Differential Core Pharmacotherapy in Bipolar I Versus Bipolar II Disorder and European versus American Patients Not in a Syndromal Episode

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ABSTRACT

Aims. Assess bipolar disorder (BD) subtype and treatment location effects on BD core pharmacotherapy.

Methods. Outpatients not in a syndromal episode referred to University of Milan and Stanford University BD Clinics were assessed with SCID for DSM-IV, and the STEP-BD ADE, respectively. Prevalence and clinical correlates of antidepressant (AD), antipsychotic (AP), and mood stabilizer (MS) use, in aggregate and individually, were compared in bipolar I (BDI) versus II (BDII) patients in Milan/Stanford and in Milan versus Stanford patients, stratified by subtype.

Results. Milan/Stanford pooled BDI versus BDII patients significantly more often took APs (69.8% versus 44.8%), MSs (68.6% versus 57.7%), and valproate (40.1% % versus 17.5%), less often ADs (23.1% versus 55.6%) and lamotrigine (9.9% versus 25.2%). Milan versus Stanford patients (stratified by BD subtype) significantly more often took APs (BDI and BDII), ADs (BDII), and valproate (BDII), less often lamotrigine (BDI).

Conclusion. Milan/Stanford pooled BDI versus BDII patients significantly more often took APs, MSs, and valproate, less often ADs and lamotrigine. Milan versus Stanford patients more often took APs (BDI and BDII), ADs (BDII), and valproate (BDII), less often lamotrigine (BDI). Research regarding BD core pharmacotherapy relationships with bipolar subtype and treatment location is warranted to enhance clinical management.

Key words: Bipolar I Disorder (BDI); Bipolar II Disorder (BDII); mood stabilizers (MSs); antidepressants (ADs); antipsychotics (APs); pharmacotherapy

INTRODUCTION

The allocation of Bipolar and Related Disorders and Depressive Disorders into separate chapters in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) stemmed from various reasons (American Psychiatric Association, 2013), including the notion that Bipolar Disorder (BD) management had distinctive short- and long-term aims and pharmacological treatments. Nonetheless, little is definitively established about differential pharmacological management of BD type I (BDI) versus BD type II (BDII) (Parker, 2015). Indeed, BD pharmacological treatment choices have historically been more based on specific clinical dimensions rather than BD diagnostic subtype (Gelenberg and Pies, 2004).

For instance, the presence of psychotic symptoms has historically represented a distinctive domain in BDI versus BDII and an important issue in choosing an antipsychotic (AP) versus a mood stabilizer (MS) (Frangou *et al.*, 2002, Parker, 2015). Although hypomanic episodes in BDII remained by definition non-psychotic, DSM-5 (in a fashion similar to DSM-IV) permitted psychotic features to occur in depressive episodes in BDII patients (American Psychiatric Association, 2013). In addition, some APs, like quetiapine monotherapy, olanzapine (plus fluoxetine), and lurasidone (as monotherapy or combined with lithium or valproate) have United States (US) Food and Drug Administration approval for acute bipolar depression (Ketter, 2015) and are commonly used in the treatment of BDII patients, who commonly experience pervasive, recurrent, treatment-resistant major depressive episodes (Miller *et al.*, 2014). Also, combined treatments, such as atypical APs plus MSs, may be preferred for acute mania management from the outset (Yatham *et al.*, 2013). Moreover, among clinical features influencing choice of specific pharmacologic agents in BD, presence of suicidal ideation, which in bipolar patients has been estimated to be 20-30 times higher than in general population (Pompili *et al.*, 2013), represents an important marker for taking into consideration lithium (Benard *et al.*, 2016).

Moreover, a history of rapid cycling represents a feature that may discourage antidepressant (AD) use, for some clinicians (El-Mallakh *et al.*, 2015), but not for others (Amsterdam *et al.*, 2013), with consensus statements on the argument (Pacchiarotti *et al.*, 2013). As stated by Pacchiarotti and colleagues (Pacchiarotti *et al.*, 2013), ADs should be avoided in patients with a high mood instability or with a history of rapid cycling. Several case series from literature in fact, showed that AD may induce or prolong rapid cycling (Pacchiarotti *et al.*, 2013).

