Characterization of Bipolar Disorder I and II: Clinical Features, Comorbidities, and Pharmacological Pattern

ABSTRACT

Objective: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition provides precise diagnostic criteria to differentiate between bipolar disorder (BD) type I and II; nevertheless, it can be challenging to come up with the right diagnosis. The aim of this study is to evaluate the sociodemographic differences, clinical features, comorbidities, and pharmacological pattern between patients with BD type I and II.

Methods: A total of 680 patients with BD type I and II were consecutively recruited to our psychiatry department. A semi-structured interview was used to collect several information.

Results: Patients with BD type I were mostly males, single, with a lower current age, and unemployed compared to patients with BD type II. Furthermore, patients with BD type I showed an earlier age at onset and a significant higher prevalence of psychotic and residual symptoms, a higher number of hospitalizations, and involuntary admissions. On the other hand, patients with BD type II were associated with a significant higher prevalence of lifetime suicide attempts, psychiatric comorbidities, and use of alcohol. Finally, antidepressant drugs were prescribed more often to patients with BD type II, while antipsychotics and mood stabilizers were mostly prescribed in patients with BD type I.

Conclusion: the differentiation of the 2 nosologic bipolar diagnosis is in line with the current scientific interest, confirming the existence of a markedly different profile between BD type I and II. This differentiation could reduce the heterogeneity of bipolar presentation in research, optimize clinical assessment, and increase the interest in developing more precise and individualized therapeutic strategies, also implementing psychosocial therapies.

Keywords: Bipolar disorder, affective disorder, comorbidity, psychosis, suicidal behavior

Andrea Aguglia[1,2]
Gabriele Giacomini[2]
Clio F. De Michiel[1]
Nicolò Garbarino[1]
Alessio Lechiara[1]
Caterina Magni[1]
Matteo Meinero[1]
Edoardo Verrina[1]
Alessandra Costanza[3,4,5]
Andrea Amerio[1,2]
Mario Amore[1]
Gianluca Serafini[12]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy
[2]IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[3]Department of Psychiatry, Geneva University Hospital (HUG), Geneva, Switzerland
[4]Department of Psychiatry, Faculty of Biomedical Sciences, University of Italian Switzerland, Lugano, Switzerland
[5]Department of Psychiatry, Faculty of Medicine, Geneva University, Geneva, Switzerland

Corresponding author: Andrea Aguglia
✉ andrea.aguglia@unige.it

Introduction

The differentiation of bipolar disorder (BD) type I and II as a separate diagnostic entity is a fairly recent innovation in the history of psychiatry. Prior to the release of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, (DSM-IV) in 1994, this diagnostic framework was not considered, although the scientific evidence was focused on a better definition of mood disorders for several years, providing a potential differentiation in a spectrum of clinical presentations and subdividing into different syndromes.[1,2]

An important historical definition of mood disorders was given by Emil Kraepelin, who proposed the introduction of the concept of "manic-depressive insanity" to indicate a less severe mental illness than dementia praecox, usually characterized by affective recurrence, sometimes in association with the co-occurrence of psychotic symptoms, i.e., delusions and hallucinations.[3] This broad definition included several mood conditions, including major depressive disorder and BD, the latter characterized by an alternation of (hypo)manic and major depressive episodes.[4] This categorical distinction officially appeared in DSM-III,[5] published in 1980, thanks to the work of Karl Leonhard and others.[6,7] Furthermore, the DSM-IV provided a further

Aguglia et al. Bipolar Disorder I and II

Alpha Psychiatry 2024;25(4):472-479

differentiation in BD type I and II, also included in the last version of DSM 5-TR,[8] following the concept of Dunner and colleagues.[9]

The BD type I, according to the DSM 5-TR, can be diagnosed if 2 diagnostic criteria are met: the first is the presence of at least 1 current or lifetime manic episode, the second is the exclusion of psychotic disorders such as schizoaffective, schizophreniform, or delusional disorder. On the contrary, the diagnosis of BD type II is defined by the presence of at least 1 current or lifetime hypomanic episode and at least 1 current or lifetime major depressive episode, as well as the absence of a lifetime manic episode.[8] The distinction between manic and hypomanic episodes considers different clinical aspects as follows: first, the duration of a minimum of 7 and 4 days for manic and hypomanic episodes, respectively; second, the negative impact on functioning and the presence of certain clinical dimensions such as psychotic, confusional, or pantoclastic symptoms, constitute surely a manic episode. It should be noted that hypomanic and major depressive episodes can be present in both disorders. In addition to differentiation according to the DSM 5-TR, BD type II seems to be characterized by marked reactivity of mood, the affective and biographical instability of the clinical condition, and a complex association of anxious, panic, behavioral, and impulsive manifestations underlying a cyclothymic temperamental dysregulation.[10]

For a long time, BD type II was considered a "milder" disorder compared to BD type I, but it seems a superficial mistake for several reasons: BD type II can present psychotic symptoms during a major depressive episode, have a higher delay in a proper diagnosis and adequate pharmacological treatment, show a possible conversion to rapid bipolar cycle for an incorrect use of antidepressant medications.[11,12] Furthermore, even if no significant difference on suicide risk was found between BD type I and II in a recent meta-analysis,[1] DSM 5-TR highlights a slight prevalence of suicide attempts in BD type II (32.4% for BD type I, 36.3% for BD type II).[8] The differentiation between BD type I and II is not universally accepted; several contemporary authors have supported the concept of "bipolar spectrum," as a partial return to the broad Kraepelinian category of manic-depressive insanity.[13-15] Others, however, disagree and support the importance of a differentiation between BD type I and II, considering the phenomenology, family transmission models, natural history and response to treatment[11,16-21] and confirming data about potential heterogeneity bias, if BD type II is included into BD type I.[22,23] As a matter of fact, only 5%-15% of patients affected by BD type II develop full manic episodes during prospective follow-up evaluation, remaining diagnostically stable over many years.[1,24]

