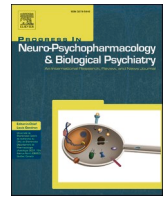




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Impact of sex and complex PTSD comorbidity on pharmacological treatment response in bipolar disorder patients

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ABSTRACT

Background: The prevalence of bipolar disorder (BD) is similar in men and women. However, factors such as sex and comorbid psychiatric conditions can influence its clinical presentation and treatment outcomes, including complex PTSD (cPTSD), a newly categorized trauma-related condition. Little is known about how sex and cPTSD comorbidity affect the response to mood stabilizers, a cornerstone treatment for BD. This observational, cross-sectional study examines the impact of sex and cPTSD comorbidity on clinical and behavioral BD features as well as their interplay in influencing pharmacological treatment response.

Methods: A cohort of BD patients (females = 177, males = 166, age range: 19–76; BD-I = 253, BD-II = 90) was recruited over three years. Clinical assessments were conducted, and patients were administered the International Trauma Questionnaire to evaluate cPTSD comorbidity and the Alda Scale to assess response to mood stabilizers.

Results: Our results show distinct clinical profiles based on sex and cPTSD. Female BD patients exhibit more hypomanic episodes, antidepressant-induced mania, and longer periods of untreated illness than males. Comorbid cPTSD was diagnosed in 154 patients (44.8%), among which 69 were females. Patients with cPTSD display more severe BD symptoms, including earlier onset, more frequent episodes, and a higher prevalence of psychosis and suicidality. Importantly, comorbid cPTSD was associated with poorer mood stabilizer response, particularly in males, who otherwise responded better to treatment than females.

Conclusions: These findings underscore the importance of addressing trauma symptoms in BD treatment and highlight the need for individualized approaches considering both sex and comorbid trauma, as standard mood stabilizers may be insufficient for certain subgroups.

1. Introduction

Sex is a recognized factor influencing the course and treatment outcomes of many psychiatric disorders, including bipolar disorder (BD), a chronic mental illness affecting forty million people worldwide (Global Burden of Disease GBD 2019 Mental Disorders Collaborators, 2022; Green et al., 2019). While large-scale epidemiologic studies show

no differences in the prevalence of BD in men and women, these aggregate data may mask crucial nuances and heterogeneity, potentially leading to false conclusions. Evidence of unequal sex distribution in the clinical manifestations of BD is accumulating, emphasizing the importance of stratifying research on mood disorders by sex (Dell'Osso et al., 2021; Menculini et al., 2022). Studies have shown that hypomania and BD type II (BD-II) are more prevalent in women, whereas men

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experience more manic episodes and are more frequently diagnosed with BD type I (BD-I) (Diflorio and Jones, 2010). Compared to men, women with BD are more likely to suffer from depressive episodes, rapid cycling, anxiety and eating disorders (Dell'Osso et al., 2021; Parial, 2015). Women may face challenges associated with misdiagnosis or delayed diagnosis and the commencement of treatment, given that depressive episodes are a prominent feature of their condition (Rhee et al., 2023; Williams et al., 2018). In addition, treatment in women is often complicated by hormonal fluctuations, which have been linked to mood instability and a high incidence of antidepressant-induced mania (Parial, 2015; Williams and McInnis, 2019). The pharmacokinetics and pharmacodynamics of some medications can also differ between the sexes (Marazziti et al., 2013; Smith et al., 2016).

Although BD is highly heritable (O'Connell and Coombes, 2021), genetic predisposition is not the only aspect promoting its expression; environmental risk factors also play a significant role (Nierenberg et al., 2023). This is important because, unlike genetic factors, these risks can potentially be addressed. Importantly, BD has high comorbidity with other psychiatric disorders (Leda-Rego et al., 2024) and is associated with early mortality (Chan et al., 2022; Nierenberg et al., 2023). Several medical comorbidities may cause premature death in BD, but suicide represents a major burden (Chan et al., 2022; Schaffer et al., 2015; Tondo et al., 2016). In the general population, suicidal ideation and attempts are more frequent in women than in men, a trend that is mirrored in BD patients (D'Angelo and Steardo Jr., 2024; Diflorio and Jones, 2010; Tondo et al., 2016), although some reports have provided conflicting results (Diflorio and Jones, 2010). Traumatic or adverse life circumstances can precipitate post-traumatic stress disorder (PTSD) and exacerbate BD symptoms, further increasing the risk of suicidal ideation and attempts (Carter et al., 2017; Iazzolino et al., 2024b).

We have recently observed a higher risk of suicide attempts in BD patients with comorbid complex PTSD (cPTSD) (Iazzolino et al., 2024b), a novel diagnostic construct that shares the core symptoms of PTSD - trauma reexperiencing and avoidance, and hypervigilance - but also includes severe and persistent impairments in emotion regulation, self-concept and interpersonal relationships (Nestgaard Rod and Schmidt, 2021; WHO, 2022). A diagnosis of cPTSD increases the risk of developing other psychiatric disorders, including BD (Marques-Feixa et al., 2023), and increases the risk of suicide (Jannini et al., 2023). Due to the recent characterization of cPTSD, few studies have explored its clinical features, and findings regarding sex differences in diagnosis rates and symptomatology remain inconsistent (Lonnen and Paskell, 2024).

