Journal of Affective Disorders 170 (2015) 95–103

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

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

Giulio Perugi [a,b,*], Giuseppe Quaranta [a], Serena Belletti [a], Francesca Casalini [a], Nicola Mosti [a], Cristina Toni [b], Liliana Dell'Osso [a]

[a] Department of Clinical and Experimental Medicine, Clinica Psichiatrica Università di Pisa, Via Roma, 67, Pisa 56126, Italy
[b] Institute of Behavioural Sciences "G. De Lisio", Pisa, Italy

ARTICLE INFO

Article history:
Received 13 June 2014
Accepted 29 August 2014
Available online 6 September 2014

Keywords:
Bipolar disorder
General medical conditions
Metabolic disorders
Autoimmunity

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.
© 2014 Elsevier B.V. All rights reserved.

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

* Corresponding author at: Department of Clinical and Experimental Medicine, Clinica Psichiatrica Università di Pisa, Via Roma, 67, Pisa 56126, Italy.
Tel.: +39 50 835414; fax: +39 50 21581.
E-mail address: giulio.perugi@med.unipi.it (G. Perugi).

http://dx.doi.org/10.1016/j.jad.2014.08.052
0165-0327/© 2014 Elsevier B.V. All rights reserved.

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).

Finally, in order to assess the presence of GMC a standardized procedure was utilized. The diagnosis of GMC was recorded only if formulated by a specialist or by a general practitioner, in the case the latter prescribed a treatment for the condition. Except for the registration of any medical comorbidity, the priority of the onset of any physical illness over the beginning of the psychopharmacological treatment was registered, as well as the presence of the disease in first-degree relatives. In particular, the following conditions were systematically investigated: *Systemic Lupus Erythematosus*, *Rheumatoid Arthritis*, *Sjögren's Syndrome*, *Vasculitis*, *Fibromyalgia*, *Psoriasis*, *Vitiligo*, *Alopecia Areata*, *Seborrheic Dermatitis*, *Hyperthyroidism*, *Hypothyroidism*, *Hashimoto's Thyroiditis*, *Subacute Thyroiditis*, *Grave's Disease*, *Diabetes Mellitus*, *Obesity*, *Hypertension* ($PA_{sist} > 140$ mmHg/PAdiast > 90 mmHg), *Hypercholesterolemia (total cholesterol > 200 mg/dl), Hypertriglyceridemia (triglycerids > 150 mg/dl), Metabolic Syndrome, Stroke, Cerebral Hemorrhage, Multiple Sclerosis, Alzheimer's Disease, Pick's Disease, Parkinson's Disease, Huntington's Disease, Amyotrophic Lateral Sclerosis, Cephalea, Myocardial Infarction, Angina Pectoris, Cardiac Arrhythmias, Mitral Valve Prolapse, Heart Failure, Chronic Obstructive, Pulmonary Diseases (COPD), Pulmonary Fibrosis, Chronic Pulmonary Edema, Pulmonary Embolism, Kidney Disease, Asthma, Urticaria, Allergic Rhino-Conjunctivitis, Atopic Dermatitis, Blood Disorders, Irritable Bowel Syndrome, Meteorism, Chronic Constipation, Hiatal Hernia, IBD (Inflammatory Bowel Disease), Vaginismus, Dyspareunia, Post-coital Headache, Dysmenorrhea, and PCOS (Polycystic Ovary Syndrome).*

Finally a trained physician (S.B.) reviewed the charts of all patients included in the present report and assigned a score on a Cumulative Illness Rating Scale (CIRS). The CIRS is an instrument originally developed to assess chronic medical burden in adults (Linn et al., 1968) and geriatric populations (Miller et al., 1992). Many studies have confirmed good criterion validity (Conwell et al., 1993), good concurrent validity (Miller et al., 1992), and good inter-rater reliability (Hudon et al., 2005). Although the scale was meant by the authors to be completed during clinical assessment, many studies have used CIRS scores based on chart reviews (Hudon et al., 2005). This method has shown good reliability and offers some practical advantages (Hudon et al., 2005). The CIRS is structured in 13 organ systems (we excluded psychiatric rating, which was assessed with more specific instruments) and rates the severity for each system on a 5 point Likert-type scale, ranging from 0 = no impairment to 4 = life-threatening. The scale computes a Total Score as the sum of ratings across the 13 categories and a Severity Index, which is computed by dividing the Total Score by the number of categories endorsed. Further severity indices, according to the CIRS scale scoring guideline, are the number of categories endorsed and the number of categories scored at level 3. Since all the scores were assigned by the same rater (S.B.), we did not calculate inter-rater reliability.

2.1. Statistical analysis

The prevalence of GMC was assessed in the entire sample; frequency estimates were determined with 95% confidence limits. Comparative analyses were conducted by means of chi-square test for categorical variables, while dimensional variables were compared using the Student's *t*-test. Significance was set at a Bonferroni's corrected level of $p < .0013$, however, given the exploratory nature of this study, we decided to comment also differences at $p < .05$ level (two tailed). A stepwise backward logistic regression model was then used to identify the predictive value of the clinical characteristics of BD on the different subtypes of GMC. An alpha of .05 in the univariate comparison was utilized as the cutoff for the inclusion of a variable in the regression model. The stepwise modeling procedure started with the full model and consisted, for each step, of eliminating the least statistically significant variable from the model and re-computing the revised model, until all remaining variables were at $p < .1$. Odds ratios with 95% confidence intervals were used for observed associations. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, 20.0 version for MAC).

3. Results

Lifetime prevalence and confidence interval of GMCs observed in our sample are reported in Table 1. The most common conditions (more than 5% of the cases) were: Headache, Hypercholesterolemia (> 200 mg/dl), Chronic Constipation, Obesity, AH (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.

Table 1
Prevalence of General Medical Conditions (GMC) in 347 Bipolar patients.

