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RESEARCH ARTICLE

Who's the Leader, Mania or Depression? Predominant Polarity and Alcohol/Polysubstance Use in Bipolar Disorders

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Abstract: ***Background*:** Predominant polarity characterises patients who mainly manifest recurrences of depression or mania/hypomania. Alcohol use disorder (AUD) and polysubstance use (PSU), which often complicate bipolar disorder (BD) and affect its clinical course, can influence predominant polarity. Nevertheless, previous studies have not clarified if BD patients differ in predominant polarity from BD patients with substance use disorder (SUD) comorbidity.

***Objective*:** The aim of this study was to compare predominant polarity between BD without SUD, BD with AUD and BD with PSU. We also investigated the association between predominant polarity and first episode polarity in each diagnostic group.

***Method*:** We evaluated predominant polarity (≥2:1 lifetime depressive *vs*. manic/hypomanic episodes) in 218 DSM-IV-TR BD patients. Specifically, data were obtained from 86 patients with BD without SUD, 69 patients with BD and AUD, and 63 patients with BD and PSU with alcohol as the primary substance abused.

***Results*:** The three groups significantly differed for predominant polarity. The most common predominant polarity in BD without SUD was manic, while in BD with AUD and in BD with PSU it was depressive. Uncertain predominant polarity was the least common in BD without SUD and BD with PSU, whereas in BD with AUD, manic predominant polarity was least common. Predominant polarity matched onset polarity in all groups.

***Conclusion*:** BD without SUD, BD with AUD, and BD with PSU have different predominant polarities. The correspondence between predominant polarity and polarity at the onset may impact diagnosis and treatment of BD.

Keywords: Alcohol use disorder, bipolar disorders, comorbidity, depression, mania, predominant polarity, polysubstance use.

1. INTRODUCTION

Since Kraepelin, although bipolar disorders (BD) were regarded as a single clinical entity, it was understood that they may have several variants that need to be carefully evaluated. In fact, only an accurate description of the clinical course of BD patients can reveal the complexity of manic-depressive illness, which presents significant inter-individual differences [1].

In this context, it is well known that alcohol use disorder (AUD) and polysubstance use (PSU), which are quite common in BD [2], can impact on treatment and prognosis of BD and recent studies have shown that they can be considered as both course and episode modifiers of the illness [3]. It follows that BD patients should be differently evaluated if they are complicated with such "dual" diagnosis. Nevertheless, it is not yet clear if this subgroup of patients differs from the BD group that is non-comorbid with substance use disorder SUD for its psychopathological profile, and whether there is a relationship of the profile with the type of the abused substance.

The idea of predominant polarity was proposed by Colom *et al*. as they tried to identify subgroups of patients who mainly manifest recurrences of depression or mania/hypomania [4]. Across clinical studies, 42% to 71% of patients may be labelled according to their predominant polarity [5], meaning that at least two-thirds of lifetime episodes in a single person are restricted to one pole of the illness. Several studies tried to identify the most common predominant polarity in BD patients. Their results were related to BD type, with depressive polarity found to prevail

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in studies including mainly BD type II [4, 6, 7] and studies including only BD type I patients reporting manic polarity to predominate [8-10]. Different clinical features and responses to treatment were described following predominant polarity, which was recently proposed as a course specifier for BD [5].

Regarding predominant polarity and SUD, data are contrasting. Two studies found that SUD before the first mood episode was associated with a manic predominant polarity, but they did not specify which type of psychoactive substance was involved [4, 7]. Furthermore, they found no association between predominant polarity and current AUD or SUD comorbidity. Nevertheless, a recent prospective study found a significant longitudinal decrease of alcohol/ other drug abuse during the course of the illness in the manic predominant polarity group [11]. Moreover, another study found increased frequency of depressive episodes in patients with comorbid BD and AUD [12].

