

# DOES POST-TRAUMATIC SPECTRUM COMORBIDITY INFLUENCE SYMPTOM SEVERITY IN BIPOLAR DISORDERS? A CROSS-SECTIONAL STUDY IN A REAL-WORLD SETTING

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## SUMMARY

**Background:** The present cross-sectional study investigates the relationship between post-traumatic spectrum comorbidity and the severity of symptoms in subjects diagnosed with Bipolar Disorders (BD).

**Subjects and methods:** In- and outpatients diagnosed with BD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) were consecutively recruited. Sociodemographic and clinical data were collected. Psychopathology was evaluated by means of the Hamilton Rating Scale for Depression (HAM-D), the Young Mania Rating Scale (YMRS), and the Positive and Negative Syndrome Scale (PANSS). Sociodemographic, clinical and psychopathological characteristics of BD subjects with and without sub-threshold PTSD were compared by means of bivariate analyses ( $p < 0.05$ ).

**Results:** BD subjects with post-traumatic spectrum comorbidity ( $n=24.49\%$ ) presented a significantly higher number of hospitalizations when compared to those who did not present the co-occurrence of the two conditions ( $2.67 \pm 2.3$  versus  $1.65 \pm 2.32$ ,  $p=0.039$ ). As for treatment features, subjects with subthreshold PTSD were more frequently prescribed benzodiazepines at the moment of evaluation or in the past ( $n=18$ ,  $100\%$  versus  $n=22.55\%$ ,  $p=0.032$ ). When assessing differences in terms of psychopathological characteristics, subjects with subthreshold PTSD showed higher HAM-D total score ( $16.22 \pm 9.06$  versus  $10.22 \pm 7.23$ ,  $p=0.032$ ) and higher PANSS negative symptom scale score ( $16.06 \pm 6.92$  versus  $11.41 \pm 4.68$ ,  $p=0.017$ ).

**Conclusions:** Findings from the present study suggest that subthreshold PTSD may underpin higher symptom severity and worse outcomes when occurring as a comorbid condition in BD.

**Key words:** bipolar disorders - affective symptoms - psychotic symptoms - PTSD - subthreshold PTSD

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## INTRODUCTION

During the last decades, growing evidence has pointed towards the frequent comorbidity between Bipolar Disorders (BD), traumatic events, and Post-Traumatic Stress Disorder (PTSD) (Otto et al. 2004, Pollack et al. 2006, Cerimele et al. 2017). Indeed, subjects affected by BD frequently report a history of traumatic experiences, with a rate of exposure up to 98% (Kessler et al. 1995, Mueser et al. 1998), compared to an estimated rate of 51-61% among the general population. Particularly, childhood trauma is reported in up to 50% subjects with BD (Garno et al. 2005).

The comorbidity between BD and PTSD has been well elucidated in various epidemiological studies. The prevalence of PTSD among BD subjects was estimated to range from 4 to 40%, with a higher frequency among inpatients, in type I Bipolar Disorder (BDI) and female subjects (Otto et al. 2004, Merikangas et al. 2007, Cerimele et al. 2017). To note, Kessler et al. demonstrated a prevalence of 38.8% in subjects with BDI (Kessler et al. 1997).

A wide range of clinical manifestations, possibly occurring as a result of a traumatic event, can be considered as part of a "post-traumatic spectrum". The concept of "spectrum" suggests that symptoms are located along a continuum and are related to specific vulnerabilities or non-specific factors, which could determine different psychopathological consequences (Dell'Osso et al. 2009).

Indeed, some studies have highlighted how specific clinical features belonging to the post-traumatic spectrum can arise even in subjects exposed to minor, low-magnitude traumatic events, e.g., abortion, divorce, serious illnesses, economic difficulties, highlighting the role of subjectivity in the impact that these events may exert on the individual (Friedman et al. 2011, Lewis et al. 2017). Previous research thus emphasized the importance of determining whether the event was traumatizing for the individual, regardless of its form, or whether it was able to produce post-traumatic stress symptoms (Galea et al. 2005). The concept of subthreshold PTSD was introduced for better investigating the phenomenology of these forms (Stein et al. 1997, Marshall et al. 2001, Hepp et al. 2005).