The different variety of psychopathological dimensions, clinical conditions, and phenotypes, characterizing the bipolar and related disorders, makes the classification, correct diagnosis, and consequent

adequate treatment quite complex, even because this symptomatology could be related to other psychiatric disorders such as schizoaffective disorder or, in a milder form, to cyclothymic-irritable-hyperthymic temperament.[25]

Controversies aside, the current scientific literature shows several differences between BD type I and II; in a recent meta-analysis, patients with BD type II showed significantly more additional psychiatric diagnoses, depressions per year, rapid cycling, family psychiatric history, female gender, and antidepressant treatment, but less treatment with lithium or antipsychotics, fewer hospitalizations or psychotic features, and lower unemployment rates than patients with BD type I.[1] Other significant differences from clinical studies were a lower number of hospitalizations and higher maintenance of acceptable functioning, higher suicidal risk, prevalence of comorbidities and affective recurrences for BD type II, while BD type I seems to be associated with male gender and more involuntary admissions.[26,27]

The aim of this study is to evaluate potential differences in terms of sociodemographic, clinical, and pharmacological pattern in a sample of patients with a primary diagnosis of BD type I and II, in order to characterize better this psychiatric disorder and contribute to the current literature, providing further scientific evidence on the differentiation between the 2 disorders.

Methods

Sample

A cross-sectional study was conducted including all patients with a primary diagnosis of BD, according to DSM 5,[28] consecutively admitted or visited to the in- and out-patient at Section of Psychiatry, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI – University of Genoa) and IRCCS Ospedale Policlinico San Martino (Genoa - Italy) in the last 7 years (from January 2017 to December 2023). The diagnosis of BD was performed by clinicians with at least 10 years of postgraduate clinical experience by means of the Structured Clinical Interview for DSM 5 Clinical Version (SCID-5 CV). Our psychiatric unit works as a tertiary referral center mainly for patients from Liguria but also for patients from other close regions located in the northwest of Italy. Patients are referred by general practitioners or psychiatrists, although a few are self-referred. A detailed explanation of the research study was provided to all participants that gave written informed consent for the data collection used for research purposes, anonymously.

The inclusion criteria were having a primary diagnosis of BD type I or II, current age > 18 years old, and availability to participate voluntarily in the study. The exclusion criteria were as follows: (a) primary diagnosis of schizophrenia and related disorders; (b) pregnancy or recent childbirth; (c) any condition affecting the ability to fill out the assessment, such as major neurocognitive disorders; (d) any severe neurological disorder or positive history of acute neurological injury, including an intellectual disability; and (e) the inability or refusal to provide a valid written informed consent.

The study was designed in agreement with the guidelines from the Declaration of Helsinki and was approved by the local ethics committee (129/2018).

MAIN POINTS

- *Bipolar disorder (BD) type I should be considered a psychiatric disorder differentiated by BD type II.*
- *Bipolar disorder type I was significantly associated with male gender, the presence of psychotic and residual symptoms, and number of hospitalizations.*
- *Bipolar disorder type II was significantly associated with the presence of psychiatric comorbidity, use of alcohol, and the ongoing antidepressant treatment.*

Alpha Psychiatry 2024;25(4):472-479

Aguglia et al. Bipolar Disorder I and II

Clinical Assessment

All participants responded to a semi-structured interview to collect sociodemographic and clinical characteristics, used in previous studies.[29-33] In particular, sociodemographic variables included age, gender, marital, occupational status, and education level. Clinical variables investigated were psychiatric family history, age at onset, duration of illness in years, psychotic and residual symptoms, number and type (voluntary and involuntary) of hospitalizations, presence of lifetime suicide attempts and non-suicidal self-injury (NSSI), presence of psychiatric and medical comorbidities, presence and type of illicit substance use (alcohol, cannabinoids, psychostimulants such as cocaine or amphetamine, heroin), and ongoing drug treatment grouped as antidepressants, antipsychotics, mood stabilizers (i.e., lithium, valproate, lamotrigine, and carbamazepine), benzodiazepines, and others (i.e., gabapentin, pregabalin, and oxcarbazepine), including the presence of complex polypharmacy. The characteristics investigated were chosen on the basis of current literature by expert psychiatrists on BD with the certainty of being easy to investigate, collect, and reproduce by all clinicians in their daily clinical activity, representing a cross-sectional clinical validity.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL, USA), and the significance level was set at $P < .05$.

Patient characteristics were reported as mean and standard deviation (SD) or frequency and percentage for continuous and categorical variables, respectively. The sample was divided into 2 subgroups, based on the primary diagnosis (BD type I and II). The Kolmogorov–Smirnov test was used to confirm if all variables in the sample followed a normal distribution.

Therefore, the following statistical analyses were performed for bivariate comparisons: continuous variables were compared using the unpaired Student's t-test for 2-class comparisons and categorical variables using Pearson's chi-square test in contingency tables.

Subsequently, a logistic regression analysis was used to explore the relationship between patients with BD type I and II and each of the significant independent variables found in univariate analysis, correcting for age and gender.

Results

A total of 680 bipolar patients were included in this study, of which about half were patients with BD type I (n = 332, 48.8%).

Regarding the sociodemographic comparisons, patients with BD type I were mostly males (169 (50.9%) vs. 139 (39.9%), P = .004), single (161 (48.5%) vs. 132 (37.9%), P = .035), with a lower current age (48.03 (SD = 14.12) vs. 50.21 (SD = 13.95), P = .044), and unemployed (241 (72.6%) vs. 197 (56.6%), P < .001) compared to patients with BD type II. The sociodemographic characteristics of the total sample and the comparisons between BD type I and II are summarized in Table 1.