GMC	*no.*	%	CI-95%
Headache	108	31.1	26.5–36.0
Hypercholesterolemia (> 200 mg/dl)	92	26.5	21.9–30.8
Chronic Constipation	85	24.5	20.5–29.4
Obesity	82	23.6	19.0–28.0
AH (BP > 140/90 mmHg)	69	19.9	15.9–23.9
Hypothyroidism	66	19.0	15.0–23.3
Allergic Rhino-Conjunctivitis	62	17.9	13.8–21.9
Irritable Bowel Syndrome	57	16.4	12.7–20.5
Hypertriglyceridemia (> 150 mg/dl)	49	14.1	10.7–17.9
Metabolic Syndrome	49	14.1	10.7–17.6
Hiatus Hernia	45	13.0	9.5–16.4
Dysmenorrhea	37	10.7	7.5–14.1
Urticaria	32	9.2	6.3–12.1
Atopic Dermatitis	32	9.2	6.3–12.4
Psoriasis	31	8.9	5.8–12.1
Seborrheic Dermatitis	30	8.6	5.8–11.8
Diabetes Mellitus	30	8.6	5.8–12.1
Bronchial Asthma	30	8.6	6.1–11.5
Cardiac Arrhythmias	23	6.6	4.0–9.2
Biliary Lithiasis	21	6.1	3.7–8.9
COPD	19	5.5	3.5–7.8
Fibromyalgia	17	4.9	2.9–7.2
Hashimoto's Thyroiditis	13	3.7	1.7–5.8
Arthrosis	11	3.2	1.4–5.2
Urolithiasis	11	3.2	1.4–5.2
Hepatitis	11	3.2	1.4–5.2
Alopecia Areata	10	2.9	1.2–4.6
Mitral Valve Prolapse	10	2.9	1.2–4.9
PCOS	10	2.9	1.4–4.6
Other Allergies	8	2.3	.9–4.0
Graves–Basedow Disease	7	2.0	.6–3.5
Stroke	7	2.0	.6–3.5
Myocardial Infarction	7	2.0	.6–3.5
Angina Pectoris	7	2.0	.6–3.7
Pruritus	7	2.0	.6–3.5
Peptic ulcer	5	1.4	.3–2.9
Vasculitis	4	1.2	.0–2.6
Hyperthyroidism	4	1.2	.3–2.3
Vitiligo	3	.9	.0–2.0
Subacute Thyroiditis	3	.9	.0–2.0
Inflammatory Bowel Diseases (IBD)	3	.9	.0–2.0
Acne	3	.9	.0–2.0
Reumatoid Arthritis	2	.6	.0–1.4
Multiple Sclerosis	2	.6	.0–1.4
Heart Failure	2	.6	.0–1.4
Bowel Cancer	2	.6	.0–1.4
Sjögren's Syndrome	1	.3	.0–0.9
Pulmonary Fibrosis	1	.3	.0–0.9
Pulmonary Embolism	1	.3	.0–0.9
Lung Adenocarcinoma	1	.3	.0–0.9

The most common subgroups of GMCs were the metabolic (Hypercholesterolemia, Obesity, Hypertriglyceridemia, Diabetes Mellitus, and Metabolic Syndrome) and autoimmune-allergic diseases (Allergic Rhino-Conjunctivitis, Urticaria, Atopic Dermatitis, Psoriasis, Seborrheic Dermatitis, Bronchial Asthma, Hashimoto's Thyroiditis, Alopecia Areata, Other Allergies, Graves-Basedow Disease, Vasculitis, Vitiligo, Subacute Thyroiditis, Inflammatory Bowel Diseases (IBD), Reumatoid Arthritis, and Sjögren's Syndrome) respectively observed in 148 (42.7%) and 167 (48.1%) cases. Cardiovascular diseases (AH with BP $>140/90$ mmHg, Cardiac Arrhythmias, Mitral Valve Prolapse, Myocardial Infarction, Angina Pectoris, and Heart Failure) were observed in 81 patients (23.3%). Interestingly, in our sample the lifetime prevalence of cancer and neoplastic diseases was very low, only 1 (.3%) patient reported Lung Adenocarcinoma and 2 (.6%) patients Bowel Cancer.

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 and patients with (AAD) and without (No-AAD) Autoimmune-Allergic Diseases.

3.1. Comparison between bipolar patients with and without Metabolic Diseases (MD)

Obesity, Diabetes Mellitus, Hypercholestolemia, Hypertrygliceridemia, and Metabolic Syndrome were included within MD. Lifetime history of MD was observed in 42.6% ($n=148$) of the whole sample.

Demographic and clinical features in bipolar patients with and without MD are reported in Table 2. Mean age was significantly higher in patients with MD compared to those without MD. The 2 groups did not show any significant difference in gender and in diagnostic distribution. BD type I was more common than BD II in both groups of patients, with (58.1% vs 40.5%) and without MD (57.3% vs 39.2%).

Age at the onset of first mood episode and age of first treatment were significantly higher in MD than in No-MD. Similarly length of the illness and duration of current episode was significantly longer in MD. Concerning the mean number of hospitalizations, no significant difference between the two groups was observed. Number of previous episodes did not significantly differ between the two groups. No significant difference was also reported in illness course characteristics, as well as in Global Functioning, recorded by the GAF, and in global severity of the simptomatology, measured by CGI scale.

The comparison of lifetime comorbidity rates with other mental disorders showed a significantly higher rate of Panic Disorder and Generalized Anxiety Disorder in MD than in No-MD patients. In this latter group, a higher prevalence of substance abuse than in MD was observed. As expected, Anorexia Nervosa was more represented in No-MD than in MD.

The Severity Index (SI) and the Comorbidity Index (CI), as evaluated with the CIRS scale, were significantly prevalent in subjects with MD.

As far as affective temperaments are concerned, the evaluation by means of *Brief-TEMPS-35* showed no statistically significant differences in temperamental profile between the two groups with and without MD.

Presence of MD was significantly associated with a more extensive use of *Antidepressants* (mostly TCA) in comparison with No-MD. Furthermore, the global duration of pharmacological treatments was significantly longer in MD patients than in those without MD.

In the backward stepwise logistic regression, 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.

Table 2
Comparison of demographic and clinical features between bipolar patients with (M) and without (No-M) metabolic diseases.

