frontiers | Research Topics

Comorbidity in bipolar disorder, volume II

Edited by
Domenico De Berardis, Michele Fornaro and Claudia Carmassi

Published in
Frontiers in Psychiatry

ISSN 1664-8714
ISBN 978-2-83251-906-6
DOI 10.3389/978-2-83251-906-6

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Comorbidity in bipolar disorder, volume II

Topic editors

Domenico De Berardis — Department of Mental Health, ASL 4, Italy
Michele Fornaro — University of Naples Federico II, Italy
Claudia Carmassi — University of Pisa, Italy

Citation

De Berardis, D., Fornaro, M., Carmassi, C., eds. (2023). *Comorbidity in bipolar disorder, volume II*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-83251-906-6

Table of contents

frontiers | Frontiers in Psychiatry

TYPE Editorial
PUBLISHED 28 February 2023
DOI 10.3389/fpsyt.2023.1115357

OPEN ACCESS

EDITED AND REVIEWED BY
Andrea Fagiolini,
University of Siena, Italy

*CORRESPONDENCE
Domenico De Berardis
✉ domenico.deberardis@aslteramo.it

SPECIALTY SECTION
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

RECEIVED 03 December 2022
ACCEPTED 13 February 2023
PUBLISHED 28 February 2023

CITATION
De Berardis D, Fornaro M and Carmassi C (2023) Editorial: Comorbidity in bipolar disorder, volume II. *Front. Psychiatry* 14:1115357. doi: 10.3389/fpsyt.2023.1115357

Editorial: Comorbidity in bipolar disorder, volume II

Domenico De Berardis[1,2,3]*, Michele Fornaro[4] and Claudia Carmassi[5]

[1]Department of Psychiatry, Azienda Sanitaria Locale 4, Teramo, Italy, [2]School of Nursing, University of L'Aquila, L'Aquila, Italy, [3]International Centre for Education and Research in Neuropsychiatry, Samara State Medical University, Samara, Russia, [4]School of Medicine and Surgery, University of Naples Federico II, Naples, Italy, [5]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

KEYWORDS

bipolar (affective/mood) disorders, comorbidity, anxiety, ADHD, substance use disorder, posttraumatic stress disorder (PTSD), dissociative symptoms, overweight/obese

Editorial on the Research Topic
Comorbidity in bipolar disorder, volume II

Bipolar disorder (BD), with a lifetime prevalence of about 2 per cent in the general population and a recurrent course tending toward chronicity, represents one of the most severe, frequent and costly psychiatric disorders, characterized by significant rates of disability, a high incidence of suicidality and multiple medical and psychiatric comorbidities (1). In addition, literature reviews estimate that at least 50 per cent of BD patients meet the criteria for other mental or organic disorders, with obvious repercussions on diagnostic framing, treatment and healthcare costs (2).

The presence of comorbidities, a concept that originated in general medicine in the 1970s but which finds its fullest expression in psychiatry, becomes fundamental for any in-depth study of the etiopathogenic hypotheses, the prognostic judgement and, above all, for the relevant therapeutic strategies (3).

Alarming data on the co-presence of other disorders in bipolar patients come from both large community epidemiological studies and those conducted on clinical samples. For example, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), conducted in 2001–2002, confirmed that substance use and psychiatric disorders continue to be highly comorbid, and, in particular, bipolar disorder was steadily associated with panic disorder, agoraphobia, posttraumatic stress disorder, and borderline, schizotypal and antisocial personality disorders (4). The National Comorbidity Survey Study (NCS) and various clinical studies also reported high rates of comorbidity in BD patients (5–7). The works carried out by the Stanley Foundation Bipolar Treatment Outcome Network on about 300 patients with BD-I and BD-II showed that 65% of these subjects had met the diagnostic criteria for at least one other Axis I disorder at some point in their lives, with an earlier onset of affective symptoms and a worse prognosis (8, 9). On the other hand, Strakowski et al. (10), in a famous study of inpatients suffering from DB, showed psychiatric comorbidity of about 40 per cent and general medical comorbidity of 20 per cent, with a higher frequency in the female sex.

