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ORIGINAL RESEARCH

Gender-related differences in patients with bipolar disorder: a nationwide study

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Objective. The possible presence of gender-related differences in patients with bipolar disorder (BD) may have diagnostic and therapeutic implications. This multicenter study aimed to investigate gender differences in BD in the largest Italian database collected to date, on behalf of the Italian Chapter of the International Society of Bipolar Disorders.

Methods. A total of 1674 patients (males: n = 714; females: n = 960) from different psychiatric departments were compared according to gender on demographic/clinical variables. Owing to the large number of variables statistically related to the dependent variable (gender) at the univariate analyses, preliminary multiple logistic regression analyses were performed. A final multivariable logistic regression was then performed, considering gender as the dependent variable and statistically significant demographic/clinical characteristics as independent variables.

Results. The results of the final multivariable logistic regression analysis with previous statistically significant demographic and clinical variables were the following: female gender was less frequently associated with employment (odds ratio [OR] = 0.7, $P < 0.01$), lifetime single marital status (OR = 0.45, $P < 0.01$), and substance abuse in the last year (OR = 0.35, $P < 0.01$), whereas it was more frequently associated with a major number of lifetime major depressive episodes (OR = 1.78, $P < 0.01$) and psychiatric visits in the last year (OR = 1.38, $P = 0.01$).

Conclusion. Few significant differences were found between genders in BD, particularly for those clinical features that are associated with poor prognosis (substance abuse for males and number of depressive episodes for females). Transcultural studies are needed to identify cultural versus illness-related variables possibly explaining the different clinical presentation of BD in relation to gender.

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Key words: Bipolar disorder (BD), clinical aspects, gender, outcome, substance abuse.

Introduction

Bipolar disorders (BDs) are prevalent, comorbid, and impairing conditions burdened by relevant rates of disability and suicidal behaviors.[1]

Differently from major depressive disorder and anxiety disorders, whose prevalence has been found consistently higher in female versus male gender (female-to-male ratio of prevalence rates for anxiety disorders, 1.5–2.3; female-to-male ratio of prevalence rates for major depression, 1.9–2.0),[2,3] most epidemiologic investigation in bipolar patients has shown no gender differences in terms of prevalence rates.[4] However, previous and more recent

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studies reported higher frequencies of hypomania or bipolar II disorder in women as well as other sociodemographic and clinical gender-related differences.[4-9]

Beyond epidemiological aspects, female BD patients have shown specific clinical peculiarities that may be of relevance in relation to presentation and outcome, even though results in this field may be not always consistent because of limited sample size, enriched samples, and geographic and other methodological issues.[10] In a Danish study, for instance, women with BD showed distinct patterns of in- versus outpatient treatment and prevalence of mixed depression and comorbidity with substance abuse, compared with male bipolar patients.[11] In a subsequent study,[12] male gender was reported to be associated with mania at the onset of bipolar I disorder (BD-I). In addition, men were found to have higher rates of comorbid alcohol abuse/dependence, cannabis abuse/dependence, pathological gambling, and conduct disorder. On the other hand, female bipolar patients reported higher rates of comorbid eating disorders and weight change, appetite change, and central insomnia during depression. In a subsequent American study, female gender was associated with significantly higher risk of rapid cycling, cycle acceleration, and increased severity of mood episodes over time in a large sample of bipolar patients.[13] More recently, an European-American collaborative study found that severe mood episodes lead more often to hospitalizations in bipolar women.[9] Another recent British study reported that sleep loss triggering episodes of expanded mood was associated with female gender and BD-I subtype.[14]

Gender differences in BD may also be relevant in light of treatment.[15] For instance, a recent collaborative European study reported for the first time that the risk profiles for the development of an antidepressant treatment-emergent mania differ significantly according to gender.[16]

As an increasing interest toward patient-oriented medicine and gender-related issues has been observed in many medical and psychiatric conditions, this study sought to assess gender differences and clinical correlates in the largest multicenter sample of Italian bipolar patients analyzed to date. We hypothesized that bipolar patients may exhibit specific differences in terms of sociodemographics and clinical features according to gender.