In our recent work, we identified differences in symptoms and response to mood stabilizers in BD patients with comorbid cPTSD (Iazzolino et al., 2024a). Mood stabilizers are the treatment of choice for BD, but research on sex differences in response to these medications is limited and has only recently gained attention. Emerging evidence suggests that their efficacy may vary depending on individual factors (Nierenberg et al., 2023), including sex (Ercis et al., 2024). However, it is still unclear whether sex differences affect treatment outcomes in BD patients with comorbid cPTSD. Understanding this could provide clinicians with valuable insights to optimize and personalize treatment strategies (Nature Editorial, 2020; Williams and McInnis, 2019). This study aims to fill this gap using a comprehensive analysis to study the impact of sex and cPTSD on pharmacological treatment response in BD patients.

2. Methods

2.1. Study design and sample selection

The present observational, cross-sectional study analyzed a cohort of BD patients followed and treated at the Psychiatry Unit of the Mater Domini University Hospital in Catanzaro, Italy, between January 2021 and December 2023. The study was approved by the Ethics Committee of the University of Catanzaro in Italy (307/2020) and conducted in

accordance with the Declaration of Helsinki. All participants were informed about the research protocol and data privacy protections and provided written informed consent.

Inclusion criteria: (1) a diagnosis of bipolar disorder (BD) based on DSM-5 criteria, assessed via clinical interviews and psychometric scales; (2) age between 18 and 75 years; and (3) provision of written informed consent; (4) clinically stable, as demonstrated by a Clinical Global Impression for Bipolar Patients (CGI-BP) score ≤ 2 on item 1 (severity of illness) at enrollment.

Exclusion criteria: (1) inability to provide written consent; (2) a diagnosis of major neurological or psychiatric conditions (e.g., epilepsy, cognitive disabilities, or genetic syndromes with psychiatric manifestations); and (3) any condition that prevents completion of assessments, such as language barriers or severe cognitive disabilities.

After recruitment, the participants underwent clinical and psychopathological assessment during outpatient visits. Clinical history and sociodemographic information were collected in clinical interviews. Data were collected on employment, marital status, diagnosis, family history of psychiatric disorders, history of substance abuse, age at BD onset, number of previous depressive, manic and hypomanic episodes, as well as number of hospitalizations. Lifetime head trauma or other traumatic experiences, including physical, emotional and sexual abuse, as well as severe neglect and exposure to violent environment were recorded. In addition, the presence of seasonality, mixed features, psychotic symptoms, aggressive behavior, and antidepressant-induced mania were assessed.

2.2. Psychometric tools

Diagnosis was conducted by trained psychiatrists using the Clinician Version of the Structured Interview for DSM-5 Disorders (SCID-5-CV).

The International Trauma Questionnaire (ITQ) was used to diagnose complex PTSD (cPTSD) according to the ICD-11 guidelines (Seiler et al., 2023; WHO, 2022). The 18-item ITQ questionnaire measures PTSD and Disturbances in Self-Organization (DSO) symptoms on a 5-point Likert scale (0 = not at all, 4 = very strongly). A cPTSD diagnosis requires at least one symptom from each of the three PTSD clusters (re-experiencing, avoidance, and sense of current threat) and the three DSO clusters (affective dysregulation, negative self-concept, and relationship disturbances). Functional impairment must be linked to both PTSD and DSO symptoms. A person can only be diagnosed with either PTSD or cPTSD, with the latter characterized by prominent DSO symptoms resulting from prolonged interpersonal trauma, such as abuse, severe neglect, or war. The maximum score for PTSD or DSO is 24, and 48 for cPTSD. Symptoms are considered present with a score ≥ 2 .

The patient response to pharmacological treatment was assessed using the Alda scale. This was initially developed to assess the effectiveness of Lithium in treating BD (Grof et al., 2002; Scott et al., 2017). Still, it can be applied to evaluate responses to various mood stabilizers, such as valproate, lamotrigine, and carbamazepine, with inter-rater reliability ranging from 0.54 to 0.75 for assessing long-term treatment response (Manchia et al., 2013). The scale consists of two components: (A) assesses the correlation between clinical improvement and treatment, and (B) evaluates the causal connection between improvement and prophylactic treatment. Scores on the Alda scale range from 0 to 10, with higher scores indicating a better response to treatment.

2.3. Statistical analysis

Descriptive statistics were used to summarize socio-demographic and clinical variables. The Shapiro-Wilk test was applied to assess the normality of data distribution. Non-normally distributed numerical variables are presented as median (Mdn) and interquartile range (IQR) and were analyzed using the Mann-Whitney *U* test. Categorical variables are presented as frequencies and percentages (%) and were analyzed using the chi-square test. Ordinal logistic regression was performed to

examine the effects of cPTSD status and sex on Alda scores, including their interaction. Pairwise comparisons were conducted using the Mann-Whitney *U* test to explore differences between specific groups. Statistical significance was set at $p \leq 0.05$. All data were analyzed using SPSS version 26 (SPSS, Chicago, IL, USA) and Statistica 7 (StatSoft Inc., Tulsa, OK). Data were graphed using Prism 8 for Windows (version 8.4.2, GraphPad Software, LLC).