When clinical comparisons were made, patients with BD type I showed an earlier age at onset (26.79 (SD = 11.51) vs. 30.38 (SD = 13.76), P < .001) and a significantly higher prevalence of psychotic (161 (48.5%) vs. 37 (10.6%), P < .001) and residual symptoms (78 (23.5%) vs. 51 (14.7%), P = .003). Furthermore, a higher number of hospitalizations

Table 1. Sociodemographic Characteristics of Total Sample and Comparison According to the Diagnosis of Bipolar Disorder

Characteristics n (%) or Mean (SD)	Total Sample (n = 680)	Bipolar Disorder Type I (n = 332)	Bipolar Disorder Type II (n = 348)	P
Gender (male)	308 (45.3)	169 (50.9)	139 (39.9)	.004
Current age (years)	49.14 (SD = 14.07)	48.03 (SD = 14.12)	50.21 (SD = 13.95)	.044
Marital status				
Single	293 (43.1)	161 (48.5)	132 (37.9)	.035
Married	212 (31.2)	91 (27.4)	121 (34.8)	
Separated/divorced	140 (20.6)	66 (19.9)	74 (21.3)	
Widowed	35 (5.1)	14 (4.2)	21 (6.0)	
Educational level (years)	11.63 (SD = 3.57)	11.70 (SD = 3.60)	11.56 (SD = 3.53)	.628
Occupational status, employed	242 (35.6)	91 (27.4)	151 (43.4)	<.001

SD, standard deviation.

(7.15 (SD = 6.54) vs. 3.98 (SD = 3.65), P < .001) and involuntary admissions (108 (32.5%) vs. 41 (11.8%), P < .001) were observed mostly in patients with a primary diagnosis of BD type I. On the other hand, patients with BD type II were associated with a significantly higher prevalence of lifetime suicide attempts (133 (38.2%) vs. 101 (30.4%), P = .032), psychiatric comorbidities (166 (47.7%) vs. 107 (32.2%), P < .001), and use of alcohol (104 (29.9%) vs. 74 (22.3%), P = .024).

Finally, regarding the pharmacological treatment, antidepressant drugs were prescribed more often to patients with BD type II (199 (57.2%) vs. 117 (35.2%), P < .001), while antipsychotics (271 (81.6%) vs. 249 (71.6%), P = .002) and mood stabilizers (289 (87.0%) vs. 272 (78.2%), P = .002) were mostly prescribed to patients with BD type I.

The clinical characteristics, comorbidities, and pharmacological treatment of the total sample and the comparisons between BD type I and II are displayed in Table 2, Figures 1 and 2.

When the logistic regression analysis (R^2 Nagelkerke = 0.510, P < .001) was performed, the male gender, the presence of psychotic and residual symptoms, as well as the number of hospitalizations, remained significantly associated with the primary diagnosis of BD type I. On the contrary, the presence of psychiatric comorbidity, the use of alcohol, and the ongoing antidepressant treatment were significantly associated with the primary diagnosis of BD type II (see Table 3).

Discussion

This study was aimed at evaluating the usefulness of a diagnostic differentiation between BD type I and II in terms of sociodemographic characteristics, clinical features, comorbidities, substance use, and pharmacological pattern.

As expected, concerning sociodemographic characteristics, patients with BD type I were more often males, single, not working compared to those with BD type II, in keeping with the recent literature, as demonstrated by both clinical studies and systematic review with meta-analysis.[1,11,20,34] Furthermore, Karanti and coworkers[20] found that patients with BD type II were more likely to have children, to live

Aguglia et al. Bipolar Disorder I and II

Alpha Psychiatry 2024;25(4):472-479

Table 2. Clinical Features of Total Sample and Comparison According to the Diagnosis of Bipolar Disorder