Besides patients' clinical features, the differential efficacy of certain drugs in preventing depressive versus manic/hypomanic episodes has been considered in developing the construct of psychotropic polarity index in BD (Carvalho *et al.*, 2014). Such an approach confirmed that most available BD treatments have more robust acute and relapse prevention efficacy for manic versus depressive episodes (Popovic *et al.*, 2012). In addition, clinical decisions for BD drug selection can be approached by attempting to balance likelihood of benefit (number needed to treat, NNT for response or emission) (Popovic *et al.*, 2011) versus harm (number needed to harm, NNH for side effects), while integrating clinical urgency and patient preferences (Ketter *et al.*, 2011, Ketter, 2014), with superior safety/tolerability (i.e., lower side effect burdens) commonly seen with ADs compared to MSs compared to APs, and with newer compared to older approved medications (Ketter *et al.*, 2014). Furthermore, other specific conditions can influence BD treatment choices. In particular, special BD populations, including pregnant (Yonkers *et al.*, 2004), elderly (Dunner, 2017) and pediatric (Goldstein *et al.*, 2017) patients, are taken into account when choosing pharmacological treatments.

Finally, qualitative (class of compounds) and quantitative (number and association patterns) differences in relation to the treatment of BD may exist within geographic regions across time (Baldessarini *et al.*, 2007, Hayes *et al.*, 2011, Hooshmand *et al.*, 2014) and between different geographic regions (Holtzman *et al.*, 2015), likely depending on multiple factors, including the presence or absence of national drug

indications, availability/approval status, cost, and clinician/family/patient attitudes regarding specific psychotropic compounds.

On the basis of growing concern of more pernicious course of BD in the US compared to Europe (Post *et al.*, 2014), and considering the relative lack of investigation comparing psychotropic prescription patterns in BD patients with specific emphasis on BDI versus BDII, we compared demographic and clinical correlates and usage rates for core BD psychotropic classes (ADs, APs, and MSs) and for individual MSs (lithium, valproate, and lamotrigine) in BDI versus BDII pooled American/European samples, and in American versus European samples, stratified by BD subtype.

METHODS

At the European center, the University of Milan (Italy) recruited BD patients not currently in a syndromal episode (to avoid the potentially confounding effect(s) of a current mood episode upon pharmacotherapy), at the University Department of Mental Health of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico in Milan, Italy, between 2011 and 2016. In order to better represent the phenomenology of BD in the Northern Italian population, patients referred by community-based psychiatric services, including day hospital, outpatient, and inpatient units, were also included. The University of Milan protocol was approved by the Fondazione IRCCS Ca' Granda Institutional Review Board (IRB), and subjects provided verbal and written informed consent to have their clinical charts reviewed for research purpose.

The details of the recruitment in Milan were the same as those previously reported in the Cremaschi and colleagues study (Cremaschi et al., 2017).

At the American center, the Stanford University sample included outpatients with BDI and BDII not currently in a syndromal episode (to avoid the potentially confounding effect(s) of a current mood

episode upon pharmacotherapy), referred by community practitioners (primarily psychiatrists) to the Stanford University Bipolar Disorder Clinic between 2000 and 2011. In order for the analysis to reflect phenomenology and treatment as encountered in the community (as opposed to as encountered in a BD research clinic), patients referred from the Stanford University Bipolar Disorder Research Program or previously treated in the Stanford University Bipolar Disorder Clinic were excluded. The American protocol was approved by the Stanford University Administrative Panel on Human Subjects, and patients provided verbal and written informed consent prior to participation.

The Stanford recruitment methods were the same of those reported in the article of Dell'Osso and co-author (Dell'Osso et al., 2015).