The aim of this study was to clarify if BD patients differ in predominant polarity from BD patients with SUD comorbidity. On the basis that AUD is the most prevalent addictive disorder and that substances and alcohol are used in increasingly complex patterns [3], we considered three groups of BD patients, *i.e*., those without SUD, those with AUD comorbidity, and those with PSU with alcohol as the primary abused substance. We predicted that BD patients with AUD or PSU will differ for predominant polarity from BD patients without SUD comorbidity. We hypothesised that manic/hypomanic episodes will be frequent and recurrent in BD without SUD, thus providing support for the "primacy of mania" concept [13, 14].

We also investigated the association between predominant and first-episode polarity. Several studies have found that a first depressive episode was associated with a depressive predominant polarity [6, 7, 9, 15] and that a manic onset of illness was associated with a manic predominant polarity [7, 9, 15]. We would expect to find the same type of association in each diagnostic group (*i.e.*, BD, BD with AUD, and BD with PSU).

2. MATERIALS AND METHODS

2.1. Participants

Data were obtained from 86 outpatients with bipolar disorders (BD) without substance use disorders (SUD) comorbidity, 69 outpatients with BD and alcohol use disorder (AUD), and 63 outpatients with BD and polysubstance use (PSU) with alcohol as the primary abused substance. Patients were recruited at two sites, *i.e*., the Day-Hospital of Psychiatry of the "A. Gemelli" University Hospital and the inpatient service of "Villa Maria Pia" Neuropsychiatric Hospital, both located in Rome, Italy. Participants were screened for DSM-IV-TR [16] Axis I disorders and clinical diagnoses were confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I disorders, patient edition (SCID-I/P) [17]. Inclusion criteria were (i) age 18 to 65; (ii) BD type I or BD type II diagnoses, as assessed through the SCID-I/P; (iii) no additional diagnoses, as assessed through the SCID-I/P; (iv) at least five years of education; and (v) being fluent in Italian. Exclusion criteria were (i) psychotic features; (ii) lifetime history of major medical disorders or organic brain syndromes; (iii) presence of delirium tremens or hallucinosis; (iv) mental retardation or documented IQ<70; and (v) suspected cognitive impairment based on a Mini-Mental State Examination [18] score lower than 24. For patients with BD without AUD/PSU, an additional exclusion criterion was a history of substance abuse disorder (SUD), as assessed through the SCID-I/P. All participants were on condition-specific drug treatment. Anonymity was guaranteed to all participants. The study was in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1964) and subsequent revisions (59th WMA General Assembly, Seoul, South Korea, October 2008 and 64th WMA General Assembly, Fortaleza, Brazil, October 2013). All patients gave their written informed consent, after a complete description of the study was provided. Participants received no retribution.

2.2. Clinical Assessment

According to the original Colom *et al*. (2006) criteria [4], we considered patients to have depressive predominant polarity if they showed a ratio during their life time of at least 2:1 major depressive/manic–hypomanic episodes meeting DSM-IV criteria and patients to have manic predominant polarity if they presented the opposite pattern. Patients who did not meet these criteria were considered as having uncertain predominant polarity (UP). Mixed episodes were recorded, but not considered as related to any particular predominant polarity [4].

The severity of mania was assessed with the Young Mania Rating Scale (YMRS) [19] and the severity of depression with the 17-item Hamilton Rating Scale for Depression (HAM-D) [20]; both rating scales referred to the week before the assessment. Clinical characteristics were collected during a clinical interview.

2.3. Statistical Analyses

We compared sociodemographic and clinical characteristics betwixt BD without SUD, BD with AUD, and BD with PSU. Nominal variables were compared through the *chi*-squared test, using the Fisher or the Yates corrections as appropriate, followed by pairwise *post-hoc* analyses. Continuous variables were expressed as means ± standard deviation (SD); we used one-way analysis of variance (ANOVA) for intergroup comparisons, followed by *post-hoc* Scheffé tests.