|	Total Sample (n=680)	Bipolar Disorder Type I (n=332)	Bipolar Disorder Ttype II (n=348)	P
Clinical Characteristics, n (%) or mean (SD)				
Psychiatric family history	341 (50.1)	159 (47.9)	182 (52.3)	.251
Age at onset	28.63 (SD=12.83)	26.79 (SD=11.51)	30.38 (SD=13.76)	<.001
Duration of illness (years)	20.18 (SD=13.18)	20.78 (SD=13.02)	19.60 (SD=13.32)	.243
Psychotic symptoms	198 (29.1)	161 (48.5)	37 (10.6)	<.001
Residual symptoms	129 (19.0)	78 (23.5)	51 (14.7)	.003
Number of hospitalizations	5.97 (SD=5.11)	7.15 (SD=6.54)	3.98 (SD=3.65)	<.001
Involuntary hospitalization	149 (21.9)	108 (32.5)	41 (11.8)	<.001
Lifetime suicide attempts	234 (34.4)	101 (30.4)	133 (38.2)	.032
Lifetime non suicidal self-injuries	114 (16.8)	50 (15.1)	64 (18.4)	.245
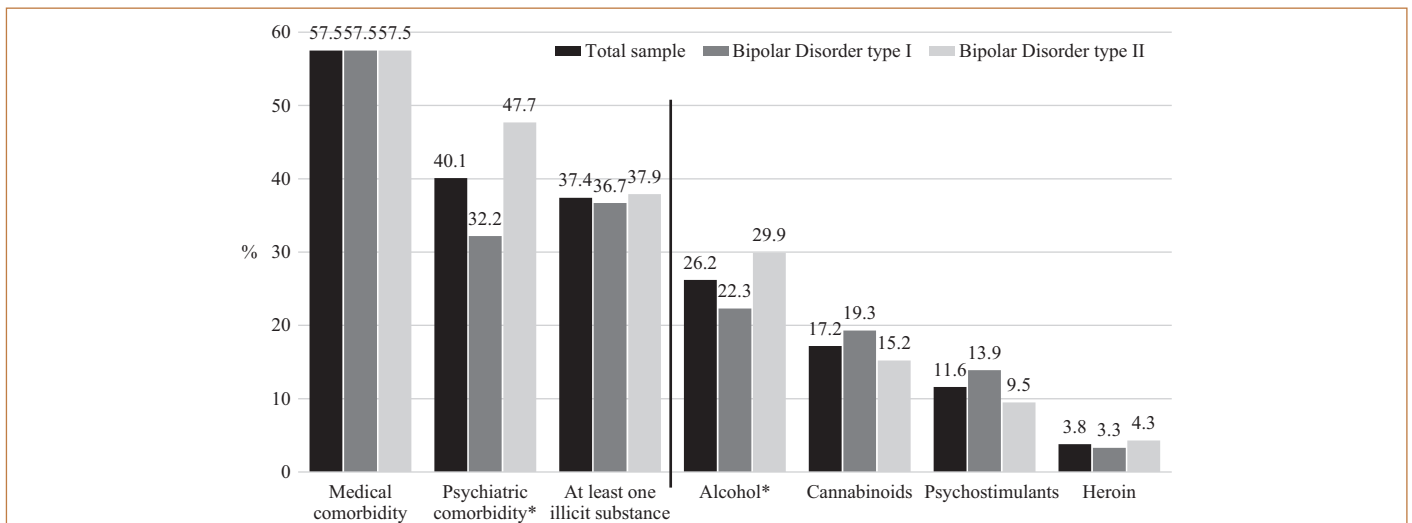
Figure 1. Comorbidities of the total sample and comparison according to the diagnosis of bipolar disorder. * *P* <.05
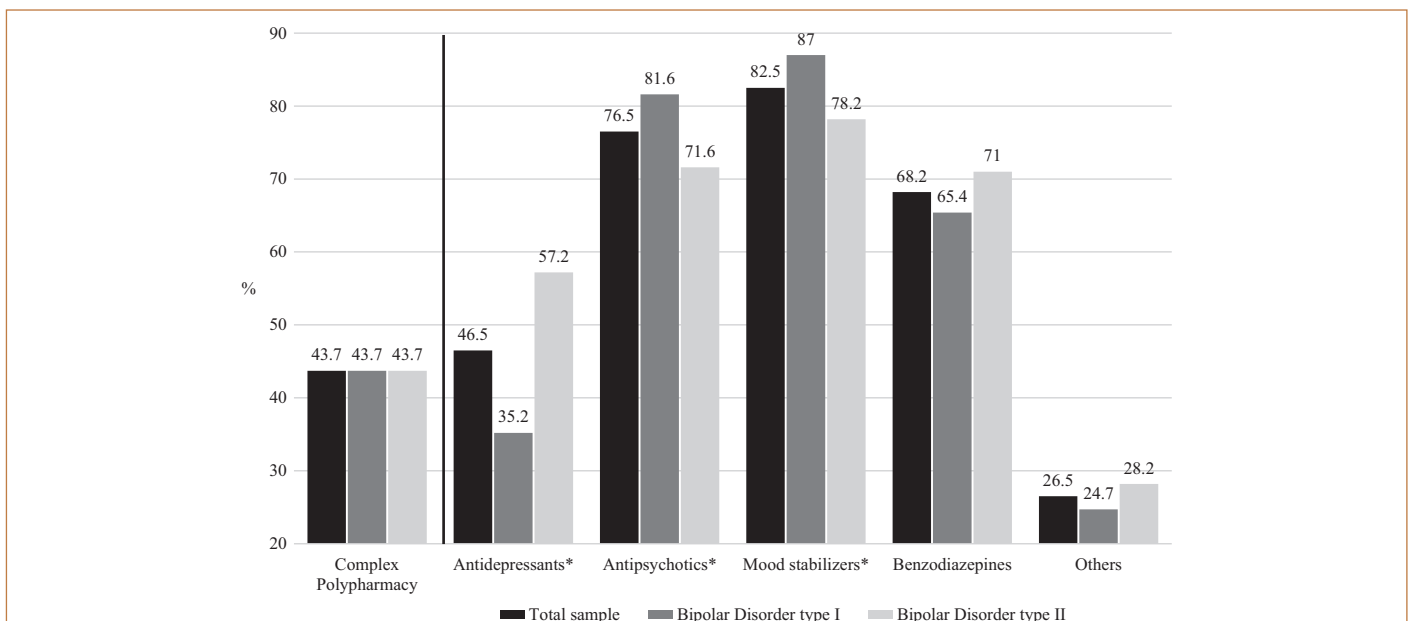

Figure 2. Pharmacological treatment of the total sample and comparison according to the diagnosis of bipolar disorder. * *P* <.05

Alpha Psychiatry 2024;25(4):472-479

Aguglia et al. Bipolar Disorder I and II

Table 3. Logistic Regression Analysis Considering Characteristics Associated with Bipolar Disorder Type I