3. Results

3.1. Clinical and demographic description of the patients

The cohort of BD patients analyzed comprised 166 males (48 %) and 177 females (52 %) with a median age of 46.8 years, ranging from 19 to 76 years. Two hundred and fifty-three patients (74 %) were affected by BD-I and 90 (26 %) by BD-II. The median years of education was 13 (range 0–22), which correspond to obtaining the high-school diploma in Italy. The medication regimens are summarized in Table 1, with Lithium (Li) being the most commonly prescribed treatment, either as a monotherapy or in combination with other drugs. Approximately 20 % of the patients were treated with Lithium alone, while a combination of Lithium and an antipsychotic drug (Li + Ap), such as quetiapine, olanzapine, lurasidone, or aripiprazole, was prescribed to 32 patients (9.3

%). Divalproex (DVP) was administered in combination with Lithium (Li + DVP) to 90 patients (26.2 %), or with an antipsychotic drug (DVP + Ap) to 82 patients (23.9 %). Lamotrigine, combined with an antipsychotic, was used in 66 patients (19.2 %). The least commonly prescribed regimen was Carbamazepine combined with an antipsychotic, which was used in only 6 patients (1.7 %).

By delving into the sociodemographic, clinical, and behavioral features of our patients, we identified several sex differences as summarized in Table 2. First, a higher proportion of male patients (91 %) had completed secondary education or higher and were employed (66 %) compared with female patients (53 % and 35 %, respectively), with significant differences between sexes ($p < 0.001$). The prevalence of BD-I and BD-II did not differ significantly between sexes. However, a higher proportion of females were diagnosed with BD-II than males (29.4 % vs. 22.9 %). In general, females experienced more years with untreated BD than males ($p < 0.001$), with a very high variability (median 4 years, IQR = 18). Females also had a higher rate of BD episodes (median 10 vs. 8, $p < 0.01$) than males, especially of hypomanic episodes (median 3 in females vs. 1 in males, $p < 0.001$). However, a significantly higher proportion of females reported antidepressant-induced mania (26.6 %, $p < 0.001$), seasonality (61.6 %, $p < 0.001$), and aggressive behavior (63.3 %, $p < 0.05$). In contrast, a higher prevalence of mixed traits was observed in males than females (78.9 % vs. 35.0 %, $p < 0.001$). We did not detect significant differences between sexes in the prevalence of lifetime drug abuse, head trauma, suicidality, and suicide attempts in our cohort.

We also explored whether BD patients affected by cPTSD showed different clinical features. As cPTSD is characterized by persistent emotional and interpersonal difficulties rather than the specific nature of the traumatic event, our study focused on its impact on BD features rather than categorizing different trauma types. To this end, we administered the ITQ questionnaire and divided our sample into two groups, depending on whether comorbid cPTSD was present or not, irrespective of sex. The results of such comparison are summarized in Table 3. In our sample, cPTSD-positive patients were younger than

Table 1

Therapeutic management of the BD patients enrolled in the study ($N = 343$).

Medication	N (%)
Li	67 (19.5)
Li + Ap	32 (9.3)
Li + DVP	90 (26.2)
DVP + Ap	82 (23.9)
Lamotrigine + Ap	66 (19.2)
Carbamazepine + Ap	6 (1.7)

Ap: antipsychotic (quetiapine, olanzapine, lurasidone, or aripiprazole); DVP: valproate; Li: Lithium.

Table 2

Demographic, clinical, and behavioral characteristics of patients based on their sex.

	Male ($N = 166$)	Female ($N = 177$)	<i>p</i> -value
Demographic Characteristics			
Age, Mdn (IQR)	43.0 (24.75)	52 (15)	<i><0.001</i>
Diploma of secondary education or higher, N (yes, %)	151 (90.96 %)	94 (53.1 %)	<i><0.001</i>
Employed, N (yes, %)	110 (66.3 %)	62 (35.0 %)	<i><0.001</i>
Clinical Characteristics			
Diagnosis of BD type I, N (yes, %)	128 (77.1 %)	125 (70.6 %)	0.214
Diagnosis of BD type II, N (yes, %)	38 (22.9 %)	52 (29.4 %)	0.214
Family history of psychiatric disorder, N (yes, %)	90 (54.2 %)	100 (56.5 %)	0.75
Age at BD onset, Mdn (IQR)	22.0 (9.75)	24.0 (10.0)	0.08
Years of untreated BD, Mdn (IQR)	0.0 (2.0)	4.0 (18.0)	<i><0.001</i>
Number of depressive episodes, Mdn (IQR)	3.0 (5.0)	3.0 (5.0)	0.19
Number of manic episodes, Mdn (IQR)	2.0 (3.25)	3.0 (4.0)	0.41
Number of hypomanic episodes, Mdn (IQR)	1.0 (3.0)	3.0 (2.0)	<i><0.001</i>
Total number of episodes, Mdn (IQR)	8.0 (9.75)	10.0 (8.0)	<i>0.009</i>
Psychotic symptoms, N (yes, %)	78 (47.0 %)	66 (37.3 %)	0.13
Antidepressant-induced mania, N (yes, %)	38 (22.9 %)	47 (26.6 %)	<i><0.001</i>
Head trauma, N (yes, %)	20 (12.1 %)	19 (10.7 %)	0.83
Behavioral Characteristics			
Seasonality, N (yes, %)	62 (37.3 %)	109 (61.6 %)	<i><0.001</i>
Aggressive behaviors, N (yes, %)	82 (49.4 %)	112 (63.3 %)	<i>0.013</i>
Mixed features, N (yes, %)	131 (78.9 %)	62 (35.0 %)	<i><0.001</i>
Lifetime drug abuse, N (yes, %)	59 (35.5 %)	65 (36.7 %)	0.91
Suicidality, N (yes, %)	59 (35.5 %)	54 (30.5 %)	0.38
Suicide attempts, Mdn (IQR)	0 (1)	0 (1)	0.65