In this study we performed the chi-square test, followed by pairwise *post-hoc* analyses to analyse differences in predominant polarity betwixt BD without SUD, BD with AUD, and BD with PSU. In an ancillary analysis we also performed the *chi*-squared test in the BD with PSU group to investigate the association between predominant polarity and type of abused substance. Moreover, we performed for each diagnostic group, ANOVA to compare clinical variables (age at onset of illness, duration of illness, number of episodes, and number of hospitalizations) between patients with different predominant polarities. To investigate the association

Table 1. Sociodemographic characteristics of the sample.

Characteristic	BD (*n*= 86)	BD with PSU (*n*= 63)	BD with AUD (*n*=69)	F or χ^2	df	*p*
Age (years): mean ± (SD)	45.91 (10.58)	43.33 (9.85)	45.53 (9.27)	1.34	2	0.26
Males: *n* (%)	37 (43.02)	37 (58.73)	30 (43.47)	4.31	2	0.11
Educational Level (years): mean ± (SD)	13.43 (3.79)	12.20 (3.61)	13.47 (3.56)	2.56	2	0.07
Marital status:	*N* (%)			10.39	6	0.10
Single:	36 (41.86)	31 (49.20)	21 (30.43)			
Married:	32 (37.20)	17 (26.98)	31 (44.92)			
Separated/divorced:	13 (15.11)	14 (22.22)	16 (23.18)			
Widowed	5 (5.81)	1 (1.58)	1 (1.44)			
Employment condition:	*N* (%)			7.26	8	0.50
Regular job:	47 (54.65)	30 (47.61)	40 (57.97)			
Occasionally employed:	4 (4.65)	4 (6.34)	4 (5.79)			
Unemployed:	22 (25.58)	24 (38.09)	19 (27.53)			
Student:	4 (4.65)	2 (3.17)	4 (5.79)			
Retired:	9 (10.46)	3 (4.76)	2 (2.89)			
Smoking: *n* (%)	32 (37.20)	42 (66.66)	27 (39.13)	14.79	2	0.0006

Legend: Patients with bipolar disorders; PSU= polysubstance use; AUD= alcohol use disorder; S.D.=Standard deviation; df=Degrees of freedom.

between predominant polarity and depressive/manic onset of the illness in each group, we performed the *chi*-squared test, after stratifying our sample by diagnosis. The level of significance was set at $p<0.05$.

3. RESULTS

3.1. Sociodemographic and Clinical Characteristics

Regarding sociodemographic characteristics (Table **1**), the three groups (*i.e.*, BD without SUD, BD with AUD, and BD with PSU) were homogeneous for age, gender and educational level and did not differ significantly for employment conditions and marital status. The three groups significantly differed for smoking; in particular, *post-hoc* testing showed that BD with PSU were more frequently smokers than BD (BD n = 32 %=37.20; BD with PSU n=42 %=66.66; χ^2 =12.62, df=1, p=0.0004) and BD with AUD (BD with AUD n=27 %=39.13; χ^2 =10.00, df=1, p=0.001).

Regarding clinical assessment (Table **2**), the three groups differed for type of BD, age at onset, depressive/manic onset of illness, and number of hospitalisations. Specifically, *post-hoc* testing showed that BD without SUD, as compared to BD with AUD, belonged more often to BD type I (BD n = 42 % = 48.83; BD with AUD n=19 %=27.53; χ^2=7.27, df=1, p=0.007) and presented more often with a manic onset (BD n = 43%=50.00; BD with AUD n=21% = 30.43; χ^2 = 6.04, df=1, p=0.01). Furthermore, BD without SUD were younger at onset of illness than BD with AUD (BD =26.33±9.81; BD with AUD =31.54±8.24; p=0.01) and BD with PSU had more hospitalisations than BD with AUD (BD with PSU =3.41±5.74; BD with AUD=1.08±2.47; p=0.002). Moreover, they differed for HAM-D scores; in particular, BD with AUD scored higher on the HAM-D than BD (BD = 5.83 ± 3.25; BD with AUD = 10.86 ± 6.81; p = <0.0001) and BD with PSU (BD with PSU = 6.11 ± 3.34; F = 19.77, df = 1, p= < 0.0001), whereas they did not differ for scores on the YMRS. Regarding drug treatment, the three groups differed

Table 2. Clinical characteristics of the sample.