Methods

An overall sample of 1674 patients was enrolled from different Italian psychiatric clinics. This sample, in light of the size and the number of involved psychiatric units, may be considered satisfactory and representative of the entire national territory. The protocol was approved by the local Ethical Committees. Patients had a diagnosis of BD according to *DSM-IV-TR* (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*) criteria.[17] Diagnoses were made by expert psychiatrists, who had regularly followed up with the selected patients and confirmed by the Mini-International Neuropsychiatric Interview.[18] Patients consecutively afferent to outpatient or inpatient services were included in the study. Clinical information was extrapolated through a review of the clinical charts and clinical interviews with patients and available relatives. Data were entered into an electronic central database (electronic Case Report Form: e-CRF). Collected data included the following sociodemographic and clinical variables divided into 3 clusters:

- Cluster 1 (sociodemographic variables): age, gender, education (years), employment, marital status (at least 1 marriage or partnership), and living alone.
- Cluster 2 (lifetime clinical variables): age at onset of BD, age at first pharmacological prescription (including benzodiazepines), age at first contact with psychiatric services, first psychiatric diagnosis, age at first psychiatric diagnosis, age at first diagnosis of BD, age at first mood stabilizer/atypical antipsychotic, polarity of first episode, lifetime number of manic episodes, lifetime number of depressive episodes, prevalent polarity, prevalent course, lifetime psychotic symptoms, and lifetime attempted suicide.
- Cluster 3 (clinical variables—last year of observation): type of current episode, number of hypomanic/manic episodes, number of depressive episodes, presence of psychotic symptoms, presence and number of attempted suicides and the degree of lethality, comorbidity with substance misuse, presence of hospitalizations, presence of insight, attribution of symptoms to a psychiatric disorder, treatment adherence, number of visits, and administration of psychoeducational interventions (according to Colom's model).[19]

Prevalent polarity was calculated according to the Barcelona proposal, defined as at least two-thirds (2/3) of the total number of past episodes being from the same polarity.[20]

Lethality of suicide attempts was evaluated according to global impression of Scale for Assessment of Lethality of Suicide Attempt (score 1–2: low; score 3: medium; score 4–5: high).[21]

Exclusion criteria were the following: (1) patients who had not been examined in the last 12 months for the impossibility of collecting data on cluster 3 variables (last year of observation); (2) patients whose clinical information was incomplete; and (3) patients with a diagnosis of dementia, mental retardation, or other medical conditions (eg, untreated endocrine disorders) associated with an increased risk of psychotic symptoms or other clinical features (eg, suicidal attempts).

Descriptive analyses of the total sample were performed. Gender was compared by Student's t test for

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TABLE 1. Sociodemographic variables of the total sample and of the two gender groups

Variables		Total sample N = 1674	Males N = 714 (42.7%)	Females N = 960 (57.3%)	P^a
Education (years) Missing: n = 5	< 8	120 (7.2%)	23 (3.3%)	97 (10.2%)	< **0.01**
	8–13	484 (29.0%)	211 (29.6%)	273 (28.5%)	
	14–18	749 (44.9%)	325 (45.6%)	424 (44.3%)	
	> 18	316 (18.9%)	153 (21.5%)	163 (17.0%)	
Employed Missing: n = 3	Yes	1265 (75.7%)	552 (77.4%)	713 (74.4%)	< **0.01**
	No	406 (24.3%)	161 (22.6%)	245 (25.6%)	
Marriage or partnership Missing: n = 2	≥ 1	1140 (68.2%)	413 (57.9%)	727 (75.8%)	< **0.01**
	Never	532 (31.8%)	300 (42.1%)	232 (24.2%)	
Living alone Missing: n = 2	Yes	285 (17.0%)	131 (18.4%)	154 (16.1%)	< **0.01**
	No	1387 (83.0%)	582 (81.6%)	805 (83.9%)	
Age[b]		48.65 (±13.46)	47.27 (±14.16)	49.68 (±12.82)	< **0.01**

[a]In bold are statistically significant *P* values resulting from χ^2 and from unpaired Student's *t* test for the variable "age."
[b]Standard deviations are reported in parentheses for the variable "age."

quantitative variables and chi-square tests for qualitative variables. Owing to the large number of variables statistically related to the dependent variable (gender) at the univariate analyses, preliminary multiple logistic regression analyses (1 for each abovementioned cluster) were performed including only statistically significant variables. Finally, statistically significant variables from these final models were then inserted in a new global starting multivariable logistic regression model in order to obtain the variables independently associated with gender.