IQR: interquartile range; Mdn: median; N: numerosity; *p*-values from chi-square or Mann-Whitney tests; statistically significant *p*-values are shown in italics.

Table 3
Demographic, clinical, and behavioral characteristics of patients with and without cPTSD.

	cPTSD-negative (N = 189)	cPTSD-positive (N = 154)	p-value
Demographic Characteristics			
Age, Mdn (IQR)	50 (19.0)	44 (17.0)	<i>0.005</i>
Female, N (yes, %)	108 (56.8 %)	69 (44.8 %)	<i>0.03</i>
Diploma of secondary education or higher, N (yes, %)	126 (66.7 %)	119 (77.3 %)	<i>0.04</i>
Employed, N (yes, %)	96 (50.8 %)	76 (49.4 %)	0.87
Clinical characteristics			
Diagnosis of BD type I, N (yes, %)	115 (60.9 %)	138 (89.6 %)	<i><0.001</i>
Diagnosis of BD type II, N (yes, %)	74 (39.2 %)	16 (10.4 %)	<i><0.001</i>
Family history of psychiatric disorder, N (yes, %)	91 (48.2 %)	99 (64.3 %)	<i>0.004</i>
Age at BD onset, Mdn (IQR)	24 (10.0)	22 (9.25)	<i><0.001</i>
Years of untreated BD, Mdn (IQR)	2.0 (13.0)	0.0 (7.0)	0.12
Number of depressive episodes, Mdn (IQR)	3 (3)	4 (6)	<i>0.002</i>
Number of manic episodes, Mdn (IQR)	2 (2)	4 (4.75)	<i>0.005</i>
Number of hypomanic episodes, Mdn (IQR)	2 (3)	2 (4)	0.67
Total number of episodes, Mdn (IQR)	7 (6)	10 (10)	<i><0.001</i>
Psychotic symptoms, N (yes, %)	14 (7.4 %)	130 (84.4 %)	<i><0.001</i>
Antidepressant-induced mania, N (yes, %)	20 (10.6 %)	65 (42.2 %)	<i><0.001</i>
Head trauma, N (yes, %)	14 (7.4 %)	25 (16.2 %)	<i>0.02</i>
Behavioral Characteristics			
Seasonality, N (yes, %)	78 (41.3 %)	93 (60.4 %)	<i><0.001</i>
Aggressive behaviors, N (yes, %)	83 (43.9 %)	111 (72.1 %)	<i><0.001</i>
Mixed features, N (yes, %)	71 (37.6 %)	122 (79.2 %)	<i><0.001</i>
Lifetime drug abuse, N (yes, %)	45 (23.8 %)	79 (51.3 %)	<i><0.001</i>
Suicidality, N (yes, %)	28 (14.8 %)	85 (55.2 %)	<i><0.001</i>
Suicide attempts, Mdn (IQR)	0 (0)	1 (1)	<i><0.001</i>

IQR: interquartile range; Mdn: median; N: numerosity; p-values from chi-square or Mann-Whitney tests; statistically significant p-values are shown in italics.