	B	SE	Wald	P	Exp (B)	95% CI
Male gender	−.439	.224	3.857	.050	.644	.416-.999
Current age	−.020	.010	3.506	.061	.981	.961-1.001
Single status	−.029	.267	.012	.913	.971	.576-1.638
Occupational status	−.308	.231	1.782	.182	.735	.467-1.155
Age at onset	−.004	.010	.137	.712	.996	.977-1.016
Psychotic symptoms	2.017	.272	55.044	<.001	7.517	4.412-12.808
Residual symptoms	.934	.307	9.265	.002	2.546	1.395-4.646
Number of hospitalizations	.135	.026	26.877	<.001	1.145	1.088-1.205
Involuntary admissions	.177	.292	.367	.544	1.194	.673-2.117
Lifetime suicide attempts	−.357	.228	2.437	.119	.700	.447-1.095
Psychiatric comorbidity	−.748	.220	11.622	.001	.473	.308-.728
Alcohol	−.661	.259	6.500	.011	.516	.311-.858
Ongoing antidepressant treatment	−.708	.225	9.884	.002	.493	.317-.766
Ongoing antipsychotic treatment	.061	.256	.056	.813	1.062	.643-1.754
Ongoing mood stabilizer treatment	.231	.284	.660	.416	1.259	.722-2.196
Constant	.761	.706	1.162	.281	2.140	

CI, confident interval.

in ordinary housing, to be working or studying, and to be self-sustained. These results highlight how patients with BD type II may have a greater possibility of developing a better social and relational functioning lifelong than BD type I and, therefore, they identify less with a pathological psychiatric condition; in particular, due to hypomanic symptoms, these patients seem to be more exposed to stressful life events, including job failures, relationships or family breakups, and traumatic events.

Regarding the clinical symptomatology, several statistical differences were found. In particular, patients affected by BD type I showed an earlier age at onset than patients with BD type II, confirming the main literature findings.[1,11,35-37] However, the failure to identify an early hypomanic phase, combined with the disorder's tendency to have a depressive onset, could have a negative impact on determining accurately the age at onset, particularly in patients with BD type II.[10,38] This main issue inevitably implies a delay in a correct diagnosis, leading to an inappropriate drug prescription with a greater risk of chronicity and mood destabilization.

Furthermore, patients with BD type I were more likely to experience psychotic and residual symptoms, with a higher prevalence of involuntary admissions and the number of hospitalizations during the illness course and affective recurrences, confirming the pre-existing data literature.[1,11,20,37,39-42] In particular, a higher rate of psychotic and residual symptoms, more impactful behavioral alteration and social functioning impairment in BD type I could explain the higher number of hospitalizations, both voluntary and involuntary in these patients.[1] Hospitalization could be considered a predictor of greater severity of illness for the BD type I, also burdened by a higher association with psychotic symptoms.[43] Furthermore, a previous systematic review demonstrated that residual symptoms, especially cognitive impairment and depressive subsyndromal symptoms,[44] affect the psychosocial functioning of bipolar patients being considered potential predictors of illness course worsening in euthymic patients with BD. This clinical awareness could be useful to promptly set evidence-based therapeutic strategies, such as cognitive-behavioral therapy and cognitive remediation, even for

older patients.[45] On the other hand, BD type II has traditionally been seen as a less severe and disabling disorder than BD type I, mainly because of the absence of psychotic features in hypomanic episode, which should not cause marked functional impairment or hospitalization. However, a higher total burden of illness more disabling in BD type II than BD type I[20,37] was demonstrated, but not in all studies.[42,46] Therefore, it would be erroneous to consider BD type II as an attenuated form of BD, as emerged by our findings: lifetime suicide attempts, psychiatric comorbidity, and alcohol abuse were more frequent in patients with BD type II. These data can be explained by the failure of the patient's coping strategies in response to painful or stressful life events, tendency to self-medicate, and a higher possibility to have a rapid bipolar cycle for a higher use of antidepressants. In this case, a significant and protective role is given by evidence-based non-pharmacological treatment, such as psychoeducation and social skills training.

Regarding lifetime suicide attempts, although literature data are controversial, our findings are consistent with several previous studies.[47-49] Very recently, a systematic review with meta-analysis did not find any statistical differences.[1]

Furthermore, BD commonly occurs alongside other psychiatric comorbidities such as substance abuse, anxiety, and personality disorders.[49-51] Among psychiatric disorders, BD seems to have the highest risk of having a comorbid DSM-IV axis I disorder. Our sample highlights significant psychiatric comorbidity in BD (n = 107 (32.2%) in BD type I and n = 166 (47.7%) in BD type II). According to our results, other studies found a higher rate of co-occurring symptoms with BD type II.[51] Long duration of major depressive episodes and anxiety symptoms are also considered significant risk factors for treatment resistance[52] and complex pharmacotherapy, confirming the complexity of the phenotypic and psychopathological presentation of BD.[53] Multiple diagnoses could increase the complexity of patient management, with the potential incoherence of treatment and worsening of clinical care. However, further studies with specific psychometric tools should be carried out to better categorize psychiatric comorbidities.

Aguglia et al. Bipolar Disorder I and II

Alpha Psychiatry 2024;25(4):472-479

Finally, analyzing illicit substances use in BD, one out of four reported the use of at least a substance with the highest rate of alcohol (n = 178, 26.2%), followed by cannabis (n = 117, 17.2%), psychostimulants (n = 79, 11.6%) and heroin (n = 26, 3.8%); our results are in line with other clinical studies on substance abuse and bipolar comorbidity in real-world.[54-57] Specifically, only alcohol use was reported mostly prevalent in patients with BD type II. No other statistical differences were found. Similar temperament traits, such as sensation seeking behavior, may play a decisive role in BD and alcohol use disorder.[56] The presence of alcohol use in patients with BD type II could be explained in different ways: first, alcohol may be used as self-medication to mitigate the co-occurrence of anxious or mixed symptomatology; second, patients may seek mild disinhibition in case of chronic or persistent depressive symptomatology; third, alcohol use may have started before the first manifestation of BD, due to the possibility of fostering new affective episodes. Surely, the use of substances, particularly alcohol, can unfavorably influence the clinical course of BD,[57] with lower affective recovery, more frequent mood switches, rapid cycling, mixed states and suicidal behaviors.[57,58]