The main difference in recruitment among the two sites was represented by the use of different diagnostic tools, the Structured Clinical Interviews for Diagnostic and Statistical Manual of Mental Disorders for Axis I and Axis II disorders, Fourth Edition (DSM-IV) (SCID I and II) (American Psychiatric Association, 2000, First *et al.*, 1996, First *et al.*, 1997) in Milan and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation (ADE) (Sachs *et al.*, 2003) in Stanford. Another important difference between the two centers was represented by the different period of recruitment (from 2011 to 2016 for Milan and from 2000 and 2011 for Stanford).

At both sites, BD subtype (BDI versus BDII) was assessed by the above-mentioned structured diagnostic assessments as well as from available medical records and patient (and in most cases significant-other) reports, and subjects with and without current pharmacological treatment were recruited. Current psychotropic medication use was based upon patient (and in most cases significant-other) reports, as assessed by the above-mentioned structured diagnostic assessments, and review of medical records at the time of enrollment. APs included first-generation APs and second-generation APs at University of Milan, and second-generation APs (only) at Stanford University. ADs included selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), atypical ADs (e.g., bupropion,

mirtazapine), and first-generation ADs (e.g., heterocyclic ADs, monoamine oxidase inhibitors). MSs included lithium, valproate, and lamotrigine. Anxiolytic/hypnotic agents were not considered core BD psychotropics and were thus not reported in this manuscript.

As described below, demographic and clinical characteristics of participants were evaluated. At both sites, trained medical and research staff collected data on 6 demographic parameters and 16 illness characteristics/current psychotropic medications. The demographic parameters assessed were (A) Age (in years); (B) Gender; (C) Race/Ethnicity; (D) Education; (E) Marital Status; and (F) Employment status. Illness characteristics/current psychotropic medications assessed were (1) lifetime anxiety disorder (main comorbidity: i.e., the one causing clinician-determined most significant distress in Milan, and any comorbidity at Stanford); (2) lifetime alcohol/substance use disorder (main comorbidity in Milan, any comorbidity at Stanford); (3) lifetime eating disorder (main comorbidity in Milan, any comorbidity at Stanford); (4) lifetime personality disorder (main comorbidity in Milan, any comorbidity at Stanford); (5) BD subtype (BDI versus BDII); (5A) lifetime psychosis (which is very commonly associated with BDI); (5B) lifetime prior psychiatric hospitalizations (which is also very commonly associated with BDI); (6) family history ($\geq$ one first- or second-degree relative with mood disorder in Milan, $\geq$ one first-degree relative with mood disorder at Stanford); (7) onset age (in years); (8) illness duration (in years); (9) lifetime suicide attempt; current (baseline) (10) subthreshold mood symptoms in Milan (baseline YMRS > 7 but < 11, or baseline HDRS > 4 but < 7) and continued symptoms or roughening STEP-BD clinical status at Stanford; (11) depressive most recent episode; (12) AP; (13) AD; (14) MS (lithium, valproate, and/or lamotrigine); (15) lithium; (16) valproate; and (17) lamotrigine use. Medication categories were not mutually exclusive, so patients could be taking diverse combinations of APs, ADs, and MSs.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 20, Release 20.0.0 (IBM Corporation, Somers, NY) software on an Apple MacBook Pro Computer (Apple

Corporation, Cupertino, CA). Demographic and clinical correlates and prevalence of AD, AP, and MS (with the latter considered in aggregate and individually) use were compared in BDI versus BDII, with the Milan and Stanford sites pooled, and for Milan versus Stanford, with BDI and BDII considered separately). Analytic statistics included unpaired t-tests for comparisons of continuous variables and χ^2 tests or Fisher's exact tests, as indicated, for comparisons of categorical variables. Corresponding non-parametric tests were used when indicated. Moreover, multivariate analyses were performed only for significant parameters. A two-tailed significance level was used with a threshold of $p < 0.05$, not adjusted for multiple comparisons.

RESULTS

Socio-demographic and clinical features and core BD psychotropic medications in 663 patients not in a syndromal episode referred to the University of Milan, Italy (N=380) or Stanford University, California, USA (N=283) BD clinics, stratified by bipolar subtype (424 BDI versus 239 BDII) with sites pooled and by bipolar subtype/site (i.e., Milan BDI versus Stanford BDI, and Milan BDII versus Stanford BDII) are reported in Table 1.