Characteristics	BD (*n*= 86)	BD with PSU (*n*= 63)	BD with AUD (*n*=69)	*F* or χ^2	df	*p*
BDI: *n* (%)	42 (48.83)	23 (36.50)	19 (27.53)	7.48	2	0.02
Age at onset of illness: mean ± (SD)	26.33 (9.81)	27.92 (10.08)	31.54 (8.24)	4.26	2	0.01
Depressive onset of illness: *n* (%)	43 (50.00)	39 (61.90)	48 (69.56)	6.27	2	0.04
Duration of illness (years): mean± (SD)	19.56 (12.31)	15.57 (11.10)	16.31 (10.90)	2.28	2	0.10
Number of episodes: mean± (SD)	5.15 (3.62)	6.60 (5.79)	5.54 (5.12)	1.51	2	0.22
Number of hospitalisations: mean± (SD)	1.89 (2.38)	3.41 (5.75)	1.08 (2.47)	6.39	2	0.002
HAM-D score: mean ± (SD)	5.83 (3.25)	6.11 (3.34)	10.86 (6.81)	18.95	2	<0.0001
YMRS score: mean ± (SD)	3.06 (2.11)	3.14 (1.87)	3.62 (2.28)	0.64	2	0.52
Drugs:						
Antidepressants: *n* (%)	31 (36.04)	23 (36.50)	13 (18.84)	6.71	2	0.03
Mood stabilizers/anticonvulsants: *n* (%)	76 (88.37)	58 (92.06)	66 (95.65)	2.69	2	0.26
Antipsychotics: *n* (%)	51 (59.30)	26 (44.82)	13 (18.41)	25.90	2	<0.0001
Benzodiazepines: *n* (%)	11 (12.79)	11 (17.46)	3 (4.34)	5.82	2	0.06

Legend: BD = Patients with bipolar disorders; PSU= polysubstance use; AUD= alcohol use disorder; S.D.=Standard deviation; df=Degrees of freedom.

Table 3. Predominant Polarity in BD, BD with PSU and BD with AUD.

	BD (*n*= 86)	BD with PSU (*n*= 63)	BD with AUD (*n*=69)	χ^2	df	*p*	BD *vs.* BD with PSU * (*p*)	BD *vs.* BD with AUD * (*p*)	BD with PSU *vs.* BD with AUD * (*p*)
Predominant Polarity:	*n* (%)			23.69	4	<0.0001	0.13	<0.0001	0.02
DP	35 (40.69)	33 (52.38)	37 (53.62)						
MP	40 (46.51)	19 (30.15)	9 (13.04)						
UP	11 (12.79)	11 (17.46)	23 (33.33)						

Legend: BD=Patients with bipolar disorders; PSU=polysubstance use; AUD=alcohol use disorder; DP=depressive predominant polarity; MP=manic predominant polarity; UP=uncertain predominant polarity; df=Degrees of freedom.
*pair-wise post hoc test.

for prescriptions of antidepressants and antipsychotics. In fact, the *post-hoc* test indicated that there was a higher proportion of patients on antidepressants in the BD with PSU than in the BD with AUD (BD with PSU *n*=23 %=36.50; BD with AUD *n*=13 %=18.84; χ^2=5.18, df=1, *p*=0.02) group, and in the BD without SUD than in the BD with AUD (BD *n*=31 %=36.04 χ^2=5.57, df=1, *p*=0.01) group. The proportion of patients on antipsychotic drugs was higher in the BD with PSU group than in the BD with AUD (BD with PSU *n*=26 %=44.82; BD with AUD *n*=13 %=18.84; χ^2=10.00, df=1, *p*=0.001) and in the BD without SUD than in the BD with AUD group (BD *n*=51 %=59.30 χ^2=25.85, df=1, *p*=<0.0001).

Table 4. Association between Predominant Polarity and onset of illness.