Subjects affected by BD who were exposed to traumatic events more frequently present rapid cycles (Aldinger & Shultze 2017, Quarantini et al. 2010), an earlier age at onset (Li et al. 2014, Janiri et al. 2015, Janiri et al. 2019, Souza-Queiroz et al. 2016), and a worse disease outcome (Reddy et al. 2017, Mandolini et al. 2019). Furthermore, this population of subjects reports more frequent suicide attempts, a worse quality of life and a higher prevalence of substance abuse (Freeman et al. 2002, Aldinger & Schultze 2017).

Despite growing evidence that traumatic experiences are associated with a wide variability of negative outcomes in BD (Agnew-Blais & Danese 2016, Quarantini et al. 2010), it is currently unclear whether the presence of BD in comorbidity with post-traumatic spectrum disorders predisposes to higher symptom severity. Previous studies show that the exposure to traumatic events is associated with a higher prevalence of psychotic symptoms (Aldinger & Shultze 2017). On the contrary, another study detected lower prevalence of psychotic symptoms in a population on BDI inpatients with comorbid PTSD, compared to subjects without a diagnosis of PTSD (Reddy et al. 2017). Moreover, BD subjects with comorbid PTSD are more likely to be depressed, to have a comorbid personality disorder, and a history of suicide attempts (Reddy et al. 2017).

Despite the relevance of a dimensional approach to PTSD symptoms in BD, most literature on the topic focused on clear-cut PTSD in this population, whilst evidence concerning the comorbidity between subthreshold PTSD and BD is scanty (McLaughlin et al. 2015).

As a consequence, this study aimed to investigate the association between subthreshold PTSD and specific psychopathological features in BD, with particular interest in symptom severity. Furthermore, the secondary aim of the study was to assess socio-demographic and clinical correlates of comorbid subthreshold PTSD in BD.

## **SUBJECTS AND METHODS**

This study was designed as an observational cross-sectional study. Subjects were recruited at the Psychiatric Inpatient Unit of the General Hospital "Santa Maria della Misericordia"/University of Perugia, at the outpatient service of the Section of Psychiatry, Clinical Psychology and Rehabilitation of the General Hospital/University of Perugia, and at the Community Mental Health Centers of the Local Health Units AUSL 1 and 2 of the Umbria region. The study was conducted between February 2018 and December 2020.

The study included subjects diagnosed with BD according to the 5<sup>th</sup> edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and aged  $\geq 18$  years. Subjects  $< 18$ , subjects with mental retardation, cognitive impairment, Borderline Personality Dis-

order, and subjects with inadequate comprehension of Italian language were excluded from the study. All subjects gave their consent for participation in the research and the study was approved by the local Ethic Committee of the Umbria region.

Trained clinicians with expertise in the field of affective disorders collected socio-demographic and clinical features, namely: outpatient or hospital setting, diagnosis of BDI or type II BD (BDII) according to DSM-5 criteria, gender, marital status, age, nationality, scholarship, occupation, living status, current or previous alcohol/substance abuse, diagnosis of Borderline Personality Disorder, organic comorbidities, number of previous BD episodes, number of depressive and hypo/manic episodes, predominant polarity, number of episodes per year, rapid-cycling, number of previous hospitalizations, history and number of previous suicide attempts, presence of psychotic symptoms, current or past psychopharmacological treatment (antidepressants, mood stabilizers, benzodiazepines, antipsychotics), psychiatric comorbidity.

The Structured Clinical Interview for DSM-5, clinician version (SCID-5-CV) was used for the diagnostic assessment (First et al. 2017). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al. 1997) was used for the exclusion of patients with Borderline Personality Disorder.