	MD ***N*=148** **(42.6%)** ***n* (%)**	**No-MD** ***N*=199** **(57.4)** ***n* (%)**	***t* or χ^2** **(df=1)**	***p***
Age	53.96 (12.7)	43.15 (13.8)	7.48	.00
Gender				
-Female	96 (64.9)	122 (61.3)		
-Male	52 (35.1)	77 (38.7)	.46	.49
Diagnosis				
Bipolar I disorder	86 (58.1)	114 (57.3)	.02	.87
Bipolar II disorder	60 (40.5)	78 (39.2)	.06	.80
Cyclothymic Disorder	10 (6.8)	17 (8.5)	.37	.53
First episode polarity				
-Depressive	103 (72.5)	123 (63.7)		
-Manic	13 (9.2)	30 (15.5)		
-Mixed	26 (18.3)	40 (20.7)	3.78 (2)	.15
Age of onset	32.72 (13.4)	28.17 (11.8)	3.27	.00
Length of the illness	21.24 (12.4)	14.98 (11.1)	4.99	.00
Age of first treatment	33.26 (12.9)	29.82 (11.4)	2.52	.01
Length of drug treatments	20.30 (12.5)	13.69 (11.5)	5.01	.00
Duration of current episode	1.81 (1.4)	1.47 (1.2)	2.17	.03
No. of hospitalizations	2.87 (4.9)	2.63 (6.4)	.33	.74
No. previous episodes				
- Depressive	5.27 (7.19)	4.94 (6.66)	.33	.73
- Manic	4.93 (5.25)	3.97 (7.60)	.60	.54
- Mixed	4.30 (4.54)	4.19 (7.12)	.08	.93
- Hypomanic	4.41 (3.89)	5.13 (9.57)	−.38	.70
Illness course				
Rapid cycling	11 (7.4)	8 (4.0)	1.90	.16
Complete remission	57 (38.8)	89 (44.7)	1.22	.26
Residual symptoms	88 (59.5)	106 (53.3)	1.32	.25
AD-induced hypomania	48 (32.4)	61 (30.7)	.12	.72
Melancholic features	45 (30.4)	49 (24.6)	1.43	.23
Atypical features	80 (54.1)	102 (51.5)	.21	.64
Severity index				
CGI severity	3.76 (1.19)	3.70 (1.27)	.49	.62
GAF	58.80 (12.84)	59.86 (13.09)	−.75	.45
BPRS total score	33.59 (8.53)	32.81 (8.39)	.85	.40
Lifetime comorbidity				
Panic Disorder	90 (60.8)	97 (48.7)	4.97	.02
Generalized Anxiety Disorder	48 (32.4)	38 (19.1)	8.09	.00
Social Phobia	19 (12.8)	16 (8.0)	2.15	.14
Obsessive-Compulsive Disorder	34 (23.0)	46 (23.1)	.00	.97
Anorexia Nervosa	1 (.7)	15 (7.5)	9.09	.003
Bulimia Nervosa	3 (2.0)	9 (4.5)	1.58	.20
Impulse Control Disorder	7 (4.7)	11 (5.5)	.11	.74
Bordeline Personality Disorder	22 (15.0)	36 (18.8)	.88	.34
Alcohol abuse	14 (9.5)	24 (12.1)	.58	.44
Substance abuse	9 (6.1)	32 (16.1)	8.15	.004
TEMPS-35				
Depressive	18.34 (6.7)	18.43 (6.5)	−.12	.90
Cyclotymic	17.97 (7.7)	18.83 (7.6)	−1.02	.30
Hyperthymic	17.40 (6.5)	18.18 (6.6)	−1.07	.28
Irritable	12.60 (5.6)	13.22 (5.9)	−.98	.32
Anxious	17.27 (6.8)	16.83 (6.2)	.62	.53
CIRS				
Comorbidity Index	2.27 (1.47)	.91 (1.32)	8.97	.00
Severity Index	1.51 (.28)	1.18 (.34)	9.57	.00
Drug treatments				
Typical Antipsychotics	79 (55.2)	103 (53.4)	.12	.74
Atypical Antipsychotics	79 (56.0)	110 (57.0)	.03	.91
Lithium	85 (57.4)	101 (50.8)	1.52	.23
Valproate	105 (70.9)	133 (66.8)	.66	.48
TCA	111 (77.1)	128 (65.6)	5.21	.02
SSRI	122 (84.1)	151 (76.6)	2.91	.10

3.2. Comparison between bipolar patients with and without Autoimmune-Allergic Disease (AAD)

Within AAD we included: Vasculitis, Rheumatoid Arthritis, Sjögren Syndrome, Psoriasis, Vitiligo, Seborrheic Dermatitis, Hashimoto Thyroiditis, Subacute Thyroidites, Graves-Basedow Disorder, Asthma Bronchiale, Urticaria, Allergic Rhinoconjunctivitis, Atopic Dermatitis, Alopecia Areata, Other Allergies, and Chronic Inflammatory Bowel Diseases. Lifetime history of AAD was observed in 48.1% ($n=167$) of the whole sample.

Comparisons of demographic and clinical features in bipolar patients with and without AAD are reported in Table 3. Mean age, age of onset, duration of current episode and number of previous episodes were similar in patients with and without AAD. No significat differences were also observed in gender and diagnostic distribution, as well as first episode polarity. Concerning course of illness, the rates of rapid cycling, residual symptoms and melancholic or atypical features were similar in the two groups, while a significantly higher prevalence of drug-induced hypomania was observed in the AAD group compared to no-AAD.

CGI illness severity score, *GAF Global Functioning* and *BPRS total score* were similar in patients with and without AAD. Concerning psychiatric comorbidities, AAD are associated with Generalized Anxiety Disorder and Borderline Personality Disorder. In affective temperament scales, evaluated by means of the *Brief-TEMPS-35*, AAD reported higher mean scores than No-AAD in cyclothymic and anxious temperaments.

The Comorbidity Index (CI), evaluated with the CIRS scale, was significantly higher in AAD than in no-AAD, while the Severity Index (SI) was similar in the two groups. Looking at previous pharmacological treatments, the use of lithium is significantly less common in patients with AAD than in those with no No-AAD, while the mean duration of the treatment was similar in the two groups. In the backward stepwise logistic regression, 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.

Table 3
Comparison between bipolar patients with (AA) and without (NoAA) autoimmune-allergic diseases.