	BD (*n*= 86)						BD with PSU (*n*= 63)						BD with AUD (*n*=69)					
	DP (*n*=35)	MP (*n*=40)	UP (*n*=11)	χ^2	df	*p*	DP (*n*=33)	MP (*n*=19)	UP (*n*=11)	χ^2	df	*p*	DP (*n*=37)	MP (*n*=9)	UP (*n*=23)	χ^2	df	*p*
Manic onset: *n*	5	30	8	30.13	2	<0.0001	0	18	6	47.41	2	<0.0001	1	9	12	37.29	2	<0.0001
(%)	(14.28)	(75.00)	(72.00)				(0.00)	(94.73)	(54.54)				(2.70)	(100.00)	(52.17)			
Depressive onset: *n*	30	10	3				33	1	5				36	0	11			
(%)	(85.71)	(25.00)	(27.27)				(100.00)	(5.26)	(45.45)				(97.29)	(0.00)	(47.82)			

Legend: BD=Patients with bipolar disorders; PSU=polysubstance use; AUD=alcohol use disorder; DP=depressive predominant polarity; MP=manic predominant polarity; UP=uncertain predominant polarity; df=Degrees of freedom.

In BD patients with PSU, where alcohol was the primary abused substance, 20 patients (31.74%) had AUD and cannabis use, 19 patients (30.15%) AUD and cocaine/ stimulant use, 19 patients (30.15%) AUD, cannabis, and cocaine/stimulant use, and 5 patients (7.93%) AUD and opioid use.

We found no association between predominant polarity and type of abused substance in BD patients with PSU.

3.2. Predominant Polarity

The three groups significantly differed for predominant polarity (Table **3**). In particular, pair-wise *post-hoc* tests showed that (i) BD *vs*. BD with AUD and (ii) BD with AUD *vs*. BD with PSU differed significantly. We found the manic polarity to be the most represented predominant polarity in BD and the depressive one in BD with AUD and in BD with PSU. The least represented predominant polarities in each group were the uncertain polarity in BD without SUD and BD with PSU, and the manic one in the BD with AUD group.

In each diagnostic group we found no differences betwixt patients with different predominant polarities in age at onset of illness, duration of illness, number of episodes, and number of hospitalisations.

3.3. Association between Predominant Polarity and Depressive/Manic Onset of Illness

In each group (*i.e.*, BD, BD with AUD, and BD with PSU), patients with depressive/manic/uncertain predominant polarity significantly differed for manic/depressive onset of illness (Table **4**). In detail, in all three groups, the onset of illness in patients with depressive predominant polarity was most often depressive, while that of patients with a manic or uncertain predominant polarity was most often manic.

4. DISCUSSION

The aim of this study was to clarify if BD patients differ in predominant polarity from BD patients with SUD comorbidity, specifically with AUD or PSU. We partly confirmed our hypothesis; in fact, results showed that the three groups significantly differ and, in particular, BD patients without SUD are different from BD patients with AUD and BD patients with AUD differ from BD patients with PSU. However, BD patients without SUD are not significantly different from BD patients with PSU.

Data showed that the most represented polarity in the BD patient group without SUD is the manic one, while in BD with AUD it is the depressive. The former is not surprising: in fact, excitement in manic-depressive illness is not exceptional but, conversely, it is frequent and recurrent. Heinroth in 1818 had stated that "excitement is not a mere somatic accessory symptom, but the fundamental affection of the psyche" [21] and Kraepelin, in his unitary conceptualisation of manic-depressive illness, viewed mania as a manifestation of the illness and not just the opposite pole of depression [1]. In contemporary psychiatry, depression is seen as more prominent, common, and difficult to treat [14]. Depression is more striking than excitement because hypomania is difficult to identify and patients usually do not complain having it or having the more recognisable mania, while all patients report their sufferance from depression. Besides the above consideration, hypomania is also difficult to treat due poor compliance [22]. Nevertheless, mania and hypomania, broadly conceived as excitement, cannot be separated from depression because they are interdependent, as they belong to the same nosological entity. Koukopoulos has gone as far as to claim that they are unidirectionally connected and proposed the primacy of mania hypothesis [13, 14], according to which depression is a consequence of mania: "*Mania is the fire and depression is its ash*", he claimed. Previous studies which did not exclude patients with SUD, attempted to identify the more common predominant polarity in BD patients, but found discordant results. We suggest that considering BD patients with AUD together with BD patients without SUD comorbidity could be confounding. In fact, in our study we found that they differ for predominant polarity. The depressive prevalent polarity we found in BD patients with AUD is in line with the previously observed association between alcohol abuse and increased frequency of depressive episodes in BD [12, 23]. Accordingly, this finding may also be consistent with the decrease in alcohol abuse longitudinally observed in a group with manic predominant polarity [11]. The relationship between AUD and depressive polarity in BD could be bidirectional, as a depressive polarity could represent a risk factor for AUD and/or AUD could influence the course of bipolar disorders in terms of depressive recurrence. In the first case, AUD could be