The selection of the variables has been done according to a backward procedure; in the last multivariable logistic model, the age (not statistically significant) has been kept in the model in order to obtain the estimates adjusted for this variable. The goodness of fit has been assessed by the Hosmer-Lemeshow test.

The level of statistical significance was set at $P \leq 0.05$. Statistical analyses have been performed using SAS® 9.2.

Results

The case series included 1674 patients: 714 males (42.7%) and 960 females (57.3%). Patients had an age between 18 and 80 (mean: 48.65 ± 13.46). Descriptive analyses of the total sample and according to gender are reported in Tables 1-3.

There were not significant differences between the 2 genders in the age at first pharmacological prescription, age at first contact with psychiatric services, age at first psychiatric diagnosis, presence of lifetime psychotic symptoms, type of current mood episode, number of depressive episodes in the last year, number of hypomanic episodes in the last year, number of manic episodes in the last year, presence of psychotic symptoms in the last year, presence of hospitalizations, treatment adherence, and administration of psychoeducational interventions. The 2 genders showed a statistically borderline difference for the age at onset of BD ($P = 0.06$), age at first diagnosis of BD ($P = 0.08$), and age at first mood stabilizer/atypical antipsychotic ($P = 0.07$).

Female versus male BD patients were older ($P < 0.01$), less educated ($P < 0.01$), and less often employed ($P < 0.01$), but more often married or in a civil partnership ($P < 0.01$) and less often living alone ($P < 0.01$). They more often had a first psychiatric diagnosis of major depressive disorder ($P < 0.01$), first episode of depressive polarity ($P < 0.01$), lifetime depressive predominant polarity ($P < 0.01$), more lifetime major depressive episodes ($P < 0.01$), fewer lifetime manic episodes ($P < 0.01$), more lifetime depression-mania-euthymia cycles ($P = 0.02$), and suicide attempts ($P < 0.01$), as well as more prior-year suicide attempts ($P = 0.05$) and prior-year psychiatric visits ($P < 0.01$), but lower prior-year suicide attempt lethality ($P = 0.05$), and less prior-year substance abuse ($P < 0.01$), better prior-year insight ($P = 0.04$), and more prior-year attributing symptoms to a psychiatric disorder ($P = 0.01$).

The results of the goodness-of-fit test (Hosmer-Lemeshow test: $\chi^2 = 6.84$, $df = 8$, $P = 0.55$) showed that the multivariable logistic regression model including previously significant sociodemographic/clinical variables as possible predictors of the type of gender was adequate. In particular, female gender was less frequently associated with employment (odds ratio [OR] = 0.7, $P < 0.01$), lifetime single marital status (OR = 0.45, $P < 0.01$), and substance abuse in the last year of observation (OR = 0.35, $P < 0.01$) (Figure 1), whereas it was more frequently associated with a major number of lifetime major depressive episodes (OR = 1.78, $P < 0.01$) and psychiatric visits in the last year of observation (OR = 1.38, $P = 0.01$) (Table 4).

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TABLE 2. Clinical variables of the total sample and of the two gender groups