	AAD ***n*=167 (48.1%)** ***n* (%)**	**No-AAD** ***n*=180 (51.9%)** ***n* (%)**	χ^2 **(df)**	***p***
Age	49.96 (14.2)	48.49 (14.4)	−.98	.32
Gender				
-Female	110 (66.3)	105 (59.0)		
-Male	56 (33.7)	73 (41.0)	1.94	.16
Diagnosis				
Bipolar I disorder	91 (54.4)	109 (60.6)	1.30	.25
Bipolar II disorder	72 (43.1)	66 (36.7)	1.50	.22
Cyclothymic Disorder	17 (10.2)	10 (5.6)	2.58	.10
First episode polarity				
- Depressive	110 (67.9)	116 (67.1)		
- Manic	17 (10.5)	26 (15.0)		
- Mixed	35 (21.6)	31(7.8)	1.93(2)	.38
Age of onset	29.44 (11.7)	30.77 (13.4)	−.96	.33
Length of the illness	20.52 (15.8)	17.72 (14.7)	.99	.32
Age of first treatment	31.7 (12.8)	32.1 (12.7)	−.36	.71
Length of drug treatments	16.41 (12.2)	16.68 (12.4)	−.20	.84
Duration of current episode	1.59 (1.3)	1.64 (1.3)	−.35	.72
No. previous episodes				
- Depressive	4.90 (5.7)	5.24 (7.9)	−.36	.71
- Manic	3.91 (4.5)	4.52 (8.1)	−.39	.69
- Mixed	4.46 (4.3)	3.98 (7.9)	−.35	.72
- Hypomanic	4.68 (4.5)	5.07 (10.3)	−.22	.82
Illness course				
Rapid Cycling Bipolar	9 (5.0)	10 (6.0)	.69	.43
Complete remission	77 (43.0)	69 (41.3)	.75	.83
Residual symptoms	97 (58.1)	97 (53.9)	.61	.43
AD-induced hypomania	62 (37.1)	49 (27.2)	3.91	.05
Melancholic features	41 (11.8)	53 (15.3)	1.05	.31
Atypical features	88 (52.7)	94 (52.5)	.97	.99
Severity index				
CGI severity	3.65 (1.2)	3.79 (1.2)	−1.05	.29
GAF	60.65 (12.9)	58.25 (12.9)	1.72	.08
BPRS total score	33.54 (8.4)	32.76 (8.5)	.86	.39
Lifetime comorbidity				
Panic Disorder	94 (56.3)	93 (51.7)	.74	.38
Generalized Anxiety Disorder	50 (29.9)	36 (20.0)	4.59	.03
Social Phobia	21 (12.6)	14 (7.8)	2.19	.13
Obsessive–Compulsive Disorder	41 (24.6)	39 (21.7)	.4	.52
Anorexia Nervosa	8 (4.8)	8 (4.4)	.88	.54
Bulimia Nervosa	7 (4.2)	5 (2.8)	.51	.47
Impulse Control Disorder	12 (7.2)	6 (3.3)	2.61	.10
Borderline PD	37 (22.2)	23 (13.5)	4.39	.04
Alcohol abuse	15 (9.0)	23 (12.8)	1.28	.25
Substance abuse	18 (10.8)	23 (12.8)	.56	.62
TEMPS-35				
Depressive	18.68 (6.90)	18.12 (6.34)	.78	.43
Cyclothymic	19.37 (7.64)	17.63 (7.61)	2.10	.03
Hyperthymic	18.04 (6.59)	17.67 (6.61)	.51	.60
Irritable	13.55 (5.99)	12.41 (5.54)	1.84	.06
Anxious	18.12 (6.60)	16.00 (6.31)	3.06	.00
CIRS				
Severity Index	1.46 (.32)	1.20 (.34)	7.07	.00
Comorbidity Index	2.04 (1.70)	.99 (1.18)	6.58	.00
Drug treatments				
Typical Antipsychotics	84 (51.9)	98 (56.3)	.68	.41
Atypical Antipsychotics	89 (54.9)	100 (58.1)	.35	.55
Lithium	87 (47.9)	106 (58.9)	4.20	.04
Valproate	120 (71.9)	118 (65.6)	1.59	.25
TCA	113 (69.3)	126 (71.6)	.21	.72
SSRI	135 (81.8)	138 (78.0)	.79	.42

4. Discussion

Most of the patients of our sample were hospitalized, accounting for the predominance of BD I in the sample (60% compared to 40% of patients with a BD II or Cyclothymic Disorder).

The systematic evaluation of GMC showed a relatively high prevalence of MD including Hypercholesterolemia, Obesity, Hypertriglyceridemia, Diabetes Mellitus, and Metabolic Syndrome. In our sample also AAD such as Rheumatoid Arthritis, Sjögren Syndrome, Psoriasis, Vitiligo, Hashimoto Thyroiditis, Subacute Thyroidites, Graves-Basedow Disorder, Asthma Bronchiale, Urticaria, Allergic Rhinoconjunctivitis, Atopic Dermatitis, Alopecia Areata, and Chronic Inflammatory Bowel Diseases were very common. Other physical illness frequently reported were Headache, Chronic Constipation, AH, Hiatus Hernia, Dysmenorrhea, Cardiac Arrhythmias, Biliary Lithiasis, and COPD. On the contrary, in our patients the lifetime prevalence of cancer and neoplastic diseases was very low.

A recent meta-analysis summarized the increasing evidence strongly supporting the claim that patients with BD are at high risk for metabolic diseases, Metabolic Syndrome and related cardiovascular morbidity and mortality (Vancampfort et al., 2013). In this report, older age had a modest effect on the Metabolic Syndrome rate and the strongest moderator was the region in which the study took place, with the highest rates observed in New Zealand and Australia (64.2% [95% CI=38.3–83.9]) followed by North America (49.3% [95% CI=29.7–69.3]) The lowest rates were detected in South America at 38.2% (95% CI=20.2–60.0) and in Europe at 32.4% (95% CI=17.4–52.1). Furthermore, the risk of Metabolic Syndrome seems greater in bipolar patients treated with antipsychotic medication. In our sample, the prevalence rates of MD and Metabolic Syndrome were lower than those reported for the European country in the above-mentioned meta-analysis. This discrepancy could be attributed to different rates of prevalence of MD in Italy or differences in sample

selection. Most of our patients are treated with adjunctive psychoeducation, which also focused on the prevention of weight gain and MD. Consistently with this meta-analysis, however, we found an association with age, length of the illness and time spent in pharmacological treatment. As expected, patients with MD were about 10 years older when compared to non-dysmetabolic patients. We also recorded higher age at onset and at first treatment and longer duration of the current episode and of the illness in patients with MD than in the rest of the sample. Nonetheless, MD and No-MD bipolar patients did not display significant differences in terms of Illness Severity, Global Functioning and total score of the BPRS. This finding is not consistent with other studies (Beyer et al., 2005; Fagiolini et al., 2005; Fagiolini et al., 2003; Kemp et al., 2010) reporting more severe symptomatology, impaired social functioning and worse treatment outcome in BD patients with comorbid MD in comparison with non-MD.

Concerning comorbidity with other mental disorders, MDs were associated with high rates of panic/agoraphobic and social anxiety disorders and low rate of drug abuse. An extensive body of literature supports the hypothesis that substance abuse and pathological over-eating may be a phenotypic expression of a competing brain reward system (McIntyre et al., 2007; Volkow and Wise, 2005). This hypothesis is also supported by the high rates of cyclothymic temperament found in obese patients (Alciati et al., 2007; Amann et al., 2009), and the high rates of obesity observed in Bipolar Depression (Vannucchi et al., 2014). Sensation seeking and self-stimulating behavior might involve different types of potentially addictive substance or activity, such as food, alcohol, drugs, sex, gambling, shopping, etc. (Perugi and Akiskal, 2002).

Surprisingly, no significant statistical difference among patients with and without MD was found regarding the distribution of affective temperaments and the type of drugs assumed lifetime, with the only exception of TCA. In the multivariate analysis, the length of the period taking pharmacological treatments is the variable more strongly related to the presence of MD, suggesting a major role of long-term drug assumption in favoring the development of metabolic problems and syndrome.