1) All Bipolar Disorder Patients Referred to Milan or Stanford (BDI/BDII Subtypes and Milan/Stanford Sites Pooled)

Among these 663 BD patients (Table 1, rightmost column), mean ± SD age was 42.5±15.2 years; 50.1% were female; 87.3% were Caucasian, onset age was 24.0±11.2 years, illness duration was 18.5±13.0 years, and 37.9% had subthreshold symptoms. In rank order, the most common core BD psychotropic classes were MSs (66.6%), followed by APs (63.6% versus 66.6%, χ^2=1.3, df=1, p=0.3), and ADs (35.6% versus 66.6%, χ^2=128.1, df=1, p<0.0001) (not illustrated). In rank order, the most common individual

MSs were valproate (33.0%), followed by lithium (25.7% versus 33.0%, χ^2=9.4, df=1, p=0.003), followed by lamotrigine (15.2% versus 33.0%, χ^2=59.1, df=1, p<0.0001) (not illustrated).

2) Bipolar I Versus Bipolar II Disorder Patients (Milan and Stanford Sites Pooled)

Among BD patients (N=663, sites pooled) referred to either University of Milan (N=380) or Stanford University (N=283), almost two-thirds had BDI (64.0%, N=424), whereas only just over one-third had BDII (36.0%, N=239) (64.0% versus 36.0%, binomial test, df=1, p<0.0001) (Table 1, two leftmost data columns). BDI was significantly more common in Milan compared to Stanford (74.2% versus 50.3%, χ^2=40.3, df=1, p<0.0001). BDI compared to BDII patients were significantly older (43.5±14.9 versus 40.8±15.8 years, t=2.2, df=661, p=0.03) and significantly less often had a college degree (49.8% versus 63.7%, χ^2=11.8, df =1, p=0.0006). BDI compared to BDII patients also had later onset age (25.0±10.8 versus 22.3±11.9, t=3.0, df=661, p=0.003).

Although BDI compared to BDII patients had lower rates of lifetime comorbid anxiety (32.1% versus 56.1%, χ^2=38.5, df=1, p<0.0001) and eating (5.6% versus 10.5%, χ^2=5.2, df=1, p=0.03) disorders, these differences were likely related to the more restrictive definitions of comorbid disorders at Milan (main comorbidity) versus Stanford (any comorbidity). Although BDI compared to BDII patients had higher rates of lifetime psychosis (72.0% versus 10.9%, χ^2=228.6, df=1, p<0.0001) and lifetime psychiatric hospitalizations (83.5% versus 28.0%, χ^2=197.9, df=1, p<0.0001) in prior studies these have been consistently related to BDI illness subtype (Dell'Osso *et al.*, 2015; Dell'Osso *et al.*, 2017).

BDI compared to BDII patients had significantly higher rates of currently taking APs (69.8% versus 44.8%, χ^2=40.2, df=1, p<0.0001, Figure 1, left), MSs (68.6% versus 57.7%, χ^2=8.5, df=1, p=0.004, Figure 1, right), and valproate (40.1% versus 17.5%, χ^2=35.6, df=1, p<0.0001, Figure 2, middle), and significantly lower rates of taking ADs (23.1% versus 55.6%, χ^2=71.3, df=1, p<0.0001, Figure 1, middle)

and lamotrigine (9.9% versus 25.2%, χ^2=27.1, df=1, p<0.0001, Figure 2, right), but only non-significantly more often took lithium (27.8% versus 22.6%, χ^2=2.0, df=1, p=0.19, Figure 2, left).

After covarying for age, education, lifetime comorbidities, psychosis, psychiatric hospitalizations, and onset age, statistically significant pharmacotherapy differences regarding MSs (p=0.008), ADs (p=0.001), and valproate (p=0.001) survived. No other demographic or clinical or pharmacotherapy use parameter in Table 1 differed significantly between BDI and BDII patients in Milan or at Stanford (sites pooled).