Variables		Total sample N = 1674	Males N = 714 (42.7%)	Females N = 960 (57.3%)	P^a
Age at onset of BD Missing: n = 96		31.27 (±11.96)	30.62 (±12.05)	31.75 (±11.87)	0.06
Age at first pharmacological prescription (including BZPs) Missing: n = 70		30.90 (±12.56)	30.76 (±11.25)	30.82 (±11.82)	0.82
Age at first contact with psychiatric services Missing: n = 73		31.17 (±12.12)	31.29 (±12.71)	31.09 (±11.67)	0.75
Age at first psychiatric diagnosis Missing: n = 66		30.56 (±11.86)	30.73 (±12.51)	30.44 (±11.35)	0.64
First psychiatric diagnosis Missing: n = 47	MDD BD Other	714 (43.9%) 532 (32.7%) 381 (23.4%)	272 (39.0%) 259 (37.1%) 167 (23.9%)	442 (47.6%) 273 (29.4%) 214 (23.0%)	< **0.01**
Age at first diagnosis of BD Missing: n = 106		37.40 (±13.34)	36.70 (±13.90)	37.91 (±12.89)	0.08
Age at first mood stabilizer/atypical antipsychotic Missing: n = 116		37.36 (±13.36)	36.65 (±13.96)	37.89 (±12.87)	0.07
Polarity of first episode Missing: n = 45	Depressive Hypomanic/manic Unidentifiable	910 (55.9%) 577 (35.4%) 142 (8.7%)	357 (51.0%) 276 (39.5%) 67 (9.5%)	553 (59.5%) 301 (32.4%) 75 (8.1%)	< **0.01**
Lifetime number of manic episodes Missing: n = 45	0 1–2 3–5 6–8 >8	632 (38.2%) 444 (26.9%) 343 (20.8%) 100 (6.1%) 132 (8.0%)	239 (33.9%) 215 (30.5%) 155 (22.0%) 43 (6.2%) 52 (7.4%)	393 (41.5%) 229 (24.2%) 188 (19.9%) 57 (6.0%) 80 (8.4%)	< **0.01**
Lifetime number of depressive episodes	0 1–2 3–5 6–8 >8	156 (9.4%) 452 (27.2%) 463 (27.8%) 281 (16.9%) 311 (18.7%)	73 (10.3%) 238 (33.6%) 193 (27.2%) 102 (14.4%) 103 (14.5%)	83 (8.7%) 214 (22.4%) 270 (28.3%) 179 (18.8%) 208 (21.8%)	< **0.01**
Prevalent polarity Missing: n = 5	Depressive Hypomanic/manic Unidentifiable	790 (47.3%) 438 (26.2%) 441 (26.5%)	297 (41.7%) 215 (30.2%) 201 (28.1%)	493 (51.6%) 223 (23.3%) 126 (25.1%)	< **0.01**
Prevalent course Missing: n = 9	Hypomania/mania and depression Depression and hypomania/mania Other	347 (20.8%) 387 (23.2%) 931 (56.0%)	162 (22.8%) 153 (21.5%) 396 (55.7%)	185 (19.4%) 234 (24.5%) 535 (56.1%)	**0.02**
Lifetime psychotic symptoms Missing: n = 4	No Yes	891 (53.4%) 779 (46.6%)	384 (53.9%) 328 (46.1%)	507 (52.9%) 451 (47.1%)	0.68
Lifetime attempted suicides Missing: n = 2	No Yes	1232 (73.7%) 440 (26.3%)	553 (77.5%) 161 (22.5%)	679 (70.9%) 279 (29.1%)	< **0.01**

BD, bipolar disorder; BZP, benzodiazepine; MDD, major depressive disorder.
Standard deviations are reported in parentheses.
[a]In bold are statistically significant *P* values resulting from χ^2 or unpaired Student's *t* test.

These were the only variables that remained significant in this final logistic regression model.

Discussion

To date and to our knowledge, this study is the first national report about gender differences in BD.

The main results of this study (as shown by binary logistic regression) consist of an association of male gender with employment, lifetime single marital status, and substance abuse (in the last year of observation), and of female gender with a major number of lifetime major depressive episodes and with a major number of psychiatric visits in the last year of observation.

With regard to substance abuse, our result is concordant with what has been reported in the literature. Of note, several previous studies reported an association between male gender and current[7,11,12] or past substance abuse.[5,6] Furthermore a very recent meta-analysis of available studies reported an OR of 2.2 (confidence interval: 1.12–4.28) for the frequency of substance abuse in male bipolar patients versus female ones.[22] The more frequent

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TABLE 3. Clinical variables of the total sample and of the two gender groups (last year of observation)