interpreted as a patients' attempt to counteract or "self-medicate" unpleasant affective symptoms, *e.g.* anxious symptoms that often characterise depression [24]. Furthermore, anhedonia, which was found to be a possible trait of BD individuals, as it is also found in euthymia [25], may represent a condition for which alcohol is abused. Therefore, it is possible that the polarity of their illness can influence *per se* the attitude of BD patients towards alcohol. It is also possible, on the other hand, that this phenomenon could be mediated by poor treatment response, which has been actually observed in BD patients with a depressive predominant polarity [5]. Regarding the second hypothesis, it is well known that alcohol can destabilise the course of bipolar disorder, causing more mood episode recurrences [26]. In this perspective, it is possible that alcohol masks mood episodes. In fact, manic/hypomanic symptoms may be repressed or attenuated by the depressant effect of alcohol and AUD could conceal the clinical expression of a manic episode. Further longitudinal studies are needed to extend these initial speculations.

It is noteworthy that the difference we found between BD patients and BD patients with AUD in terms of predominant polarity could be influenced by the presence of BD type II [5]. In fact, BD type II diagnosis is associated with depressive predominant polarity and in our sample BD patients with AUD showed a higher proportion of BD type II than BD patients without SUD. This is in line with the finding that SUD is often associated with BD type II diagnosis [27, 28]. We also found significant differences between the two groups regarding age at onset of illness; in fact BD patients were younger at the onset of the illness than BD patients with AUD. This should be viewed in the light of previous results demonstrating an association among manic predominant polarity and younger age at illness onset [7, 9, 15]. Nevertheless, we did not find any direct association between predominant polarity and age at onset.

We found that BD patients with AUD differ in predominant polarity from BD patients with PSU with alcohol as the primary abused substance. In fact, not only this latter group, similarly to BD patients with AUD, had a depressive predominant polarity, but it also had more manic predominant polarity than BD patients with AUD and a corresponding lower proportion of uncertain predominant polarity. This may be due to the fact that substances other than alcohol can have a different impact on mood episodes. A manic/hypomanic episode, for example, tends to overlap with the mental state induced by cocaine and stimulants, which in turn may be followed by depression upon withdrawal [3]. Furthermore, previous studies found that BD patients reported the use of stimulants aimed at enhancing the positive experience of hypomania [29, 30]. Moreover, patients may combine cocaine and alcohol or cocaine and cannabis not only to counteract mood symptoms, but also to dampen the effects of the concurrently assumed substances. Therefore, any substance effects could potentially impact on predominant polarity or the combination of drugs may obscure the effects of one another. In fact, we did not find any association between predominant polarity and type of PSU, and a possible explanation could be that in the BD with PSU group the use of alcohol prevails; this may account for the high prevalence of depressive predominant polarity. Conversely, the use of stimulant or psychotomimetic substances might account for the manic polarity, but evidence is lacking in our study. In evaluating predominant polarity, our study outlines the importance – – of considering separately BD patients with AUD and BD patients with PSU with alcohol as a primary abused substance.