3) Milan Versus Stanford Patients (Stratified by Bipolar Subtype)

Among all BDI patients (N=424) referred to University of Milan or Stanford University, there was a nearly twice as high rate of BDI patients referred to University of Milan (N=282) compared to Stanford University (N=142) (66.5% versus 33.5%, χ^2=92.5, df=1, p<0.0001), so that among all BDII patients (N=239) there was a significantly lower rate of BDII patients referred to University of Milan (N=98) compared to Stanford University (N=141) (41.0% versus 59.0%, χ^2=15.5, df=1, p<0.0001).

BDI patients referred to University of Milan versus Stanford University were significantly older (47.7±14.3 versus 35.1±12.3 years, t=9.0, df=422, p<0.0001), more often Caucasian (94.7% versus 72.5%, χ^2=41.7, df=1, p<0.0001), and less often had a college degree (32.3% versus 84.5%, χ^2=103.1, df=1, p<0.0001).

BDI patients referred to University of Milan versus Stanford University also had significantly later age of onset (28.1±10.7 versus 19.1±8.3 years, t=10.7, df=422, p<0.0001) and longer illness duration (19.6±12.3 versus 15.2±13.2 years, t=3.4, df=422, p=0.0008). Although BDI patients referred to University of Milan versus Stanford University had lower rates of lifetime comorbid anxiety (22.9% versus 50.0%, χ^2=31.5, df=1, p<0.0001), alcohol/substance use (13.3% versus 30.3%, χ^2=17.3, df=1, p<0.0001), and eating (3.0% versus 11.3%, χ^2=12.6, df=1, p=0.0007) disorders.

BDI Milan patients had higher rates of lifetime psychosis (74.5% versus 64.8%, χ^2=4.3, df=1, p=0.04) and psychiatric hospitalizations (89.1% versus 72.5%, χ^2=18.6, df=1, p<0.0001) such as a significantly higher rate of current subthreshold symptoms (46.5% versus 25.7%, χ^2=17.6, df=1, p<0.0001) and family history of mood disorder (65.0% versus 50.0%, χ^2=8.7, df=1, p=0.003).

BDI patients referred to University of Milan compared to Stanford University more often took APs (85.2% versus 50.0%, χ^2=59.5, df=1, p<0.0001, Figure 3, left) and less often took lamotrigine (4.9% versus 19.0%, χ^2=21.3, df=1, p<0.0001, Figure 4, right) as well as MSs, although the latter fell short of statistical significance (68.3% versus 76.1%, Chi-square=3.4, df=1, p=0.068, Figure 3, right).

After covarying for age, race, education, lifetime comorbidities, psychosis, and psychiatric hospitalizations, family history, onset age, and illness duration, statistically significant pharmacotherapy differences related to APs (p<0.0001) and lamotrigine (p=0.001) use for BDI remained so. No other demographic, clinical characteristic, or pharmacotherapy use parameter in Table 1 differed significantly between BDI patients at Milan versus Stanford.

BDII patients referred to University of Milan compared to Stanford University were significantly older (50.4±14.1 versus 34.2±13.3 years, t=9.0, df=237, p<0.0001), were more often Caucasian (96.9% versus 80.8%, χ^2=19.7, df=1, p<0.0001), and married (51.6% versus 36.2%, χ^2=6.0, df=1, p=0.02), and less often had a college degree (26.9% versus 89.3%, χ^2=98.6, df=1, p<0.0001).

BDII patients referred to University of Milan compared to Stanford University also had later age of onset (29.9±12.9 versus 17.1±7.5, t=9.7, df=237, p<0.0001).

BDII patients referred to University of Milan had lower rates of lifetime comorbid anxiety (38.9% versus 68.1%, χ^2=20.2, df=1, p<0.0001), alcohol/substance use (5.1% versus 38.3%, χ^2=34.3, df=1, p<0.0001), eating (3.1% versus 15.6%, χ^2=9.7, df=1, p=0.002), and personality (3.1% versus 12.1%, χ^2=6.1, df=1, p=0.02) disorders. Moreover, we found a higher rate of lifetime psychiatric hospitalization in BDII Milan patients (52.1% versus 10.6%, χ^2=49.3, df=1, p<0.0001).