Variables		Total sample N = 1674	Males N = 714 (42.7%)	Females N = 960 (57.3%)	P^a
Type of current episode	Depressive	241 (14.3%)	86 (12.0%)	155 (16.1%)	0.22
Missing: n = 2	Manic	198 (11.8%)	94 (13.2%)	104 (10.8%)	
	Hypomanic	26 (1.6%)	13 (1.8%)	13 (1.4%)	
	Mixed	150 (9.0%)	64 (9.0%)	86 (9.0%)	
	Euthymia	1059 (63.3%)	457 (64.0%)	602 (62.7%)	
Number of hypomanic episodes		1.36 (±0.99)	1.47 (±1.26)	1.28 (±0.71)	0.12
Missing: n = 12					
Number of manic episodes		1.31 (±0.84)	1.32 (±0.96)	1.31 (±0.84)	0.96
Missing: n = 10					
Number of depressive episodes		1.48 (±1.04)	1.49 (±1.16)	1.47 (±0.96)	0.80
Missing: n = 10					
Attempted	No	1558 (93.1%)	675 (94.5%)	883 (92.1%)	**0.05**
suicides	Yes	115 (6.9%)	39 (5.5%)	76 (7.9%)	
Degree of lethality of attempted suicides	Low	52 (45.2%)	14 (35.9%)	38 (50.0%)	**0.05**
	Medium	44 (38.3%)	14 (35.9%)	30 (39.5%)	
	High	19 (16.5%)	11 (28.2%)	8 (10.5%)	
Number of attempted suicides	0	1558 (93.3%)	675 (94.5%)	883 (92.4%)	**0.01**
Missing: n = 4	1	92 (5.5%)	37 (5.4%)	55 (5.8%)	
	2	12 (0.7%)	0 (0.0%)	12 (1.2%)	
	3	8 (0.5%)	2 (0.1%)	6 (0.6%)	
Insight	No	78 (4.7%)	35 (4.9%)	12 (4.5%)	**0.04**
Missing: n = 3	Yes	1165 (69.7)	474 (66.5%)	412 (72.1%)	
	Partial	428 (25.6%)	204 (28.6%)	110 (23.4%)	
Attribution of symptoms to	No	131 (7.8%)	57 (8.0%)	74 (7.7%)	**0.01**
a psychiatric disorder	Yes	1065 (63.8%)	428 (60.0%)	637 (66.6%)	
Missing: n = 4	Partial	474 (28.4%)	228 (32.0%)	246 (25.7%)	
Treatment adherence	No	124 (7.4%)	54 (7.6%)	70 (7.3%)	0.6
Missing: n = 8	Yes	1155 (69.3%)	484 (68.1%)	671 (70.3%)	
	Partial	387 (23.3%)	173 (24.3%)	214 (22.4%)	
Number of visits		9.66 (±9.09)	8.91 (±7.66)	10.23 (±10.00)	**<0.01**
Missing: n = 104					
Psychoeducation	Individual	122 (7.4%)	60 (8.4%)	62 (6.5%)	0.22
Missing: n = 9	Group	149 (8.9%)	68 (9.6%)	81 (8.5%)	
	No	1394 (83.7%)	584 (82.0%)	810 (85.0%)	
Substance misuse	No	1471 (88.0%)	575 (80.6%)	896 (93.4%)	**<0.01**
Missing: n = 2	Yes	201 (12.0%)	138 (19.4%)	63 (6.6%)	
Psychotic symptoms	No	1263 (75.7%)	537 (75.5%)	726 (75.8%)	0.90
Missing: n = 5	Yes	406 (24.3%)	174 (24.5%)	232 (24.2%)	
Hospitalization	No	988 (59.1%)	419 (58.7%)	569 (59.3%)	0.79
Missing: n = 1	Yes	685 (40.9%)	295 (41.3%)	390 (40.7%)	

Standard deviations are reported in parentheses.