The psychiatric disorders most commonly associated with BD are anxiety disorders, eating disorders, attention deficit hyperactivity disorder and substance (SUD) and alcohol abuse (2). It remains to be clarified whether substance abuse is a cause or a consequence of BD. Still, the association between the two pathologies leads to increased affective mood swings, prolonged intervallic phases, a higher prevalence of physical disorders and suicide attempts, and worse adherence to treatment (11).

Concerning the main theme of the Research Topic, Aguglia et al. conducted a cross-sectional study involving 556 patients with a primary diagnosis of BD (376 without SUD, 101 with SUD, and 79 with Polysubstance Use Disorder [polySUD]). They found that younger age, male gender, early age at onset, psychotic and residual symptoms, positive family history of psychiatric disorders, and use of benzodiazepines were significantly associated with polySUD in patients with BD. Interestingly, patients with BD and polySUD were more likely to take four or more medications, particularly benzodiazepines and other drugs. The Authors pointed out that particular attention on this specific subtype of patients with BD may help implement personalized pharmacological and psychosocial therapies integrating the different professional roles.

Following the line of substance abuse and intoxication, Swoboda et al. aimed to compare intoxications due to a suicide attempt with an antidepressant (AD) and antipsychotic (AP) agents, or both with those of other medications and alcohol to illustrate the toxicity potential of these substances in a general population treated for intoxication. They conducted a retrospective and naturalistic one-year registry study that included 105 patients treated for oral intoxication at the University Department of Emergency Medicine in Vienna, Austria. AD/AP intoxications were present in 26 patients, while in the control group ($n = 79$), non-AD/AP drugs ($n = 54$) and exclusively alcohol ($n = 25$) were the toxic agents. In addition, they found that patients with AD/AP intoxication were significantly more often transferred to the psychiatric department, while discharge to home was more likely in the control group. Luckily, study results suggested that the risk of a potentially life-threatening outcome in intoxication with AD/AP wasn't substantially higher than in other readily available toxic agents, in line with the advantageous risk/benefit ratio of newer ADs and APs.

Two papers on the Research Topic addressed the problem of comorbidity between ADHD and BD. In a perspective paper, Comparelli et al. focused on specific clinical and developmental dimensions to recognize and/or differentiate the pattern of ADHD across the course of BD from a nosological perspective. They concluded that treating concurrent ADHD and BD remains an unresolved challenge regardless of the phase of illness. From a developmental perspective, such treatment might require a staged approach. By staging the introduction of treatments, it's possible to reduce the risk of overmedicating patients, better assessing the effect of each treatment. On the other hand, in the case of real comorbidity, a hierarchical approach to treatment should be followed: BD should be treated first. In contrast, ADHD should be treated by combining ADHD medications and mood stabilizers after mood stabilization. Besides, proper mood stabilizing therapy can reduce the chance of positive mood episodes that might arise if psychiatrists only use ADHD-specific medications. That is why a hierarchical approach should be followed. In another interesting study, Nunez et al. evaluated demographic, clinical, treatment, and genetic differences between BD with and without ADHD comorbidity, extending this comparison to consider the onset of attention deficits. Among patients with BD ($N = 2,198$) enrolled in the Mayo Clinic Bipolar Biobank, the researchers identified those with ADHD diagnosed in childhood (BD + cADHD; $N = 350$), those with adult-onset attention deficit symptoms (BD + aAD; $N = 254$), and those without ADHD ($N = 1,594$). A subset of the clinical sample had genotype data available. They found that attention deficits are more prevalent in men and associated with lower employment rates. In line with previous studies, they found a higher prevalence of ADHD in the offspring of BD patients. In addition, BD+ ADHD patients showed significantly higher rates of family history of affective disorders and a higher prevalence of substance use disorders. Specifically, it was observed increased rates of alcohol use disorder and stimulant use. Besides a higher prevalence of anxiety and depression disorders in patients with attentional deficits and, in terms of treatment response to mood stabilizers, the BD + cADHD group had a significantly poorer response to lithium and lamotrigine. Study results showed that BD + cADHD was associated with more significant comorbidities and reduced response to mood-stabilizing treatments. The higher ADHD polygenic risk scores (PRSs) for the BD + cADHD group may reflect a more powerful influence of genetic factors on the early presentation of ADHD symptoms.