BDII patients referred to University of Milan compared to Stanford University significantly more often took APs (72.0% versus 28.3%, χ^2=45.2, df=1, p<0.0001, Figure 3, left), ADs (68.8% versus 47.5%, χ^2=10.2, df=1, p=0.002, Figure 3, middle), and valproate (26.9% versus 11.3%, χ^2=9.2, df=1, p=0.003, Figure 4, middle).

When covarying for age, race, education, marital status, lifetime comorbidities, psychosis, and psychiatric hospitalizations, and onset age, statistical significance of APs (p=0.001), ADs (p=0.002) and valproate (p=0.032) use survived. No other demographic, clinical characteristic or pharmacotherapy use parameter in Table 1 differed significantly between BDII patients at Milan versus Stanford.

DISCUSSION

The present collaborative study sought to compare and contrast patterns of core BD pharmacotherapy in BDI versus BDII patients across two substantial European (University of Milan) and American (Stanford University) samples. According to our knowledge, this is one of few such reports in a field with considerable heterogeneity due to various reasons. Indeed, several relevant differences emerged in relation to BD subtype (BDI versus BDII) and to different geographic region (Stanford versus Milan).

Taken as a whole, (pooling bipolar subtype and treatment region), all BD patients took MSs and APs in 67% and 64% of cases, respectively, nearly twice as often as ADs (36%). This finding has noteworthy considerations. Thus, MSs and APs appeared to represent cornerstones of post-acute core BD pharmacotherapy, being the main pharmacological therapies in 2/3 of cases, consistent with International guidelines' treatment recommendations (Yatham *et al.*, 2013).

Nevertheless, ADs, despite being used only about half as often, still may have had some clinical utility in post-acute BD treatment, reflecting the ongoing debate between clinicians who focus on the strengths (Amsterdam *et al.*, 2013) versus limitations (Ghaemi *et al.*, 2003) of ADs use in BD. Anyway, the rate

of ADs usage is high both in Milan and Stanford showing that, despite the evidence from literature (Sachs et al., 2007; Sidor et al., 2010), this therapeutic option is still one of the most used in clinical practice for the treatment of bipolar depression. The pressure to manage depressive phases is compelling to clinicians and often requested by patients and it could explain the high rates of ADs utilization despite the uncertain and inconclusive state of the evidence of efficacy.

With respect to differential clinical characteristics and psychotropic use in relation to BD subtype (Milan and Stanford sites pooled), BDI versus BDII patients were found to significantly more often take APs, MSs, and valproate, and significantly less often take ADs and lamotrigine. The former findings (more APs, MSs and valproate in BDI) could be related to BDI versus BDII having higher rates of lifetime psychosis and psychiatric hospitalizations, and more severe mood elevation episodes as shown in previous studies (Dell'Osso *et al.*, 2015, 2017). More in detail, the high rate of APs could be explained not only by the more frequent lifetime psychosis but also by the manic episodes which usually were treated with APs.

On the other hand, the facts that BDII patients more often took ADs and lamotrigine could be related to the presence of more pervasive and recurrent depressive episodes as well as more frequent anxiety comorbidity (for ADs use), which have been seen as characteristic of BDII in prior studies of other (Goodwin and Jamison, 2007) and our (Dell'Osso *et al.*, 2015, 2017) groups and may also reflect a different genetic predisposition of some BDII patients to anxiety disorders (Wang *et al.*, 2014). Of note, BDI versus BDII patients were found to more often take lithium but only to a non-significant degree, likely reflecting lithium's frequent use as one of the best studied and most effective psychotropics in the post-acute treatment of BDII (Hadjipavlou *et al.*, 2003) and BDI patients, particularly in those with recognizable, recurrent episodes, separated by periods of remission (Malhi *et al.*, 2016).