cPTSD-negative patients (median age 44 vs. 50 years, $p < 0.005$). A higher proportion of cPTSD-positive patients had completed secondary education or higher (77.3 % vs. 66.7 %, $p < 0.05$). There was no significant difference in employment status between the two groups. A greater proportion of cPTSD-positive patients were diagnosed with BD-I compared to cPTSD-negative patients (89.6 % vs. 60.9 %, $p < 0.001$). Conversely, BD-II was more common in cPTSD-negative patients than in patients with cPTSD (39.2 % vs. 10.4 %, $p < 0.001$). Of the BD patients with comorbid cPTSD, approximately 64 % reported a family history of psychiatric disorders, whereas only about 48 % of patients without comorbid cPTSD did so. The onset of BD was significantly earlier in patients diagnosed with cPTSD than in patients without cPTSD (median age 22 vs. 24 years, $p < 0.001$). Patients with comorbid cPTSD experienced significantly more episodes than cPTSD-negative patients ($p < 0.001$), with a higher prevalence of depressive and manic episodes ($p < 0.002$ and $p < 0.005$, respectively). They also exhibited high rates of psychotic symptoms (84.4 %, $p < 0.001$) and antidepressant-induced mania (42.2 %, $p < 0.001$). They were also characterized by a higher % of mixed features, seasonality as well as aggressive behaviors than cPTSD-negative patients (all $p < 0.001$). Additionally, head trauma was significantly more common ($p < 0.05$) as lifetime drug abuse ($p < 0.001$). Suicidality was also more prevalent in the cPTSD-positive group than in the cPTSD-negative one (55.2 % vs. 14.8 %, $p < 0.001$), as well as the number of suicide attempts ($p < 0.001$).

3.2. Impact of chronic PTSD comorbidity and sex on response to treatment with mood stabilizers in bipolar disorder patients

The Alda Scale scores indicating response to mood stabilizers were analyzed by comparing individuals with and without a cPTSD diagnosis and then stratifying the sample by sex. As shown in Table 4, individuals diagnosed with both BD and cPTSD scored lower median Alda values than BD patients without cPTSD ($U = 20,995.5$; $p < 0.001$), regardless of sex. We then explored sex differences by computing the median and interquartile range to assess the central tendency and variability of Alda

scores within each group. As reported in Table 4, cPTSD-negative female patients show a median Alda score of 4.0, with IQR = 4.0. This spread suggests a moderate variability in pharmacological treatment response, with half of the scores ranging from 2 to 6. Male patients without cPTSD exhibited a median score of about 6.0, suggesting a generally better response to treatment. The IQR = 4.0 indicates similar variability in response as observed in females without cPTSD, albeit with a shift towards higher scores. The median score in females with cPTSD was 4.0, with a narrow IQR (2.0) indicating a more consistent and less variable response to treatment among this group of patients. The median score for males with cPTSD was also 4.0, with an IQR of 3.0. This suggests a

Table 4
Distribution of Alda scores across groups.

	cPTSD-negative	cPTSD-positive	U	p-value
N	189	154	20,995.5	<i>0.0002</i>
Mdn (IQR)	5.0 (5)	4.0 (3)		
	Female	Male	Female	Male
N	108	81	69	85
Mdn (IQR)	4.0 (4)	6.0 (4)	4.0 (2)	4.0 (3)

IQR: interquartile range; Mdn: median; N: numerosity; p and U values of Mann-Whitney test.

Table 5
Results of the ordinal regression analysis of patients' Alda score.

Variable	Coefficient	Standard error	z-Value	p-value	95 % Confidence interval
SEX	0.963	0.267	3.605	<i><0.000</i>	0.440/1.487
cPTSD	-0.364	0.268	-1.360	0.174	-0.889/0.161
SEX * cPTSD	-0.829	0.380	-2.181	<i>0.029</i>	-1.574/-0.084

Statistically significant p-values are shown in italics.

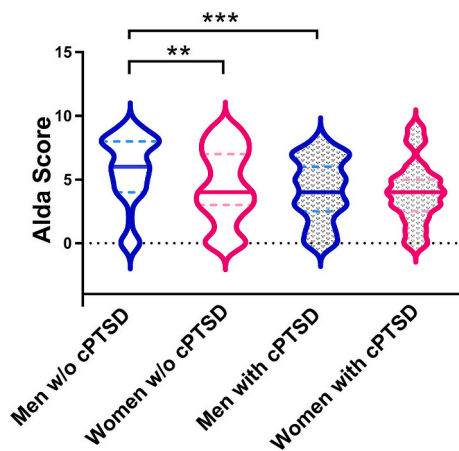


Fig. 1. The violin plot shows medians and quartiles of Alda scores in male and female BD patients with and without comorbid cPTSD. $**p < 0.01$ and $***p < 0.001$ (Mann-Whitney U test).

slightly greater variability in response than females with cPTSD, but less than their counterparts without cPTSD.

To test our hypothesis that sex also plays a key role in the response to treatment of BD patients comorbid with cPTSD, we divided the sample into four groups and conducted an ordinal logistic regression. The analysis also considered the interaction between cPTSD status (yes, no) and sex (male, female). The results shown in Table 5 and graphically presented in Fig. 1 indicated that sex significantly predicts Alda scores ($p < 0.001$), with males showing higher scores than females. The interaction term between cPTSD status and sex was significant ($p < 0.05$), suggesting a moderating effect of cPTSD on the relationship between sex and Alda scores. Taken together, the present results suggest that clinicians should take into consideration a differential response to mood stabilizers depending on the patient's sex and cPTSD comorbidity.