The diagnosis of subthreshold PTSD was attributed to patients who did not meet all DSM-5 criteria for the diagnosis of PTSD and who had: at least one symptom from each of the four DSM-5 criteria B–E; full symptoms of three of criteria B–E; full symptoms of two of criteria B–E and full symptoms of one of criteria B–E (see Table 1), according to criteria used in a 2015 McLaughlin study (McLaughlin et al. 2015).

Psychopathology was assessed by means of the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960, Cassano et al. 1995), the Young Mania Rating Scale (YMRS) (Young et al. 1978, Palma & Pancheri 1999), and the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987, Pancheri et al. 1995).

The HAM-D is a scale used to assess depressive symptom severity in adults. This scale includes, in its most used version, 21 items with a score from 0 to 4, referring to six factors: depressed mood, feelings of guilt, work and interests, psychomotor and cognitive retardation, psychic anxiety and general somatic symptoms (Bech et al. 1975). It is particularly suitable for forms of severe depression and for evaluating the pervasiveness of symptoms (Balestrieri et al. 2014).

The YMRS is one of the most frequently used scales to assess the presence of manic symptoms. The scale consists of 11 items and is based on the patient's subjective report of his or her clinical status in the previous 48 hours. Additional information is based on the clinical observations made during the course of the

clinical interview. In the YMRS there are 4 items that are graded on a scale between 0 and 8 (irritability, language, thought content and aggressive / destructive behaviors), and 7 items graded on a scale from 0 to 4. The cut-off is usually identified at 12, a score above which a diagnosis of mild hypomania is posed, while for the diagnosis of manic episode the score of 20 is considered (Young et al. 1978, Balestrieri et al. 2014).

The Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of psychotic symptoms, as well as general psychopathology. The PANSS is composed of 30 items evaluated on a 7-point scale (from "absent" to "extremely serious") whose administration must be preceded by a free interview (Kay et al. 1987). The PANSS assesses current symptoms and can be used to monitor the clinical course and pre- and post-treatment status (Balestrieri et al. 2014).

The collected information was entered into an electronic datasheet created ad hoc for the study. Descriptive analyses were performed to assess the distributional properties of the variables in the sample. Subjects with subthreshold PTSD diagnosed according to the above-mentioned operational criteria were compared to those who did not show such comorbidity by means of bivariate analyses. The Chi-Square test was performed for categorical variables, whilst the Mann-Whitney U was used for continuous variables. All tests were two-tailed and the significance was set at  $p < 0.05$ .

## RESULTS

The final sample was composed of 49 subjects, 35 (71.4%) of which were females, with a mean age of  $46.35 \pm 10.54$ . Subjects were mainly inpatients ( $n=39$ , 79.6%) and the majority of the sample was diagnosed with BDI ( $n=30$ , 61.2%).

At the time of evaluation, most subjects presented a manic episode ( $n=21$ , 42.9%). Subthreshold PTSD was detected in 18 (49%) subjects. Among those, 8 (44.4%) were diagnosed with a past PTSD according to DSM-5 criteria, whilst no current PTSD diagnosis was reported in this population. In the post-traumatic spectrum subgroup, 13 (72.2%) subjects were female and the mean age was  $46.44 \pm 10.18$ . The most represented diagnosis in the sample was BDI ( $n=10$ , 55.6%). When comparing the two subgroups, no significant differences in socio-demographic characteristics were identified. Similarly, BD subjects with post-traumatic spectrum comorbidity did not differ from those who did not present the co-occurrence of the two conditions when analyzing diagnostic and clinical features, except for number of hospitalizations, that was significantly higher in the subthreshold PTSD subgroup ( $2.67 \pm 2.3$  versus  $1.65 \pm 2.32$ ,  $p=0.039$ ). As for treatment features, subjects with subthreshold PTSD were more frequently prescribed benzodiazepines at the moment of evaluation or in the past ( $n=18$ , 100% versus  $n=22$ , 55%,  $p=0.032$ ) (see Table 1).