Studies have found that traumatic events that occurred during childhood, adolescence and adulthood are associated with an increased risk of developing BD, with a significant likelihood of suicide and psychotic evolution (12–14). As dissociative disorders are an influential group of trauma-related disorders, the co-occurrence of dissociative disorders (DD) and symptoms (DS) in bipolar disorder has been relatively understudied. Still, there is some evidence that this comorbidity may have significant mechanistic and clinical implications. Rajkumar wrote an interesting scoping review on the frequency and correlates of DS and DD in BD. He pointed out that a significant minority of patients (10–20%) with bipolar disorder might experience important DS, even during the euthymic phase. The overall severity of DS was higher in BD than in healthy controls and major depression but lower in BD compared to "trauma spectrum disorders" such as DD, complex PTSD and borderline personality disorder. The presence of DS might be associated with psychotic symptoms, suicide attempts, and a poorer response to treatment. DS also appeared to be related to the severity of childhood trauma in patients with BD. Thus, assessing DD and DS in a patient affected by BD would be helpful in everyday clinical practice to adequately address the treatment.

On the other hand, Hogg et al. started from the assumption that post-traumatic stress disorder (PTSD) is an established comorbidity in BD. They conducted a multi-center study comprising 79 adult participants with BD with a history of psychological trauma and reported baseline data from a trial registered in Clinical Trials (https://clinicaltrials.gov; ref: NCT02634372). Study findings provided further evidence of the lack of difference in how trauma symptoms were presented across BD subtypes and provided essential data regarding the high levels of trauma symptoms in BD subjects, even when criteria for a PTSD diagnosis weren't met. However, the evidence showed that there were few differences in clinical BD severity between the subjects with full PTSD and subsyndromal PTSD, although they found a possible tendency for appositive correlation between full PTSD and psychotic symptoms, as well as between sexual abuse and rapid cycling, which can be clinically helpful in the identification and treatment of both. In conclusion, the study findings highlighted

the proper investigation to understand the impact of comorbidity with a history of psychological trauma in BD patients, including subsyndromal PTSD symptoms and underlined the importance of screening for psychological trauma in the BD population.

Recently, some studies have suggested a higher risk of developing metabolic syndrome in BD than in the general population, increasing the risk of cardiovascular morbidity (15, 16). Furthermore, BD patients are at high risk of being overweight and obese, suffer more frequently from type II diabetes mellitus, and have higher cardiovascular mortality rates than the general population (17). Yi et al. conducted a retrospective, cross-sectional study to investigate the prevalence and associated factors of obesity and overweight in a sample of 1,169 inpatients with BD in China. They found that the prevalence rates of obesity and overweight were 21.0% and 32.2%, respectively, and the duration of BD was significantly associated with obesity. Besides, in a binary logistic regression analysis, the duration of BD and the levels of uric acid, ALT, triglycerides, and LDL cholesterol were identified as predictors for obesity. In contrast, male sex and uric acid level were associated with a higher frequency of overweight. The results of the present study show a need to implement early screening, prevention and interventions for obesity and overweight in patients with BD.

Finally, from a mixed psychopathological and translational perspective, gastrointestinal (GI) symptoms are widespread in BD patients but relatively understudied. Guo et al. recruited 59 BD patients that were divided into two groups. Each group was assessed with the 24-item Hamilton Depression Rating Scale (HAMD-24) according to the presence or absence of GI symptoms and compared with healthy controls. Differential metabolites were identified and further analyzed using Metabo Analyst 3.0 to identify associated metabolic pathways. The results showed that BD patients with GI symptoms experience more severe symptoms than the metabolic pathways related to GI symptoms, which may be risk factors for gastrointestinal symptoms in BD patients. Moreover, researchers found that the total HAMD-24 scores in the GI symptoms group were more significant than that of the non-GI symptoms group, consistent with past research findings. Based on metabolomic analysis results, it was also found that the common disturbances metabolic pathways of both groups of patients jointly exhibited disorders of ketone body metabolism: ketone body metabolism might be involved in the inflammation, and oxidative stress may be one of the pathogeneses of BD. Besides, the unique disturbances in metabolic pathways of BD patients with GI symptoms were fatty acid biosynthesis and tyrosine metabolism. One can argue that the abnormalities of these two metabolic pathways may be related to the disturbance of the gut microbiome, and the gut microbiome has been implicated in multiple human chronic GI disorders.