[a]In bold are statistically significant *P* values resulting from χ^2 or unpaired Student's *t* test.

comorbidity with substance abuse in male bipolar patients represents an unfavorable predictor of long-term outcome; it is noteworthy that comorbid substance abuse in BD has been associated with a higher risk of recurrences[23] and development of rapid cycles,[24,25] more psychotic symptoms,[26] and more suicidality.[22,27] Therefore, male bipolar subjects should be carefully monitored to prevent the risk of substance abuse or limit eventual current substance misuse: few data have been published about the management of BD with concomitant substance misuse, but adjunctive psychosocial interventions including psychoeducation, augmentative naltrexone to pharmacotherapy, or the choice of valproate as mood stabilizer might be all useful strategies to improve long-term outcomes of male bipolar subjects.[28]

With regard to sociodemographic factors, the finding of a higher rate of employment in bipolar males is hardly interpretable for the cultural bias linked to a lower occupational access of the female population in most of worldwide countries.[29] Even if cultural issues are excluded (eg in case of studies conducted in the same country), contrasting results have been found with regard to the association between gender and occupational status in BD; while a first study, conducted in Taiwan, reported male gender to be associated with long-term favorable psychosocial outcomes,[30] a recent study in the same country found male gender to be associated with the risk of being unemployed.[31] A reasonable explanation is that, as well as cultural issues, other clinical factors (eg, a different distribution of gender in type I and II bipolar subtypes or in rapid cyclers) may

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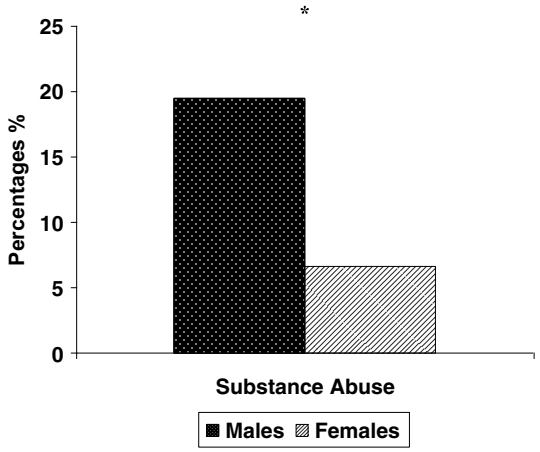


FIGURE 1. Presence of substance abuse in the last year of observation in the two gender groups. Asterisk (*) indicates $P = <0.01$ according to multivariable logistic regression.

contribute to the observation of different occupational status of male versus female bipolar subjects.[13,32] In this sense, a meta-analysis and a subsequent clinical study reported that female gender was more common in rapid cyclers compared with nonrapid cyclers.[33,34]

Similarly to what is reported in our study, previous research found male gender to be associated with single marital status.[35,36] This finding has been interpreted as the consequence of gender-related different presentations of the onset of illness. While bipolar women tend to have a depressive onset[35] and are less likely to have comorbid substance abuse,[22] male bipolar patients have a frequent onset of illness with a manic episode[35] and concomitant substance abuse.[22] Also of note, in our sample female bipolar patients presented more frequently a first depressive episode than male patients.

With regard to clinical features associated with female gender, previous studies found a predominant depressive polarity[12] and more frequent depressive onset,[12,37] but not a higher number of past depressive episodes[5,7] in female bipolar patients than in male ones. Probably our finding of a higher number of depressive episodes in female patients is the result of the mediation of other clinical factors such as age, depressive polarity of first bipolar episode, and prevalent depressive polarity. Of note, in our sample female patients were older, had a more frequent depressive polarity, and had a more frequent depressive onset. From a clinical point of view, the number of previous depressive episodes has been associated with poor functional outcomes[38,39] and less probability of pharmacological response in case of a new depressive episode.[40] In contrast, the result of more psychiatric visits in the last year of observation in female bipolar patients cannot be interpreted uniquely. On the one hand, it could be an indicator of greater insight by the female gender; on the other hand, it could be the result of greater severity of illness and poor clinical stabilization. The latter hypothesis is supported by recent data that show the female gender to be associated with poor insight especially during depressive phases of BD.[41,42] We must also highlight the fact that the result of fewer prior-year psychiatric visits in male versus female patients is consistent with more prior-year substance abuse in male versus female subjects: men more often than women seek symptomatic relief via substance abuse rather than psychiatric help.[22]

Finally, previous research found suicidal attempts to be more probable in female bipolar patients. Also in our sample the female gender presented a higher probability of lifetime suicidal attempts and more suicidal attempts in the last year of observation. However, the statistical significance of these variables was not confirmed in the final multivariable logistic regression model. Probably, the association of more lifetime depressive episodes with the female gender contributes importantly to the higher risk of prior suicide attempt in bipolar women.[43]