Comparing the pharmacological prescriptions, mood stabilizers and antipsychotics were commonly prescribed to patients with BD type I, whereas antidepressants were commonly prescribed to patients with BD type II.[59-62] These are not surprising findings because BD type I is characterized by manic episodes rather than major depressive episodes and BD type II is characterized by hypomanic episodes and long-term recurrent major depressive episodes.[20] So, for patients with BD type I, this pharmacological treatment may be explained to ameliorate the stability of the clinical course, prevent psychotic symptomatology, manic phase, recurrent hospitalizations and involuntary admissions, confirming data literature.[1,59] On the contrary, patients affected by BD type II tend also to ask for more antidepressant medications for higher rates of depressions per year with prolonged major depressive episodes, lower tolerance to depressive symptoms and nostalgia for hypomanic episode, anxiety symptomatology in particular during major depressive episodes, more chronicity than patients with BD type I.[1,60-62] Furthermore, patients with BD type II tend to have a cognitive distortion, identifying the hypomanic episode as a physiological state of mental well-being without any other disturbing symptoms. Therefore, a continuous request of antidepressants prescription, the refusal to discontinue antidepressants and the fear of adverse events of antipsychotics and mood stabilizers are frequently reported. Lastly, depressive symptoms are three times more prevalent than manic or hypomanic ones in BD, are also longer, more persistent and can be associated with higher rates of morbidity (especially in BD type II) and mortality, with greater disability, a higher risk of suicidal behaviors and a worse quality of life than other phases.[63] In patients with mood disorders, suicidal behaviors are more reported when affective phases are characterized by mixed features, often related to the antidepressant prescriptions, and are associated with the onset of agitation, dysphoria, restlessness, irritability, anger, insomnia and behavioral disinhibition. Hence, the use of antidepressants is very controversial in bipolar patients. Furthermore, if concomitant illicit substances use and previous suicidal attempts are present in the illness bipolar course, the use of antidepressants is highly not recommended.[64-66] In addition, rapid discontinuation of antidepressant treatment causes higher rates of depressive relapses,[66] with an increased risk of suicidal behavior. Therefore, the higher rate of antidepressant medications in patients with BD type II may also explain the greater presence of suicidal behavior, as emerged from our results. Clinicians, considering the risk of clinical worsening, as well as the possibility of misdiagnosis in bipolar patients with depressive onset, should monitored carefully the prescription of antidepressant medications.

Despite the clinical relevance of our findings, this study has certain limitations that should be discussed. First, as a cross-sectional design, it is not possible to study any temporal or causal relationship between the considered variables. Second, our data are collected from a single research center, in- and out-patient unit. Third, several clinical variables (i.e., number of affective episodes, type of bipolar cycle, adherence to treatment, substance switch, presence of mixed symptoms, type of medical or psychiatric comorbidity), that may affect the illness course and further differentiate, were not included in the analyses due to the high number of missing values. Finally, no assessment with psychometric tools was made to investigate the potential clinical dimensions such as impulsivity, hostility, hopelessness, and aggressiveness.

In conclusion, the differentiation of the 2 nosologic bipolar diagnoses is in line with the current scientific interest, confirming the existence of a markedly different profile between BD type I and II, based on specific sociodemographic, clinical features, and pharmacological pattern. An early diagnosis and differentiation are crucial for a favorable prognosis, in order to prevent the onset of medical comorbidities, resistance to pharmacological treatment, cognitive impairment, and progressive decline with a negative impact on social functioning and quality of life. This differentiation could reduce the heterogeneity of bipolar presentation in research, optimize clinical assessment, and increase the interest in developing more precise and individualized therapeutic strategies. In particular, a careful monitoring of subjects at risk of developing BD may be useful and should be carried out through accurate tools for recognizing BD type II, such as the hypomania checklist for the earliest possible diagnosis and treatment. BD type II should require better clinical recognition and more research. Therefore, focusing the attention on distinguishing the subtype of patients with BD might also help to implement personalized psychosocial therapies, integrating the different professional roles. The therapeutic strategy for a patient with BD should involve a multidisciplinary team including psychiatrist, nurse, psychologist, and psychiatric rehabilitation technicians, in order to integrate the main evidence-based interventions, with the aim of personalized treatment. Further longitudinal studies are needed to explore the potential relationship between possible biomarkers and endophenotypes associated with BD subtypes and treatment response over time, evaluating the effectiveness of integrated treatment approaches, further supporting the differentiation of bipolar and related disorders.