When patients were stratified according to region, a mixture of more and less severe illness characteristics emerged with respect to site. For instance, among Italian versus American patients, BDI had higher

prevalence, and Italian BDI patients were older, had a later age at onset, longer duration of illness, and more subthreshold symptoms, lifetime psychosis, and psychiatric hospitalizations, but lower rates of lifetime comorbid anxiety, alcohol/substance use, and eating disorders (possibly related to using main rather than any comorbidity in Milan). Thus, while some differences were likely due to across-site differences in inclusiveness for certain parameters (e.g., comorbidity), other differences – like the earlier onset of BDI in American patients – could reflect a more structural difference which could, in turn, depend on multiple variables (e.g., familial loading, childhood adversity) (Dell'Osso *et al.*, 2016; Post *et al.*, 2016), or could reflect the higher rate of early onset BD at Stanford.

Although BDI patients referred to University of Milan versus Stanford University had higher rates of lifetime psychosis and psychiatric hospitalizations, these differences were possibly related to the BDI subtype being more severe at Milan versus Stanford. While a higher rate of hospitalizations may be the consequence of more lifetime psychotic episodes and longer duration of illness, it is more speculative to provide reliable explanations for higher lifetime psychosis (e.g., less effective pharmacological regimens/medications/dosages).

Moreover, the significantly higher rate of current subthreshold symptoms found in BDI Milan patients may have been related to different criteria for defining this characteristic at Milan versus Stanford.

Similarly, the higher rate of family history of mood disorder observed in BDI Milan patients may have been related to the less restrictive criteria for family history of mood disorder at Milan (1st or 2nd degree relatives) versus Stanford (1st degree relatives only).

With respect to differences in pharmacotherapy, Italian compared to American BDI patients more often took APs and less often took lamotrigine. This aspect could be explained by a lower rate of anxiety symptoms in this group. The higher rate of AP use in Italian BDI patients might be explained by their higher rates of lifetime psychosis and psychiatric hospitalizations. Indeed, use of APs as first therapeutic option over MSs in the maintenance treatment of BD – BDI, in particular – has been reported in other

recent European (Kessing *et al.*, 2016) and American (Miller *et al.*, 2015) studies. Though less marked (i.e., 68.3% in Milan versus 76.1% at Stanford) compared with the differential AP use (i.e., 85.2% in Milan versus 50.1% at Stanford), the 7.8% lower use of MSs (versus the 35.1% higher use of APs) in Italian versus American BDI patients might be related to the more common overall use of MSs (as the most utilized class) in the Stanford BD Clinic, as previously reported (Hooshmand *et al.*, 2014).

Several noteworthy differences emerged in relation to BDII patients stratified according to their treatment region.

First, Italian BDII patients were less represented compared to their Stanford counterparts, with only approximately half as high a rate (25.8% versus 49.8%). In addition, Italian versus American BDII patients were older and had a later onset age. Taken as a whole, these findings confirm those in previous collaborative studies of our group, identifying Stanford patients with BDII as a prevalent population of bipolar subjects with several characteristics of high illness severity, such as earlier onset (Dell'Osso *et al.*, 2015), compared to American BDI patients in some ways and to Italian BDII patients in many other ways. Consistent with this perspective, Italian versus American BDII patients had lower rates of lifetime psychiatric comorbidity, notwithstanding the more restrictive definition of comorbidity (main versus any) in Milan compared to at Stanford. On the other hand, Italian versus American BDII patients had significantly higher rates of lifetime psychiatric hospitalizations, although this specific difference may have been related to overall older age in Milan versus Stanford BDII patients, as well as a higher rate of married patients in Milan vs Stanford (with partners likely contributing to patients' episode recognition), and different patient/clinician hospitalization attitudes at the two sites, with more limited (depending on medical insurance) access at Stanford, and easier access in Milan.

Indeed, some of the above-mentioned differences may be due to trans-site differences in inclusiveness for some variables, such as the lower rates of lifetime comorbid anxiety, alcohol/substance use, eating and personality disorders, whose differences may have been related to the more restrictive criteria for

comorbid disorders at Milan (main comorbidity) versus Stanford (any comorbidity). Some differences nonetheless, indicated that Italian BDII patients presented with some specific illness severity characteristics which were non-inferior compared to American BDI patients (Dell'Osso *et al.*, 2017).

