cassano et al., 1989). Current clinical severity of the affective illness, global functioning and symptomatology were assessed respectively by means of the Clinical Global Impression scale (CGI) (Beneke and Rasmus, 1992), the Global Assessment of Functioning scale (GAF) (Endicott et al., 1976) and the Brief Psychiatric Rating Scale (BPRS), 18 items version (Overall and Gorham, 1962). The affective temperament evaluation was performed by a Brief 35-items Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Modified self-rating scale (Brief-TEMPS-35) (Erfurth et al., 2005).