Results indicated that in each group (*i.e.*, BD, BD with AUD, and BD with PSU) patients with depressive predominant polarity exhibited a depressive onset of illness and patients with manic predominant polarity a manic onset of illness. This agrees with previous findings that predominant polarity is usually associated with an onset of illness with the same polarity [6, 7, 11, 15]. We confirmed these findings in BD patients without any SUD, but we also extended them to groups of BD patients with SUD comorbidity. This could have important implications in terms of establishing an accurate diagnosis and providing appropriate treatment. Patients with a depressive onset of illness could be more at risk to developing AUD and to developing treatment-resistance. In fact, manic predominant polarity/manic onset of illness is associated with better treatment response than depressive predominant polarity/ depressive onset of illness [31]. Furthermore, SUD negatively affects BD treatment, which is difficult *per se* [32-34], and increases complexity of drug treatment, thus rendering drug combinations necessary. For example, a combination of an anticonvulsant and lithium was shown to be preferable to lithium alone for BD with AUD or PSU [35]. Onset of illness and predominant polarity could be useful information for clinicians to treat BD and BD co-occurring with SUD. Longitudinal studies should confirm these preliminary observations.

Our study has some limitations. First, mixed episodes defy definition of predominant polarity, hence they are not counted and may contribute to uncertain polarity [31]; however, the number of these episodes in our sample was low enough to impact little our results. Second, predominant polarity is a concept based on narrow DSM-IV definitions of mania and depression that fail to consider the possible presence of mixed features during manic/depressive episodes; this shortcoming is addressed by the DSM-5, which defined mixed features specifiers [36]. However, when we started our study, the DSM-5 was not available. Third, the clinical characteristics that have been proposed to identify agitated depressions, like psychomotor agitation, irritability and mood lability, do not encode for a specific type of predominant polarity [37, 38]. This could be an important shortcoming in studying BD patients with AUD or PSU comorbidity. In fact, mixed features and mixed depression characterise the clinical picture of mood episodes in BD patients with SUD [39]. Therefore, it is possible that episodes of depression with mixed features or agitated depression, not fully identifiable as DSM-IV-TR mixed episodes, could account for the high proportion of BD patients with AUD or with PSU, who were classified as having a depressive predominant polarity [40]. This matches a context considering mania and depression not as two different entities, but rather as two interconnected and

inseparable conditions amidst a broad clinical entity comprising multiple clinical pictures.

Furthermore, distinguishing BD patients according to their predominant polarity could represent another limitation, because predominant polarity considers only indirectly the intrinsic link between depression and mania and does not take into account the concept of cyclicity in manic-depressive illness [41]. Jean-Pierre Falret (Marcilhac-sur-Célé, Lot, France, 26 May 1794 – 28 October 1870), in the sixth decade of the XIX Century, had spoken about *"folie circulaire"*, characterised by an alternation between mania and melancholia followed by a "lucid" interval [42]. BD patients could exhibit a DMI/MDI cycle (depression or mania followed by mania/depression and free-interval), or a continuous cycle, in which the interval is absent [41,43,44]. Future studies could focus on the relationship between types of cycle and predominant polarity in BD patients and BD patients with SUD and thus could better investigate psychopathological differences and clinical profiles.

CONCLUSION

Our results indicate the importance of considering separately BD patients with AUD and BD patients with PSU with alcohol as the primary abused substance when considering predominant polarity in BD patients. The depressive predominant polarity observed in BD patients with AUD, with respect to the manic one observed in the BD-only group, could have important implications in terms of diagnosis and treatment. Furthermore, the higher percentage of manic predominant polarity expressed by BD with PSU group with alcohol as a primary abused substance, in comparison to BD with AUD, underlines the importance of assessing PSU in the context of AUD. Moreover, the correspondence between predominant polarity and onset of illness found in each group of the sample could offer a clue as to the adoption of timely treatment strategies for all BD patients.

CONFLICT OF INTEREST

No author has financial relationships with any commercial organization that might appear to represent a conflict of interest with the material presented in this report.

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