Since the interaction between diagnosis and sex suggests a complex relationship between these variables, we conducted an additional analysis. Specifically, we performed pairwise comparisons using the Mann-Whitney U test. The results depicted in Fig. 1 indicate that among BD patients who are cPTSD-negative, males show significantly higher Alda scores than females ($U = 3588$, $p < 0.003$). The presence of cPTSD in male BD patients significantly lowered their score ($U = 3253.5$, $p < 0.001$). Interestingly, we found no difference in Alda scores between female cPTSD-positive and cPTSD-negative patients. This shows that women do not respond well to treatment with mood stabilizers regardless of the diagnosis of cPTSD, suggesting this factor to be more relevant in men.

4. Discussion

Sex differences in mental health are well-documented, with disparities observed in the prevalence, severity, and progression of various disorders (Riecher-Rössler, 2017). For instance, women are more frequently diagnosed with depressive and anxiety disorders, while men tend to have higher rates of substance use and neurodevelopmental disorders (Arnold, 1996; Brady and Randall, 1999; Global Burden of Disease GBD 2019 Mental Disorders Collaborators, 2022; Riecher-Rössler, 2017). A similar pattern is seen in traumatic and stress-related disorders, with women being more likely to be diagnosed with post-traumatic stress disorder (PTSD) (Bangasser and Valentino, 2014; McGinty et al., 2021). Such differences result from a complex interplay of genetic, hormonal, immunological, and psychosocial factors.

Although there is growing evidence of the impact of sex on various psychiatric disorders, limited research has examined how these differences affect bipolar disorder (BD) and its treatment, with few studies focusing on patients with comorbid psychiatric conditions. Given the

high prevalence of comorbid psychiatric disturbances in BD patients, this knowledge gap is especially pressing. Our study aimed to explore the interaction between BD and complex PTSD, a subtype of PTSD recently recognized in the ICD-11, with a focus on how sex differences influence pharmacological treatment outcomes, given the paucity of studies on that (Ercis et al., 2024). Trauma is a broad term encompassing a range of experiences, and individual responses to similar traumatic events can vary significantly, leading to psychiatric conditions or even full recovery. Given that complex PTSD is defined by persistent emotional and interpersonal difficulties rather than the nature of the trauma itself, we focused on its impact rather than the specific traumatic events that may have contributed to its development. Our work builds on recent findings suggesting lower treatment efficacy of mood stabilizers in patients with comorbid BD and cPTSD (Iazzolino et al., 2024a). To better understand these effects, we also analyzed the clinical and behavioral features of BD based on sex and the presence or absence of cPTSD comorbidity.

Our analysis of sociodemographic data identified significant disparities between sexes, with female BD patients exhibiting lower education levels and higher unemployment rates compared to males. These factors may indirectly influence treatment response, as lower education levels and socioeconomic status have been associated with reduced medication adherence in psychiatric patients, including those with BD (Busby and Sajatovic, 2010; Okasha et al., 2020). Individuals with lower education and employment status may be less likely to seek timely treatment, despite experiencing symptoms. Indeed, our data show that women had a significantly longer duration of untreated BD than men, highlighting a potential barrier to early intervention. Additionally, lower socioeconomic status is linked to greater exposure to stressful life events, which can exacerbate mood instability (Lorant et al., 2003), which aligns with our findings. Unemployment is also a well-established risk factor for psychiatric illnesses, including BD and stress-related conditions, and has been linked to an increased risk of suicidal ideation and attempts (Franke et al., 2024). Despite that, our cohort did not show sex differences in suicidality. BD diagnosis itself can impair work performance and increase the likelihood of job loss (Dean et al., 2004; Kessler et al., 2006), creating a vicious cycle between unemployment and worsening mental health. This dynamic may disproportionately affect women, given their generally lower employment rates, and could partially contribute to the poorer treatment response observed in female BD patients in our study.

Beyond sex differences in sociodemographic variables, we found compelling sex differences in the clinical features of BD (Table 2). The prevalence of BD-I and BD-II did not differ significantly between sexes, but BD-II occurred more frequently in women, which is consistent with previous literature suggesting that women are more susceptible to this subtype (Parial, 2015). Importantly, our findings show that female BD patients had more prolonged untreated illness and more frequent recurrences compared to men. This delay in correct diagnosis is often attributed to the occurrence of depressive episodes as first BD symptoms (Baldessarini et al., 2014), and this disease presentation is particularly common in women (Williams and McInnis, 2019). As mentioned also above, the here observed cohort of female patients showed a median duration of untreated BD of four years, with very high variability (IQR = 18), which was significantly longer than in males. These results highlight the need for earlier detection and intervention in female patients, as delayed diagnosis can lead to suboptimal treatment. Specifically, antidepressant monotherapy in BD increases the risk of hypomanic states, conversion to a rapid cycling course (Rhee et al., 2023), and antidepressant-induced mania (Williams and McInnis, 2019). This is confirmed by our findings showing that women with BD experience more hypomanic episodes and more antidepressant-induced mania compared to men. In contrast, our male BD patients were more likely to experience mixed features, which are associated with severe forms of BD and poor prognosis (Nierenberg et al., 2023). These results suggest that women may respond differently than men to specific