Interestingly, in our sample the lifetime prevalence of cancer and neoplastic diseases was very low, concerning less than 1% of the patients. Recent data suggested an association between certain psychiatric disorders and a lower-than-expected probability (negative comorbidity) of developing other pathologies (Tabares-Seisdedos and Rubenstein, 2013). In particular, numerous epidemiological studies suggest that schizophrenia, Anorexia Nervosa, Parkinson's disease, Alzheimer's Disease, Multiple sclerosis, Huntington's disease and Down's syndrome seem to protect against several forms of cancer (Tabares-Seisdedos et al., 2011). It has been recently suggested that the immune system and other regulatory systems, particularly the peripheral nervous system, convey signals from tumor cells to the brain, that might play a part in tumor progression and metastases, through sympathetic and parasympathetic nerves, and by modulation of the hypothalamic-pituitary-adrenal axis and adrenal medulla activity (Ondicova and Mravec, 2010). The majority of studies have focused on cancer and schizophrenia (Kredentser et al., 2014), with a paucity of studies focusing on BD (Crump et al., 2013). Although individuals with Schizophrenia and BD are exposed to more environmental noxious agents that contribute to tumor development (e.g. tobacco and alcohol) than the general population, results of several population-based studies indicate that patients with schizophrenia have a lower risk of prostate, colorectal cancers and melanoma, a higher risk of breast and lung cancer. In our sample only 1 case of Lung Adenocarcinoma and 2 Bowel Cancers were observed. The increased risk for certain tumors could be associated with diverse and not mutually exclusive factors such as drug side-effects, unhealthy lifestyle, poor access to health care and differences in socioeconomic status. On the other hand, the reduced risk of other types of cancer may be explained by genetic factors, such as the increased expression of various candidate tumor suppressor genes, or the decreased expression of some oncogenes in genomic regions implicated in schizophrenia or BD susceptibility (Beaulieu, 2012; Zheng et al., 2012). An alternative explanation may be related to the possibility of an increased immune reactivity in patients with BD and/or other mental disorders (Rege and Hodgkinson, 2013). During the process of carcinogenesis, in fact, naturally occurring antibody responses to tumor antigens were found to be associated with improved survival and protection against the spread of cancer (Toubi and Shoenfeld, 2007). In recent trials on cancer immunotherapy clinically significant antitumor responses were often associated with the induction of autoimmune toxicity (Toomer and Chen, 2014). This finding suggests that the same immune mechanisms that elicit autoimmunity may also contribute to the tumor suppression.

The most surprising result of the present study is the very high rate of AAD in our sample. The overall prevalence amounted to about 45% of the patients.This result is particularly interesting for two reasons: first of all, for the disproportion with the prevalence observed in the general population (with estimated rates in Italy being 3.2% for autoimmune diseases and around 20% for allergic conditions (The American College of Allergy, 1998, Jacobson, 1997)); second, for the lack of a difference in gender distribution, because AAD are usually more frequent in women.

The association between AAD and BD has rarely been systematically investigated in clinical samples. An increased prevalence of mood symptoms has been found in a variety of inflammatory conditions, including auto-immune diseases, cardiovascular diseases, diabetes, obesity and Metabolic Syndrome, as well as in more benign inflammatory conditions such as asthma and allergies (Brydon et al., 2009; Walker et al., 2011). Our results are consistent with this trend and showed a very high prevalence (48.1%) of AAD in our BD patients.

A large Danish cohort study showed that a history of Guillain–Barre syndrome, Crohn's disease and autoimmune hepatitis was associated with raised risk of BD (Eaton et al., 2010). The authors concluded that autoimmune processes precede the onset of BD. A subsequent study, based on Danish hospital data, reported that a broad range of autoimmune diseases and infections requiring hospitalization increases the risk of developing schizophrenia and mood disorders (Benros et al., 2013). A correlation between psychiatric symptoms and a group of autoimmune diseases characterized by the presence of brain-reactive antibodies was suggested (Benros et al., 2013). The observed associations support a possible immunological contribution in subgroups of patients with severe mental disorders, such as BD and other psychotic disorders. However, whether it is a causal relationship or an epiphenomenon due to other environmental factors common genetic vulnerability remains unclear and deserves further research. Genetically vulnerable individuals might be at a particular risk of developing mood disorders as a consequence of autoimmune reactions and inflammation affecting the brain.

Inflammatory mechanisms can affect the brain through many different pathways that are not necessarily mutually exclusive (Dalman et al., 2008; Eaton et al., 2006; Jones et al., 2005; Niebuhr et al., 2008; Yolken and Torrey, 2008). Peripheral inflammation can affect the brain without passing the blood–CNS barrier by proinflammatory cytokines activating the tryptophan–kynurenine pathway, regulating serotonin production together with N-methyl-D-aspartate (NMDA) glutamate receptor activity and may also indirectly affect dopamine regulation (Dantzer et al., 2008). The increased inflammation in autoimmune diseases may also influence the brain through increased permeability of the blood–CNS barriers, making the brain vulnerable to immune components,

such as cytokines and auto-antibodies. Furthermore, brain-reactive antibodies can induce a range of psychiatric and neurological symptoms, and are observed in association with some autoimmune diseases, cancers or after exposure to infectious agents through a mechanism involving molecular mimicry (Diamond et al., 2009; Kayser et al., 2010; Lennox et al., 2012; Rose, 1998). In fact, some of the strongest evidence for the potential for autoimmunity and immune components to cause psychiatric symptoms comes from the NMDA antibody-induced limbic encephalitis, where psychiatric symptoms are often dominant in the initial and the remission phase of the disorder in up to 70% of the cases (Dalmau, 2008; Tuzun and Dalmau, 2007), and which has been demonstrated to be treatable with immune therapies (Graus et al., 2010).

In contrast with MD comorbidity, no significant difference was detected in the terms of age, age at onset and other course characteristics between patients with and without AAD. Interestingly, we observed a significantly higher prevalence of drug-induced hypomania in AAD group. Previous reports (Brietzke et al., 2009; Cunha et al., 2008; Dickerson et al., 2007) supported an association between immune activation and manic symptoms. It remains to be investigated whether drug induced hypomania could be associated with the state of immune activation or with increased reactivity to different stimuli in BD with comorbid AAD patients.

In addition, in our sample, AAD were associated with comorbid Generalized Anxiety Disorder and anxious temperament. Although it is generally accepted that anxiety is commonly associated with AAD (Noriega, 2013), the implications and practical consequences of this link remain uncertain. Recent studies hypothesized a possible interaction among emotional stress, immune system, and hypothalamus-pituitary-adrenal axis (Camacho, 2013; Salim et al., 2012).

More controversial and understudied is the association between AAD comorbidity, cyclothymic temperament and related borderline personality disorder (BPD). Mood reactivity, emotional instability and related separation and rejection sensitivity characterize this subgroup of BD patients (Perugi et al., 2013a, 2013b; Perugi et al., 2011). Our findings suggest a possible relationship between autoimmune mediated inflammatory process, trait emotional reactivity and stress vulnerability.