**Table 1.** Benzodiazepine users, antipsychotic users, stabilizer users, antidepressant users, psychotic symptoms, suicide attempts, rapid cycling of disease in two subgroups (Bipolar Disorder with subthreshold PTSD and Bipolar Disorder without subthreshold PTSD) number of cases, percentage and p value

	Bipolar Disorder with subthreshold PTSD: number of cases and percentage	Bipolar Disorder without subthreshold PTSD: number of cases and percentage	p
Benzodiazepine users	18/40; 45%	22/40; 55%	0.032
Antipsychotic users	17/40; 42.5%	23/40; 57.5%	0.167
Stabilizer users	18/43; 41.9%	25/43; 58.1%	0.123
Antidepressant users	14/32; 43.8%	18/32; 56.2%	0.277
Psychotic symptoms	18/49; 36.7%	31/49; 63.3%	0.658
Suicide Attempts	8/19; 42.1%	11/19; 57.9%	>0.752
Rapid cycling of disease	1/2; 50%	1/2; 50%	>1.000

**Table 2.** HAM-D, YMRS and PANSS scores in patients with/without subthreshold PTSD diagnosis, Mann-Whitney U and p value. HAM-D: Hamilton Rating Scale for Depression; YMRS: Young Mania Rating Scale; PANSS pos: PANSS positive symptoms subscale; PANSS neg: PANSS negative symptoms subscale; PANSS psic gen: PANSS general psychopathological subscale; PANSS Tot: total PANSS score

	Bipolar Disorder with subthreshold PTSD: average score $\pm$ standard deviation	Bipolar Disorder without subthreshold PTSD: average score $\pm$ standard deviation	Mann-Whitney U	p
HAM-D	16.22 $\pm$ 9.06	10.82 $\pm$ 7.23	157.00	0.032
YMRS	17.33 $\pm$ 14.11	14.52 $\pm$ 10.46	221.00	0.610
PANSS - pos	13.78 $\pm$ 6.90	15.44 $\pm$ 8.31	218.00	0.560
PANSS - neg	16.06 $\pm$ 6.92	11.41 $\pm$ 4.68	140.50	0.017
PANSS - psic gen	38.28 $\pm$ 12.04	37.37 $\pm$ 12.65	226.00	0.690
PANSS - tot	65.78 $\pm$ 19.29	62.70 $\pm$ 21.35	220.50	0.600

When assessing differences in terms of psychopathological characteristics, BD with PTSD comorbid in its subthreshold form presented higher HAM-D total mean score ( $16.22 \pm 9.06$  versus  $10.22 \pm 7.23$ ,  $p=0.032$ ) and higher PANSS negative symptom scale mean score ( $16.06 \pm 6.92$  versus  $11.41 \pm 4.68$ ,  $p=0.017$ ). Mean scores at the different assessment scales in the two subgroups are reported in Table 2.

## DISCUSSION

In the present study a significant prevalence of subthreshold PTSD was detected, with 49% of our sample complying with our operational criteria. These data are in line with evidence that depicts how subthreshold PTSD represents a very frequent clinical variable (Jin Jeon et al. 2007, Bergman et al. 2015). Indeed, in previous studies (Stein et al. 1997), a prevalence of subthreshold PTSD up to 3.4% was detected among women, whilst the prevalence was 0.3% among men: these percentages were detected in a random sample of 1,002 persons in a midsized Midwestern Canadian city.

Moreover, the prevalence of subthreshold PTSD among Vietnam veterans was evaluated as 22.5% for males and 22.2% for females, whilst the prevalence of PTSD in the same population was 30.9% for males and 26.0% for females, (Weiss et al. 1992). This suggests that there may be a number of individuals that could be potentially overlooked when adhering to more stringent diagnostic criteria (Bergman et al. 2015). Studies on prevalence of PTSD among bipolar patients (Carmassi et al. 2020) detected PTSD in the 41% of the bipolar patient's sample; this could be overlap to our results. At the moment we don't have enough evidence on the prevalence of subthreshold PTSD in a bipolar patient's sample.