Alpha Psychiatry 2024;25(4):472-479

Aguglia et al. Bipolar Disorder I and II

References

1. Hernandorena CV, Baldessarini RJ, Tondo L, Vázquez GH. Status of Type II vs. Type I bipolar disorder: systematic Review with Meta-Analyses. *Harv Rev Psychiatry*. 2023;31(4):173-182. [CrossRef]
2. Ghaemi SN. Bipolar spectrum: a review of the concept and a vision for the future. *Psychiatry Investig*. 2013;10(3):218-224. [CrossRef]
3. Zivanovic O, Nedic A. Kraepelin's concept of manic-depressive insanity: one hundred years later. *J Affect Disord*. 2012;137(1-3):15-24. [CrossRef]
4. Anderson IM, Haddad PM, Scott J. Bipolar disorder. *BMJ*. 2012;345:e8508. [CrossRef]
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington: American Psychiatric Publishing, 1980.
6. Leonhard K. *The Classification of Endogenous Psychoses. New York: Irvington*; 1957.
7. Foucher JR, Gawlik M, Roth JN, et al. Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: a review of their validity. *Dial Clin Neurosci*. 2020;22(1):37-49. [CrossRef]
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed – text revision (DSM 5-TR). Washington: American Psychiatric Publishing, 2022.
9. Dunner DL, Gershon ES, Goodwin FK. Heritable factors in the severity of affective illness. *Biol Psychiatry*. 1976;11(1):31-42.
10. Perugi G, Toni C, Travierso MC, Akiskal HS. The role of cyclothymia in atypical depression: toward a data-based reconceptualization of the borderline-bipolar II connection. *J Affect Disord*. 2003;73(1-2):87-98. [CrossRef]
11. Tondo L, Miola A, Pinna M, Contu M, Baldessarini RJ. Differences between bipolar disorder types 1 and 2 support the DSM two-syndrome concept. *Int J Bipolar Disord*. 2022;10(1):21. [CrossRef]
12. Tondo L, Vázquez GH, Baldessarini RJ. Depression and mania in bipolar disorder. *Curr Neuropharmacol*. 2017;15(3):353-358. [CrossRef]
13. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *J Clin Psychopharmacol*. 1996;16(2)(suppl 1):4S-14S. [CrossRef]
14. Angst J. The bipolar spectrum. *Br J Psychiatry*. 2007;190:189-191. [CrossRef]
15. Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr Neuropsychopharmakol*. 1980;13(4):156-167. [CrossRef]
16. Swartz HA, Suppes T, eds. *Bipolar II Disorder: Recognition, Understanding, and Treatment*. Arlington: APA Publishing; 2019.
17. Judd LL, Akiskal HS, Schettler PJ, et al. Comparative clinical phenotype and long-term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *J Affect Disord*. 2003;73(1-2):19-32. [CrossRef]
18. Benazzi F. Bipolar II disorder; epidemiology, diagnosis and management. *CNS Drugs*. 2007;21(9):727-740. [CrossRef]
19. Bobo WV. Diagnosis and management of bipolar I and II disorders: clinical practice update. *Mayo Clin Proc*. 2017;92(10:1532-1551.
20. Karanti A, Kardell M, Joas E, Runeson B, Pålsson E, Landén M. Characteristics of bipolar I and II disorder: study of 8766 individuals. *Bipolar Disord*. 2020;22(4):392-400. [CrossRef]
21. Parker G. Polarised views about bipolar disorder(s): a critique of the 2020 College guidelines for mood disorders. *Aust N Z J Psychiatry*. 2021;55(6):548-552. [CrossRef]
22. Coryell W. Bipolar II disorder, a progress report. *J Affect Disord*. 1996;41(3):159-162. [CrossRef]
23. Vieta E, Gastò C, Otero A, Nieto E, Vallejo J. Differential features between Bipolar I and bipolar II disorder. *Compr Psychiatry*. 1997;38(2):98-101. [CrossRef]
24. Coryell W, Keller M, Endicott J, Andreasen N, Clayton P, Hirschfeld R. Bipolar II illness: course and outcome over a five-year period. *Psychol Med*. 1989;19(1):129-141. [CrossRef]
25. Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the interval between the onset and management of bipolar disorder. *Can J Psychiatry*. 2017;62(4):247-258. [CrossRef]
26. Angst J, Gamma A, Bowden CL, et al. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. *Eur Arch Psychiatry Clin Neurosci*. 2013;263(8):663-673. [CrossRef]
27. Arnold LM. Gender differences in bipolar disorder. *Psychiatr Clin North Am*. 2003;26(3):595-620. [CrossRef]
28. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed (DSM 5). American Psychiatric Publishing, Washington, DC; 2013.
29. Salvi V, Aguglia A, Barone-Adesi F, et al. Cardiovascular risk in patients with severe mental illness in Italy. *Eur Psychiatry*. 2020;63(1):e96. [CrossRef]
30. Fusar-Poli L, Amerio A, Cimpoesu P, et al. Lipid and glycemic profiles in patients with bipolar disorder: cholesterol levels are reduced in mania. *Medicina (Kaunas)*. 2020;57(1):28. [CrossRef]
31. Aguglia A, Natale A, Fusar-Poli L, et al. Complex polypharmacy in bipolar disorder: results from a real-world inpatient psychiatric unit. *Psychiatry Res*. 2022a;318:114927. [CrossRef]
32. Aguglia A, Natale A, Fusar-Poli L, et al. Bipolar disorder and polysubstance use disorder: sociodemographic and clinical correlates. *Front Psychiatry*. 2022b;13:913965. [CrossRef]
33. Serafini G, Gonda X, Aguglia A, et al. Bipolar subtypes and their clinical correlates in a sample of 391 bipolar individuals. *Psychiatry Res*. 2019;281:112528. [CrossRef]
34. Dagani J, Baldessarini RJ, Signorini G, Nielssen O, de Girolamo G, Large M. The age of onset of bipolar disorders. In: de Girolamo G., McGorry P. D., Sartorius N., eds. *Age of Onset of Mental Disorders: Etiopathogenetic and Treatment Implications*; 2019:75-110. Springer, Springer Nature. [CrossRef]
35. Manchia M, Maina G, Carpiniello B, et al. Clinical correlates of age at onset distribution in bipolar disorder: a comparison between diagnostic subgroups. *Int J Bipolar Disord*. 2017;5(1):28. [CrossRef]
36. Dell'Osso B, Dobrea C, Cremaschi L, et al. Italian Bipolar II vs I patients have better individual functioning, in spite of overall similar illness severity. *CNS Spectr*. 2017;22(4):325-332. [CrossRef]
37. Cremaschi L, Dell'Osso B, Vismara M, et al. Onset polarity in bipolar disorder: A strong association between first depressive episode and suicide attempts. *J Affect Disord*. 2017;209:182-187. [CrossRef]
38. Tondo L, Baldessarini RJ, Hennen J, Floris G. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. *Am J Psychiatry*. 1998;155(5):638-645. [CrossRef]
39. Baldessarini RJ, Tondo L, Visioli C. First-episode types in bipolar disorder: predictive associations with later illness. *Acta Psychiatr Scand*. 2014;129(5):383-392. [CrossRef]