pharmacotherapies, which is an important consideration for clinicians when selecting treatments. A recent systematic review reported that women experience more adverse effects from both mood stabilizers and antipsychotics than men (Ercis et al., 2024), highlighting the complexity of their therapeutic management. Consistently, our findings indicate that women respond less favorably to mood stabilizers compared to men (Fig. 1). Beyond the previously mentioned sociodemographic factors that may influence symptom severity in our female patients, a potential neurobiological explanation for their poorer overall response to pharmacological treatment could be the modulatory effects of estrogen on mood regulation and pharmacotherapy efficacy. Estrogens play an important role in sexual dimorphism in several neuropsychiatric disorders, including BD (Iqbal et al., 2024). They can influence several neurotransmitter systems that are also targeted by mood stabilizers (Bendis et al., 2024; McEwen and Milner, 2017). Fluctuating estrogen levels in women have been linked to high mood instability and alter both pharmacokinetics and pharmacodynamics (Dias et al., 2011; Eisenlohr-Moul et al., 2022; Joffe and Cohen, 1998; Marazziti et al., 2013), which may contribute to a generally low response to mood stabilizers. However, the exact neurobiological mechanisms warrant further investigation. Nevertheless, recent research is exploring the use of estrogen-modulating treatments to improve pharmacological outcomes in women with BD. Specifically, drugs that modulate estrogen receptors, such as tamoxifen and endoxifen, have demonstrated antimanic effects (Carmassi et al., 2021; Joseph et al., 2024). Our findings indeed underscore the need for sex-specific diagnostic and treatment strategies, also considering hormonal influences in BD, providing valuable insights for tailoring therapeutic interventions accordingly.

We also examined the impact of cPTSD comorbidity on BD clinical and behavioral features of our cohort of patients, regardless of sex (Table 3). Comorbid cPTSD emerged as a significant factor influencing both clinical presentation and treatment outcomes. Patients with comorbid cPTSD were younger at the time of BD diagnosis, experienced more frequent episodes, and had higher rates of both depressive and manic episodes than those without cPTSD. This suggests that cPTSD exacerbates the course of BD and leads to a more severe and recurrent illness. Additionally, patients with cPTSD exhibited higher rates of psychotic symptoms, antidepressant-induced mania, seasonality, aggressive behavior, and head trauma, further highlighting the complex interplay between these two conditions. Of particular concern is the significantly higher prevalence of lifetime drug abuse, suicidality, and suicide attempts among patients with cPTSD. These factors have been linked to poor adherence to treatment regimen (Sajatovic et al., 2009; Sajatovic et al., 2007; Tamene et al., 2025; Weiss et al., 1998), which could be a reason for the overall low Alda score in our cPTSD-positive patients. These findings emphasize the importance of thoroughly assessing trauma history in BD patients. Our findings, coupled with other literature data, show that comorbid PTSD or cPTSD is linked to a severe clinical profile and a high suicide risk (Agnew-Blais and Danese, 2016; Iazzolino et al., 2024b; Jannini et al., 2023).

The present findings also show that patients with comorbid cPTSD exhibit poor responses to mood stabilizers overall by using the Alda scale as clinical measure of treatment efficacy. Notably, our analysis revealed significant sex differences in treatment outcomes. As shown in Fig. 1, female BD patients demonstrated poor responses to mood stabilizers regardless of cPTSD comorbidity. In contrast, the response among male patients was strongly influenced by the presence of cPTSD, as males with cPTSD responded worse to mood stabilizers than the ones without cPTSD, who showed higher median Alda scores. As discussed above, hormonal fluctuations in women could be involved in the here observed result, since estrogens influence brain networks and pathways, as well as endocrine signals involved in stress response, cognition, and emotional regulation. In women vulnerable to major depression, estrogens have been shown to support the healthy functioning of these systems (Albert and Newhouse, 2019). Additionally, in healthy cycling women, high estradiol levels have been found to attenuate brain activation changes

and negative mood responses to psychosocial stress (Albert et al., 2015). Similar to their role in depressive disorders, estrogens may play a dual role by both contributing to greater vulnerability and buffering some of the negative consequences. Thus, it is reasonable to hypothesize that estrogens may also help buffer the impact of cPTSD. However, the effects of gonadal steroids are highly complex and vary across reproductive life stages. Future studies with larger sample sizes that allow for comparisons across different reproductive phases and the direct measurement of estrogen levels will be crucial to further exploring this hypothesis.

Coping mechanisms in response to traumatic stress may also play a role. Women are more frequently exposed to interpersonal trauma and tend to use emotion-focused coping strategies, whereas men are more likely to experience non-interpersonal trauma and use problem-focused coping strategies (Olf et al., 2007). These differences could influence the sex-specific expression of cPTSD and the response to treatment in BD patients. Women with PTSD often experience higher levels of emotional dysregulation and comorbid conditions such as anxiety and depression (McGinty et al., 2021; McLean and Foa, 2017; Timmer-Murillo et al., 2023), which complicates treatment by necessitating more comprehensive therapeutic approaches. Both women and individuals with BD are more likely to report child maltreatment. A reduction in the hippocampus volume has been associated with such negative experiences, which may explain the high rates of specific clinical features and anxiety (Colic et al., 2022). The overall response to mood stabilizers in our female BD patients was already quite low and exhibited high variability (Alda scale median = 4, IQR = 4, within a 0–10 range). This suggests that the potential for further measurable decline due to cPTSD comorbidity was limited. Further studies are needed to explore the sex-related neurobiological mechanisms underlying trauma exposure and their impact on BD clinical features, which have received little attention so far. Early identification and targeted interventions for trauma-related symptoms may be crucial to improve outcomes for this particular subgroup of BD patients.