Although the link between stress and mood disorders is well recognized (Weiss et al., 1994), there are no specific studies examining the role of stress, immune dysregulation, and autoimmunity in BD. Retrospective studies in autoimmune diseases have found that up to 80% of patients report uncommon emotional stress before disease onset (Stojanovich and Marisavljevich, 2008), and it has been suggested that immune system activation may vary across the affective states in BD patients (Ortiz-Dominguez et al., 2007). In a more theoretical view, in these patients it is possible to hypothesize a "constitutional" reinforcing loop between emotional/mood reactivity and autoimmune/allergic reactivity that characterizes the "usual" self of these individuals and influences the entire life span. In this sense, the comorbidity with AAD seems to define a possible clinical subtype in the context of the bipolar spectrum, characterized by early onset and mood reactivity and emotional instability.

The main strength of this study is the systematic evaluation of the clinical features and the comorbid GMC in a large sample of BD patients. The use of expert psychiatrists for clinical assessments, rather than non-clinician raters, constitutes an additional strength of the study. On the other hand, a possible limitation is that our center is a tertiary level facility for the long-term treatment of mood disorders, which may have led to a selection bias. Indeed, research exploring the prevalence of GMC in BD may be susceptible to referral and spectrum bias. However, a random selection of participants was not easily feasible in a clinical setting and the referral bias is less influential on the results of group comparisons. A second limitation is that our data were retrospectively collected and therefore subject to recall bias. Third, the cross-sectional design of the study did not allow identification of patients who would subsequently develop comorbid GMC. Fourth, psychiatrists participating in the study were directly involved in the treatment of the patients and consequently it was not possible for them to be blind to the scale ratings. The systematic nature of the evaluation and use of semi-structured interviews minimizes the biases that could arise from retrospective evaluation and non-blind methodology.

In conclusion, the systematic study of GMC in BD patients may represent a very promising area of research for the future. Medical research tends to take a reductionist approach by studying different illnesses in isolation one from another; an alternative is to explore mechanisms that are common to multiple health conditions in the same individual. MD and AAD were highly represented in our bipolar patients, while neoplastic diseases resulted quite uncommon. Interestingly, the clinical correlates of different groups of GMC suggest different implications. At least in our Italian sample, the association between BD and MD seems to be mainly explained by age, duration of the illness and chronic medication exposure. These findings tend to support the hypothesis of an "allostatic load" (Kapczinski et al., 2008), correlated with progression of BD as well as with some of its cognitive and medical complications (Vieta et al., 2013). On the other hand, the association with AAD seems to characterize a specific clinical subtype of BD, characterized by mood reactivity and temperamental mood instability. If the link with autoimmune-allergic diathesis is 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. In a more practical perspective, autoimmune-allergic diseases should be considered by clinicians in the treatment of individuals with BD, since their treatment could improve the psychiatric symptomatology, quality of life and the survival of the individuals.

Role of funding source

The authors have no funding source to declare for the present work.

Conflict of interest

All the authors assure that there are no current or past commercial or financial involvements that might present an appearance of a conflict of interest in connection with this article.

Acknowledgments

No Acknowledgment

References

Alciati, A., D'Ambrosio, A., Foschi, D., Corsi, F., Mellado, C., Angst, J., 2007. Bipolar spectrum disorders in severely obese patients seeking surgical treatment. J. Affect. Disord. 101, 131–138.

Amann, B., Mergl, R., Torrent, C., Perugi, G., Padberg, F., El-Gjamal, N., Laakmann, G., 2009. Abnormal temperament in patients with morbid obesity seeking surgical treatment. J. Affect. Disord. 118, 155–160.

Andreasen, N.C., Endicott, J., Spitzer, R.L., Winokur, G., 1977. The family history method using diagnostic criteria. Reliability and validity. Arch. Gen. Psychiatry 34, 1229–1235.

Beaulieu, J.M., 2012. A role for Akt and glycogen synthase kinase-3 as integrators of dopamine and serotonin neurotransmission in mental health. J. Psychiatry Neurosci. 37, 7–16.

Beneke, M., Rasmus, W., 1992. "Clinical Global Impressions" (ECDEU): some critical comments. Pharmacopsychiatry 25, 171–176.

Benros, M.E., Waltoft, B.L., Nordentoft, M., Ostergaard, S.D., Eaton, W.W., Krogh, J., Mortensen, P.B., 2013. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry 70, 812–820.

Beyer, J., Kuchibhatla, M., Gersing, K., Krishnan, K.R., 2005. Medical comorbidity in a bipolar outpatient clinical population. Neuropsychopharmacology 30, 401–404.