Aguglia et al. Bipolar Disorder I and II

Alpha Psychiatry 2024;25(4):472-479

40. Altamura AC, Buoli M, Cesana B, et al. Socio-demographic and clinical characterization of patients with bipolar disorder I vs II: a Nationwide Italian Study. *Eur Arch Psychiatry Clin Neurosci*. 2018;268(2):169-177. [CrossRef]

41. Brancati GE, Nunes A, Scott K, et al. Differential characteristics of bipolar I and II disorders: a retrospective, cross-sectional evaluation of clinical features, illness course, and response to treatment. *Int J Bipolar Disord*. 2023;11(1):25. [CrossRef]

42. Parker G, Fletcher K, McCraw S, Futeran S, Hong M. Identifying antecedent and illness course variables differentiating bipolar I, bipolar II and unipolar disorders. *J Affect Disord*. 2013;148(2-3):202-209. [CrossRef]

43. Sanchez-Moreno J, Martinez-Aran A, Tabarés-Seisdedos R, Torrent C, Vieta E, Ayuso-Mateos JL. Functioning and disability in bipolar disorder: an extensive review. *Psychother Psychosom*. 2009;78(5):285-297. [CrossRef]

44. Samalin L, de Chazeron I, Vieta E, Bellivier F, Llorca PM. Residual symptoms and specific functional impairments in euthymic patients with bipolar disorder. *Bipolar Disord*. 2016;18(2):164-173. [CrossRef]

45. Beunders AJM, Klaus F, Kok AAL, et al. Bipolar I and bipolar II subtypes in older age: results from the Global Aging and Geriatric Experiments in Bipolar Disorder (GAGE-BD) project. *Bipolar Disord*. 2023;25(1):43-55. [CrossRef]

46. Rihmer Z, Pestality P. Bipolar II disorder and suicidal behavior. *Psychiatr Clin North Am*. 1999;22(3):667-673. [CrossRef]

47. Baek JH, Park DY, Choi J, et al. Differences between bipolar I and bipolar II disorders in clinical features, comorbidity, and family history. *J Affect Disord*. 2011;131(1-3):59-67. [CrossRef]

48. Holma KM, Haukka J, Suominen K, et al. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. *Bipolar Disord*. 2014;16(6):652-661. [CrossRef]

49. Post RM, Leverich GS, McElroy S, et al. Prevalence of Axis-II comorbidities in bipolar disorder: relationship to mood-state. *Bipolar Disord*. 2018;20(4):303-312. [CrossRef]

50. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiologic catchment area (ECA) study. *JAMA*. 1990;264(19):2511-2518. [CrossRef]

51. Vázquez GH, Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. *Depress Anxiety*. 2014;31(3):196-206. [CrossRef]

52. McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. 2023;22(3):394-412. [CrossRef]

53. De Filippis R, Aguglia A, Costanza A, et al. Obsessive-compulsive disorder as epiphenomenon of comorbid bipolar disorder? An updated systematic review. *J Clin Med*. 2024;13(5):1230. [CrossRef]

54. Hunt GE, Malhi GS, Cleary M, Lai HMX, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: systematic review and meta-analysis. *J Affect Disord*. 2016;206:331-349. [CrossRef]

55. Haro G, Calabrese JR, Larsson C, et al. The relationship of personality traits to substance abuse in patients with bipolar disorder. *Eur Psychiatry*. 2007;22(5):305-308. [CrossRef]

56. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on alcohol and Related Conditions. *Arch Gen Psychiatry*. 2004;61(8):807-816. [CrossRef]

57. Grunze H, Schaefer M, Scherk H, Born C, Preuss UW. Comorbid bipolar and alcohol use disorder- A therapeutic challenge. *Front Psychiatry*. 2021;12:660432. [CrossRef]

58. Oquendo MA, Currier D, Liu SM, Hasin DS, Grant BF, Blanco C. Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry*. 2010;71(7):902-909. [CrossRef]

59. Shinozaki M, Yasui-Furukori N, Adachi N, et al. Differences in prescription patterns between real-world outpatients with bipolar I and II disorders in the MUSUBI survey. *Asian J Psychiatr*. 2022;67:102935. [CrossRef]

60. Lorenzo LS, Vázquez GH, Zaratiegui RM, Tondo L, Baldessarini RJ. Characteristics of bipolar disorder patients given antidepressants. *Hum Psychopharmacol*. 2012;27(5):486-491. [CrossRef]

61. Dell'Osso B, Arici C, Cafaro R, et al. Antidepressants in bipolar disorder: analysis of correlates overall, and in BD-I and BD-II subsamples. *J Affect Disord*. 2021;292:352-358. [CrossRef]

62. McInerney SJ, Kennedy SH. Review of evidence for use of antidepressants in bipolar depression. *Prim Care Companion CNS Disord*. 2014;16(5). [CrossRef]

63. Tondo L, Vázquez GH, Pinna M, Vaccotto PA, Baldessarini RJ. Characteristics of depressive and bipolar patients with mixed features. *Acta Psychiatr Scand*. 2018;138(3):243-252. [CrossRef]

64. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. *Mol Psychiatry*. 2019;24(2):198-217. [CrossRef]

65. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L. Agitated "unipolar" major depression: prevalence, phenomenology and outcome. *J Clin Psychiatry*. 2006;67(5):712-719. [CrossRef]

66. Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Illness risk following rapid vs. gradual discontinuation of antidepressants. *Am J Psychiatry*. 2010;167(8):934-941. [CrossRef]