Taken as a whole, with the exception of substance abuse and number of depressive episodes, our data confirm that there is not a substantial association between female or male gender and clinical markers of poor outcome in BD (eg, rapid cycling, psychotic symptoms, or number/lethality of suicide attempts). Gender would not seem, therefore, to represent a robust predictor of outcome in BD. This observation has also been outlined in another review of this topic.[4] On the other hand, treatment should be personalized according to gender, and clinicians should take into account the fact that bipolar males tend to develop substance abuse and may have a manic predominant polarity, whereas bipolar women can present a more depressive profile. Bipolar men should be preferentially treated with a pharmacotherapy with more efficacy in the prevention of manic/hypomania episodes and craving, whereas treatment of bipolar women should be more tailored for the prevention of depressive episodes. In addition, as gender-related clinical features of BD are partly explained by the different hormonal profile, special attention should be dedicated to women during pregnancy, postpartum, or menopause, during which hormonal fluctuations represent a concrete risk of relapse of bipolar illness[6,15,44] and the delay in treatment can have serious effects on the health of women and their offspring.[45]

The following limitations of the present research need to be mentioned:

1. Patients were treated with different drugs, which might have influenced some clinical features (eg, the use of tricyclic antidepressants and the development of rapid cycling).[46]
2. The different settings of care (in several Italian regions) may have influenced the clinical and demographic features of the sample.

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TABLE 4. Summary of the statistics for the best-fit multivariable logistic regression model applied

Variables	Categories	OR	95% CI	P[a]
Age	NA	1.01	1.00–1.02	0.09
Work	Unemployed vs employed	0.7	0.54–0.91	< **0.01**
Marital status	At least 1 marriage/civil partnership vs none	0.45	0.35–0.59	< **0.01**
Number of lifetime major depressive episodes	0 vs >6	1.45	0.95–2.22	0.09
Number of lifetime major depressive episodes	1–2 vs >6	1.78	1.35–2.34	< **0.01**
Number of lifetime major depressive episodes	3–5 vs >6	1.27	0.98–1.66	0.07
Substance abuse in the last year of observation	No vs yes	0.35	0.25–0.49	< **0.01**
Number of psychiatric visits in the last year of observation	1 vs 3	1.38	1.07–1.78	**0.01**
Number of psychiatric visits in the last year of observation	2 vs 3	1.14	0.87–1.48	0.33

CI, confidence interval; NA, not applicable.
In this analysis, the dependent variable was gender (male versus female). With regard to age, the odds ratio (OR) means the increase of the relationship at each unity increase.
Hosmer-Lemeshow test: $\chi^2 = 6.84$, $df = 8$, $P = 0.55$.
[a]In bold are statistically significant *P* values.

3. Some data were collected retrospectively (eg, number of mood episodes) so that they might not have been always as accurate as in controlled studies.
4. Transcultural studies are needed to disentangle the cultural-related variables from differences possibly due to the biological background.[47]

Conclusion

In bipolar patients, female gender is less frequently associated with employment, lifetime single marital status, and substance abuse in the last year of observation. On the other hand, female gender is more frequently associated with a greater number of lifetime major depressive episodes and psychiatric visits in the last year of observation. There is not a substantial association between female or male gender and clinical markers of poor outcome in BD (eg, rapid cycling, psychotic symptoms, or number/lethality of suicide attempts). Further large-sample prospective studies are needed to confirm the results of the present research.

Disclosures

Massimiliano Buoli, Bruno Mario Cesana, Andrea de Bartolomeis, Emi Bondi, Giuseppe Maina, and Antonello Bellomo have nothing to disclose. Bernardo Dell'Osso reports personal fees from Lundbeck and personal fees from Janssen Cilag, outside the submitted work; Andrea Fagiolini reports personal fees from Angelini, personal fees from Lundbeck, personal fees from Otsuka, and personal fees from Janssen Cilag, outside the submitted work; and A. Carlo Altamura reports personal fees from Lundbeck, outside the submitted work.

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