Our results show for the first time that comorbidity with cPTSD significantly affects the response to mood stabilizers selectively in male patients. To mitigate the possibility of a spurious association, we employed ordinal logistic regression, which demonstrated a significant interaction between sex and cPTSD status ($p < 0.05$), suggesting a moderating effect of trauma-related psychopathology on pharmacological response in males. Also, comparisons using the Mann-Whitney U test confirmed that male BD patients with cPTSD exhibited significantly lower Alda scores than those without cPTSD, while no such effect was observed in female patients. This supports the specificity of the effect in males. Such result may be partly due to the fact that men tend to conceal their symptoms and delay seeking treatment, which could exacerbate their condition and make it chronic and severe (O'Brien et al., 2005; Shi et al., 2021). The interaction of cPTSD and BD may further exacerbate mood instability and contribute to the low response to mood stabilizers in this subgroup. Another factor that could contribute to this could also be poor adherence to therapy. Men are generally less adherent to medication regimens than women, and a greater symptom burden due to comorbid cPTSD could further exacerbate this nonadherence. Finally, cPTSD symptoms are not fully controlled by mood stabilizers typically used in BD, as cPTSD involves widespread alterations in brain regions, primarily the hippocampus, amygdala, and prefrontal cortex (Marinova and Maercker, 2015). The underlying neurobiological alterations has not been studied yet, but accumulating evidence regarding non-complex PTSD show several brain changes, like dysregulated excitatory and inhibitory neurotransmission and altered neuronal and glial molecular pathways (McEwen, 2002; Sherin and Nemeroff, 2011; Valenza et al., 2024). These mechanisms are not directly targeted by conventional mood stabilizers, which may limit their efficacy in BD patients with comorbid cPTSD. All this evidence taken together suggest that mood stabilizers alone may not be sufficient to fully manage BD symptoms in men with cPTSD, as their neurobiological and behavioral characteristics may require additional or alternative pharmacological and

psychotherapeutic interventions.

4.1. Conclusion

The results presented here show high rates of suicidality, drug abuse, and poor pharmacological treatment outcomes in the cPTSD group. This highlights the need for integrated treatment approaches that address both mood symptoms and trauma-related distress. Clinicians may need to supplement standard BD treatments with therapies that specifically target trauma, such as trauma-focused psychotherapy or interventions that reduce the risk of antidepressant-induced mania. Further, the differential response to mood stabilizers based on sex and cPTSD status shown here suggests that treatment planning for BD should be tailored to the individual. In particular, women and patients with comorbid cPTSD may benefit from closer monitoring of treatment response and consideration of alternative or additional therapies if mood stabilizers prove inadequate.

4.2. Limitations

Some limitations of this study must be acknowledged. First, as this is a monocentric Italian study, results may not be easily generalized to other populations. Future studies should consider cross-cultural or multicenter designs to validate and extend these findings. Second, response to mood stabilizers was only assessed using the Alda scale, which may not fully capture all dimensions of treatment response and reflects clinical outcomes without establishing causality. Future studies may benefit from using multiple complementary measures to provide a comprehensive assessment of treatment effectiveness. Nevertheless, the large cohort size of this study strengthens the statistical power of our analyses. As such, our observations help to bridge the gap between research and clinical practice and have important implications for patient care. Although our study provides important clinical insights, we recognize that causal mechanisms underlying the observed sex-specific treatment differences require further investigation. Future studies should incorporate longitudinal designs, neuroimaging approaches, and pharmacogenetic analyses to elucidate the underlying neurobiological pathways responsible for the observed results.

In conclusion, the present findings underscore the importance of personalized treatment plans in psychiatric care, particularly for women and patients with cPTSD, and highlight the need for further research to develop more effective, individualized interventions.

CRedit authorship contribution statement

Luca Steardo Jr.: Data Curation, Resources, Methodology, Investigation, Writing - original draft, Supervision, Project administration. **Michele Fornaro:** Writing - review & editing. **Martina D'Angelo:** Investigation, Data Curation. **Valeria Di Stefano:** Investigation, Data Curation. **Francesco Monaco:** Writing - original draft. **Caterina Scuderi:** Writing - Review & Editing. **Luca Steardo:** Writing - Review & Editing. **Marta Valenza:** Conceptualization, Methodology, Formal Analysis, Visualization, Writing - original draft, Writing - Review & Editing, Project administration.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and approved by Ethics Committee of University of Catanzaro (protocol code 307/2020).

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Declaration of competing interest

The authors have no conflict of interest to disclose.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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