In our results, as above described, BD subjects with comorbid post-traumatic spectrum display a significantly higher number of hospitalizations, possibly suggesting a more severe clinical phenotype (Reddy et al. 2017, Mandolini et al. 2019, Freeman et al. 2002, Aldinger & Schultze 2017). Furthermore, this result may also indirectly reflect other clinical features that were associated with sub-threshold PTSD comorbidity in BD, such as the higher incidence of suicide attempts these subjects (Reddy et al. 2017). Concerning treatment features, in our sample subjects with subthreshold PTSD were more frequently prescribed with benzodiazepines at the moment of evaluation or in the past. This result could be due to the particular clinical features presented by subjects with PTSD who often have sleep-wake rhythm disturbances and real nightmares (Richards et al. 2020). Another possible explanation may be that often PTSD (both complete and subthreshold forms) remains misdiagnosed, and there-

fore PTSD symptoms are more easily treated with symptomatic drugs such as benzodiazepines (Guina et al. 2015). To note, consequences of an unrecognized PTSD are serious and may further contribute to worse outcomes. When a PTSD is timely diagnosed, this can allow clinicians to use integrated targeted interventions which may help reaching clinical and functional recovery (Waddington et al. 2003).

When analyzing differences in terms of psychopathological characteristics, BD comorbid with PTSD in its subthreshold form presented higher depression and total mean score negative symptom severity. Although only in PTSD complete form, because we don't have at the moment enough evidence on clinical features of bipolar comorbid with PTSD in its subthreshold form; this data had already been highlighted by other studies on the same topic (Quarantini et al. 2010) in which BD subjects with comorbid PTSD presented worse scores on the psychopathology scales, more rapid cycling and a worse quality of life. Similar results were also presented in another study (Assion et al. 2010) in which subjects with PTSD and BD showed higher HAM-D scores and a subsequent greater severity in the clinical presentation of BD. About negative symptomatology, which emerged in our study in the subgroup with subthreshold PTSD with higher PANSS negative symptom scale mean score ( $16.06 \pm 6.92$  versus  $11.41 \pm 4.68$ ,  $p=0.017$ ), we want to underline how the clinical association between PTSD and negative symptoms has already been outlined for another major psychiatric pathology such as schizophrenia. In fact, in a study on this topic (Strauss et al. 2009) it was shown that the presence of PTSD in schizophrenia was associated with increased secondary negative symptoms: this link could also be transposed in a court of bipolar patients as evidenced by our study.

As for the limitations of the study, the small sample size limits the generalizability of the results. Subthreshold PTSD was evaluated by means of operational criteria based on previous literature and no specific assessment scales were used. Furthermore, given the acute phase of the disease and the severity of the clinical conditions (most of the subjects were inpatients), this sample may not be fully representative of the population of subjects affected by BD.

## CONCLUSIONS

Subthreshold Post-Traumatic Stress Disorder represents a relatively frequent comorbidity in Bipolar Disorders, possibly underpinning higher symptom severity and worse outcomes. The timely identification of this condition and the implementation of adequate treatment strategies may help achieving an improvement of clinical outcomes in this population of subjects.

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**Conflict of interest:** None to declare.

**Contribution of individual authors:**

Giulia Menculini, Chiara Gobbicchi, Margherita Armani, Giorgio Pomili, Patrizia Moretti & Tiziana Sciarra conceived and designed the study;

Giorgio Pomili, Margherita Armani, Francesca Brufani, Chiara Gobbicchi, Federica Cirimbilli & Filippo Brustenghi administered the tests;

Giulia Menculini, Chiara Gobbicchi, Margherita Armani & Giorgio Pomili created the original dataset;

Giulia Menculini, Giorgio Pomili & Francesca Brufani performed the statistical analysis;

Giorgio Pomili, Giulia Menculini, Francesca Brufani, Valentina Pierotti & Cecilia Giulietti wrote the first draft of the manuscript;

Alfonso Tortorella, Patrizia Moretti & Tiziana Sciarra revised the first draft of the manuscript;

Alfonso Tortorella supervised all phases of the study design and writing of the manuscript.

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