Black, D.W., Hulbert, J., Nasrallah, A., 1989. The effect of somatic treatment and comorbidity on immediate outcome in manic patients. Compr. Psychiatry 30, 74–79.
Black, D.W., Winokur, G., Bell, S., Nasrallah, A., Hulbert, J., 1988a. Complicated mania. Comorbidity and immediate outcome in the treatment of mania. Arch. Gen. Psychiatry 45, 232–236.
Black, D.W., Winokur, G., Hulbert, J., Nasrallah, A., 1988b. Predictors of immediate response in the treatment of mania: the importance of comorbidity. Biol. Psychiatry 24, 191–198.
Brietzke, E., Stertz, L., Fernandes, B.S., Kauer-Sant'anna, M., Mascarenhas, M., Escosteguy Vargas, A., Chies, J.A., Kapczinski, F., 2009. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J. Affect. Disord. 116, 214–217.
Brydon, L., Walker, C., Wawrzyniak, A., Whitehead, D., Okamura, H., Yajima, J., Tsuda, A., Steptoe, A., 2009. Synergistic effects of psychological and immune stressors on inflammatory cytokine and sickness responses in humans. Brain Behav. Immun. 23, 217–224.
Camacho, A., 2013. Is anxious-depression an inflammatory state? Med. Hypotheses 81, 577–581.
Cassano, G.B., Akiskal, H.S., Musetti, L., Perugi, G., Soriani, A., Mignani, V., 1989. Psychopathology, temperament, and past course in primary major depressions. 2. Toward a redefinition of bipolarity with a new semistructured interview for depression. Psychopathology 22, 278–288.
Cassidy, F., Ahearn, E., Carroll, B.J., 1999. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am. J. Psychiatry 156, 1417–1420.
Conwell, Y., Forbes, N.T., Cox, C., Caine, E.D., 1993. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. J. Am. Geriatr. Soc. 41, 38–41.
Cruess, D.G., Evans, D.L., Repetto, M.J., Gettes, D., Douglas, S.D., Petitto, J.M., 2003. Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. Biol. Psychiatry 54, 307–316.
Crump, C., Sundquist, K., Winkleby, M.A., Sundquist, J., 2013. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 70, 931–939.
Cunha, A.B., Andreazza, A.C., Gomes, F.A., Frey, B.N., da Silveira, L.E., Goncalves, C.A., Kapczinski, F., 2008. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 258, 300–304.
Dalman, C., Allebeck, P., Gunnell, D., Harrison, G., Kristensson, K., Lewis, G., Lofving, S., Rasmussen, F., Wicks, S., Karlsson, H., 2008. Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swedish subjects. Am. J. Psychiatry 165, 59–65.
Dalmau, J., 2008. Limbic encephalitis and variants related to neuronal cell membrane autoantigens. Rinsho shinkeigaku=Clin. Neurol. 48, 871–874.
Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.
Diamond, B., Huerta, P.T., Mina-Osorio, P., Kowal, C., Volpe, B.T., 2009. Losing your nerves? Maybe it's the antibodies. Nat. Rev. Immunol. 9, 449–456.
Dickerson, F., Stallings, C., Origoni, A., Boronow, J., Yolken, R., 2007. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 952–955.
Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.
Eaton, W.W., Byrne, M., Ewald, H., Mors, O., Chen, C.Y., Agerbo, E., Mortensen, P.B., 2006. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am. J. Psychiatry 163, 521–528.
Eaton, W.W., Pedersen, M.G., Nielsen, P.R., Mortensen, P.B., 2010. Autoimmune diseases, bipolar disorder, and non-affective psychosis. Bipolar Disord. 12, 638–646.
Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33, 766–771.
Erfurth, A., Gerlach, A., Hellweg, I., Boenigk, I., Michael, N., Akiskal, H., 2005. Studies on a German (Munster) version of the temperament auto-questionnaire TEMPS-A: construction and validation of the briefTEMPS-M. J. Affect. Disord. 85, 53–69.
Fagiolini, A., Frank, E., Scott, J.A., Turkin, S., Kupfer, D.J., 2005. Metabolic syndrome in bipolar disorder: findings from the bipolar disorder center for Pennsylvanians. Bipolar Disord. 7, 424–430.
Fagiolini, A., Kupfer, D.J., Houck, P.R., Novick, D.M., Frank, E., 2003. Obesity as a correlate of outcome in patients with bipolar I disorder. Am. J. Psychiatry 160, 112–117.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1996. Structured clinical interview for DSM-IV Axis I disorders, clinician Version (SCID-CV). American Psychiatric Press, Inc., Washington, D.C.
Goldstein, B.I., Kemp, D.E., Soczynska, J.K., McIntyre, R.S., 2009. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J. Clin. Psychiatry 70, 1078–1090.
Grande, I., Magalhaes, P.V., Kunz, M., Vieta, E., Kapczinski, F., 2012. Mediators of allostasis and systemic toxicity in bipolar disorder. Physiol. Behav. 106, 46–50.
Graus, F., Saiz, A., Dalmau, J., 2010. Antibodies and neuronal autoimmune disorders of the CNS. J. Neurol. 257, 509–517.
Hope, S., Melle, I., Aukrust, P., Agartz, I., Lorentzen, S., Steen, N.E., Djurovic, S., Ueland, T., Andreassen, O.A., 2010. Osteoprotegerin levels in patients with severe mental disorders. J. Psychiatry Neurosci. 35, 304–310.
Hope, S., Melle, I., Aukrust, P., Steen, N.E., Birkenaes, A.B., Lorentzen, S., Agartz, I., Ueland, T., Andreassen, O.A., 2009. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord. 11, 726–734.
Hudon, C., Fortin, M., Vanasse, A., 2005. Cumulative Illness Rating Scale was a reliable and valid index in a family practice context. J. Clin. Epidemiol. 58, 603–608.
Jacobson, D.L., Gange, S.J., Rose, N.R., Graham, N.M., 1997. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin. Immunol. Immunopathol..
Jones, A.L., Mowry, B.J., Pender, M.P., Greer, J.M., 2005. Immune dysregulation and self-reactivity in schizophrenia: do some cases of schizophrenia have an autoimmune basis? Immunol. Cell Biol. 83, 9–17.
Kapczinski, F., Vieta, E., Andreazza, A.C., Frey, B.N., Gomes, F.A., Tramontina, J., Kauer-Sant'anna, M., Grassi-Oliveira, R., Post, R.M., 2008. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci. Biobehav. Rev. 32, 675–692.
Kayser, M.S., Kohler, C.G., Dalmau, J., 2010. Psychiatric manifestations of paraneoplastic disorders. Am. J. Psychiatry 167, 1039–1050.
Kemp, D.E., Gao, K., Chan, P.K., Ganocy, S.J., Findling, R.L., Calabrese, J.R., 2010. Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. Bipolar Disord. 12, 404–413.
Kilbourne, A.M., Cornelius, J.R., Han, X., Pincus, H.A., Shad, M., Salloum, I., Conigliaro, J., Haas, G.L., 2004. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord. 6, 368–373.
Kim, Y.K., Jung, H.G., Myint, A.M., Kim, H., Park, S.H., 2007. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J. Affect. Disord. 104, 91–95.
Kisely, S.R., Goldberg, D.P., 1993. The effects of physical illness on psychiatric disorder. J. Psychopharmacol. 7, 119–125.
Kredentser, M.S., Martens, P.J., Chochinov, H.M., Prior, H.J., 2014. Cause and rate of death in people with schizophrenia across the lifespan: a population-based study in Manitoba, Canada. J. Clin. Psychiatry 75, 154–161.
Krishnadas, R., Cavanagh, J., 2012. Depression: an inflammatory illness? J. Neurol. Neurosurg. Psychiatry 83, 495–502.
Krishnan, K.R.R., 2005. Psychiatric and medical comorbidities of bipolar disorder. Psychosom. Med. 67, 1–8.
Kupfer, D.J., 2005. The increasing medical burden in bipolar disorder. JAMA 293, 2528–2530.
Leboyer, M., Soreca, I., Scott, J., Frye, M., Henry, C., Tamouza, R., Kupfer, D.J., 2012. Can bipolar disorder be viewed as a multi-system inflammatory disease? J. Affect. Disord. 141, 1–10.
Lennox, B.R., Coles, A.J., Vincent, A., 2012. Antibody-mediated encephalitis: a treatable cause of schizophrenia. Br. J. Psychiatry 200, 92–94.
Linn, B.S., Linn, M.W., Gurel, L., 1968. Cumulative illness rating scale. J. Am. Geriatr. Soc. 16, 622–626.
McEwen, B.S., Stellar, E., 1993. Stress and the individual. Mechanisms leading to disease. Arch. Intern. Med. 153, 2093–2101.
McIntyre, R.S., Konarski, J.Z., Soczynska, J.K., Wilkins, K., Panjwani, G., Bouffard, B., Bottas, A., Kennedy, S.H., 2006. Medical comorbidity in bipolar disorder: implications for functional outcomes and health service utilization. Psychiatr. Serv. 57, 1140–1144.
McIntyre, R.S., McElroy, S.L., Konarski, J.Z., Soczynska, J.K., Bottas, A., Castel, S., Wilkins, K., Kennedy, S.H., 2007. Substance use disorders and overweight/obesity in bipolar I disorder: preliminary evidence for competing addictions. J. Clin. Psychiatry 68, 1352–1357.
Miller, M.D., Paradis, C.F., Houck, P.R., Mazumdar, S., Stack, J.A., Rifai, A.H., Mulsant, B., Reynolds 3rd, C.F., 1992. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res. 41, 237–248.
Niebuhr, D.W., Millikan, A.M., Cowan, D.N., Yolken, R., Li, Y., Weber, N.S., 2008. Selected infectious agents and risk of schizophrenia among U.S. military personnel. Am. J. Psychiatry 165, 99–106.
Noriega, N.H., 2013. [Association between anxiety and depression in allergic illnesses]. Vertex 24, 253–258.
O'Brien, S.M., Scully, P., Scott, L.V., Dinan, T.G., 2006. Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. J. Affect. Disord. 90, 263–267.
Ondicova, K., Mravec, B., 2010. Role of nervous system in cancer aetiopathogenesis. Lancet Oncol. 11, 596–601.
Ortiz-Dominguez, A., Hernandez, M.E., Berlanga, C., Gutierrez-Mora, D., Moreno, J., Heinze, G., Pavon, L., 2007. Immune variations in bipolar disorder: phasic differences. Bipolar Disord. 9, 596–602.
Overall, J., Gorham, D.T., 1962. The Brief Psychiatric Rating Scale. Psychol. Rep. 10, 790–812.
Perugi, G., Akiskal, H.S., 2002. The soft bipolar spectrum redefined: focus on the cyclothymic, anxious-sensitive, impulse-dyscontrol, and binge-eating connection in bipolar II and related conditions. Psychiatr. Clin. N. Am. 25, 713–737.
Perugi, G., Akiskal, H.S., Micheli, C., Toni, C., Madaro, D., 2001. Clinical characterization of depressive mixed state in bipolar-I patients: Pisa-San Diego collaboration. J. Affect. Disord. 67, 105–114.