In terms of pharmacological therapy, Italian versus American BDII patients significantly more often took APs. The frequent use of APs for Italian BDII patients, who lacked lifetime psychotic manifestations in the vast majority of (over 90%) cases, may be unexpected.

In general, the high rate of APs in BDII patients could be explained by some specific indication that these compounds present for the management of bipolar depression. Furthermore, this high rate of AP prescriptions in Italy could also have depended on the widespread use of quetiapine, being the only compound available in Italy approved for all three phases of BD and for bipolar depression, in particular. The high rate of AP use in Italian BDII patients, however, might in turn be related to a higher rate of prescription of ADs there. In fact, ADs were used in more than 2/3 of Italian BDII patients (68.8% versus 47.5% at Stanford), reflecting the traditionally more liberal use of ADs in BD in Europe compared with the US (Karanti *et al.*, 2016; Möller *et al.*, 2006). Indeed, a high rate of Italian AP use may counterbalance more liberal Italian use of ADs, possibly mitigating the risks of mood switching and rapid cycling with ADs. Finally, the relatively high rate of prescription of valproate in Italian BDII patients could be considered novel compared to older literature, which indicated lithium was used more than valproate in non-German speaking European countries (Kessing *et al.*, 2011), even though more recent data has been more consistent with our findings (Song *et al.*, 2016), though not specifically in BDII patients.

Our study has noteworthy strengths and limitations. Strengths included assessing BD subtypes using validated diagnostic instruments, and having substantial numbers of BDI (N=424) and BDII (N=239) patients who did not currently have a syndromal mood episode (to avoid the potentially confounding effect(s) of a current mood episode upon pharmacotherapy) at sites in Europe (Milan N=380), and the US (Stanford N=283). Limitations included the use of samples referred to urban Northern Italian and

suburban Northern California BD specialty clinics, limiting generalizability. The representativeness and comparability of the samples may have been reduced also by potential differences in terms of standards of care between the two sites as well as by the different collection period.

Another important difference between the two sites, that could have influenced some results, is represented by the recruitment area. In fact, all of the patients assessed at Stanford were also treated here, whereas, only a part of the sample recruited in Milan were treated here.

Additionally, our sample size, though substantial overall (N=633), had less robust statistical power in some subsets used in the analyses (e.g., in Milan, only 98 patients had BDII). Other limitations were across-site differences in recruitment years (2011-2016 in Milan, versus 2000-2011 at Stanford – although this difference could have been mitigated by possible later adoption of pharmacotherapy trends in Northern Italy versus Northern California), and across-site differences in assessment instruments (the SCID I and II in Milan, versus the STEP-BD ADE and MINI at Stanford), although across-site differences in inclusiveness of clinical parameters, such as lifetime comorbidities (less inclusive in Milan versus Stanford), family history (more inclusive in Milan versus Stanford), and current subsyndromal symptoms (more inclusive in Milan versus Stanford), likely raised more substantive challenges. Also, we did not assess relationships between anxiolytic/hypnotic use, location, and bipolar subtype. Although anxiolytic/hypnotic agents are often not considered core BD pharmacotherapies, comorbid anxiety disorders are very common in BD patients, and these agents are frequently administered to BD patients (Bobo *et al.*, 2015). Another limitation was represented by the lack of data about the predominant polarity, which may be useful to explain some differences in terms of treatment choices. Moreover, no information about lifetime depression had been reported in this study because the dataset used considered for the analysis had been based on retrospective cross-sectional data, without some important characteristics such as previous depressive episodes.

Finally, we did not correct for multiple comparisons, which particularly limited interpretation of findings with p-values between 0.05 and 0.01. However, this liberal statistical approach increased assay sensitivity with respect to our ability to detect relationships between core pharmacotherapies, bipolar subtype, location, and baseline clinical characteristics.

In conclusion, we contend that our observed associations between pharmacotherapy and bipolar subtype and location, suggest potentially important variations in BD pharmacotherapy administration. Given the large human and financial costs of BD, further examination of relationships between BD pharmacotherapy, bipolar subtype, and location is warranted in order to enhance clinical management.

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