Perugi, G., Angst, J., Azorin, J.M., Bowden, C., Vieta, E., Young, A.H., Group, B.S., 2013a. The bipolar-borderline personality disorders connection in major depressive patients. Acta Psychiatr. Scand. 128, 376–383.
Perugi, G., Angst, J., Azorin, J.M., Bowden, C., Vieta, E., Young, A.H., Group, B.S., 2013b. Is comorbid borderline personality disorder in patients with major depressive episode and bipolarity a developmental subtype? Findings from the international BRIDGE study. J. Affect. Disord. 144, 72–78.
Perugi, G., Fornaro, M., Akiskal, H.S., 2011. Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a common cyclothymic diathesis? World Psychiatry: Off. J. World Psychiatr. Assoc. 10, 45–51.
Rege, S., Hodgkinson, S.J., 2013. Immune dysregulation and autoimmunity in bipolar disorder: synthesis of the evidence and its clinical application. Aust. N. Z. J. Psychiatry 47, 1136–1151.
Rose, N.R., 1998. The role of infection in the pathogenesis of autoimmune disease. Semin. Immunol. 10, 5–13.
Salim, S., Chugh, G., Asghar, M., 2012. Inflammation in anxiety. Adv. Protein Chem. Struct. Biol. 88, 1–25.
Sokal, J., Messias, E., Dickerson, F.B., Kreyenbuhl, J., Brown, C.H., Goldberg, R.W., Dixon, L.B., 2004. Comorbidity of medical illnesses among adults with serious mental illness who are receiving community psychiatric services. J. Nerv. Ment. Dis. 192, 421–427.
Stojanovich, L., Marisavljevich, D., 2008. Stress as a trigger of autoimmune disease. Autoimmun. Rev. 7, 209–213.
Tabares-Seisdedos, R., Dumont, N., Baudot, A., Valderas, J.M., Climent, J., Valencia, A., Crespo-Facorro, B., Vieta, E., Gomez-Beneyto, M., Martinez, S., Rubenstein, J.L., 2011. No paradox, no progress: inverse cancer comorbidity in people with other complex diseases. Lancet Oncol. 12, 604–608.
Tabares-Seisdedos, R., Rubenstein, J.L., 2013. Inverse cancer comorbidity: a serendipitous opportunity to gain insight into CNS disorders. Nat. Rev. Neurosci. 14, 293–304.
The American College of Allergy, Asthma and Immunology Task Force on Allergic Disorders. Executive Summary Report (1998).
Toomer, K.H., Chen, Z., 2014. Autoimmunity as a double agent in tumor killing and cancer promotion. Front. Immunol. 5, 116.
Toubi, E., Shoenfeld, Y., 2007. Protective autoimmunity in cancer (review). Oncol. Rep. 17, 245–251.
Tuzun, E., Dalmau, J., 2007. Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist 13, 261–271.
Vancampfort, D., Vansteelandt, K., Correll, C.U., Mitchell, A.J., De Herdt, A., Sienaert, P., Probst, M., De Hert, M., 2013. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Am. J. Psychiatry 170, 265–274.
Vannucchi, G., Toni, C., Maremmani, I., Perugi, G., 2014. Does obesity predict bipolarity in major depressive patients? J. Affect. Disord. 155, 118–122.
Vieta, E., Popovic, D., Rosa, A.R., Sole, B., Grande, I., Frey, B.N., Martinez-Aran, A., Sanchez-Moreno, J., Balanza-Martinez, V., Tabares-Seisdedos, R., Kapczinski, F., 2013. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur. Psychiatry 28, 21–29.
Volkow, N.D., Wise, R.A., 2005. How can drug addiction help us understand obesity? Nat. Neurosci. 8, 555–560.
Walker, J.R., Graff, L.A., Dutz, J.P., Bernstein, C.N., 2011. Psychiatric disorders in patients with immune-mediated inflammatory diseases: prevalence, association with disease activity, and overall patient well-being. J. Rheumatol. 88, 31–35.
Weiss, J.M., Stout, J.C., Aaron, M.F., Quan, N., Owens, M.J., Butler, P.D., Nemeroff, C.B., 1994. Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. Brain Res. Bull. 35, 561–572.
Yolken, R.H., Torrey, E.F., 2008. Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol. Psychiatry 13, 470–479.
Zheng, W., Wang, H., Zeng, Z., Lin, J., Little, P.J., Srivastava, L.K., Quirion, R., 2012. The possible role of the Akt signaling pathway in schizophrenia. Brain Res. 1470, 145–158.