In conclusion, this Research Topic has shed light on the problem of comorbidity and BD, and researchers have profound a remarkable effort to address this topic. We would thank all of them for this and hope that the new forthcoming issue on Frontiers in Psychiatry entitled "Comorbidity in Bipolar Disorder and Schizophrenia Volume III" will further contribute to the understanding of comorbidity issues in severe psychiatric disorder, this time also in schizophrenia.

Finally, all the Guest Editors wish to dedicate the current Research Topic to Professor Gianna Sepede, MD PhD, a gifted psychiatrist whose kind manners and bright scientific and clinical skills inspired many of us as colleagues, friends, and trainees before her premature departure.

Author contributions

All Authors have contributed to the present Editorial with equal efforts.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Fornaro M, Kardash L, Novello S, Fusco A, Anastasia A, De Berardis D, et al. Carta: Progress in bipolar disorder drug design toward the development of novel therapeutic targets: a clinician's perspective. *Expert Opin Drug Discov.* (2018) 13:221–8. doi: 10.1080/17460441.2018.1428554

2. Hirschfeld RM, Vornik AL. Bipolar disorder–costs and comorbidity. *Am J Manag Care.* (2005) 11:S85—90.

3. Maj M. The aftermath of the concept of 'psychiatric comorbidity'. *Psychother Psychosom.* (2005) 74:67–8. doi: 10.1159/000083164

4. Blanco C, Compton WM, Saha TD, Goldstein BI, Ruan WJ, Huang B, et al. Grant: epidemiology of DSM-5 bipolar i disorder: results from the national epidemiologic survey on alcohol and related conditions - III. *J Psychiatr Res.* (2017) 84:310–7. doi: 10.1016/j.jpsychires.2016.10.003

5. Kendler KS, Davis CG, Kessler CR. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *Br J Psychiatry.* (1997) 170:541–8. doi: 10.1192/bjp.170.6.541

6. Schiweck C, Arteaga-Henriquez G, Aichholzer M, Edwin Thanarajah S, Vargas-Caceres S, Matura S, et al. Reif: Comorbidity of ADHD and adult bipolar disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* (2021) 124:100–23. doi: 10.1016/j.neubiorev.2021.01.017

7. Gogia M, Shah AQ, Kapczinski FT, de. Azevedo Cardoso T. The impact of substance use disorder comorbidity on cognition of individuals with bipolar disorder: a systematic review. *Psychiatry Res.* (2022) 311:114525. doi: 10.1016/j.psychres.2022.114525

8. McInnis MG, Andreassen OA, Andreazza AC, Alon U, Berk M, Brister T, et al. Young: Strategies and foundations for scientific discovery in longitudinal studies of bipolar disorder. *Bipolar Disord.* (2022) 24:499–508. doi: 10.1111/bdi.13198

9. Post RM, Altshuler LL, Kupka R, McElroy SL, Frye MA, Grunze H, et al. Nolen: 25 years of the international bipolar collaborative network (BCN). *Int J Bipolar Disord.* (2021) 9:13. doi: 10.1186/s40345-020-00218-w

10. Strakowski SM, Tohen M, Stoll AL, Faedda GL, Goodwin CD. Comorbidity in mania at first hospitalization. *Am J Psychiatry.* (1992) 149:554–6. doi: 10.1176/ajp.149.4.554

11. Fornaro M, De Berardis D, Koshy AS, Perna G, Valchera A, Vancampfort DB. Stubbs: prevalence and clinical features associated with bipolar disorder polypharmacy: a systematic review. *Neuropsychiatr Dis Treat.* (2016) 12:719–35. doi: 10.2147/NDT.S100846

12. Wrobel AL, Kohler-Forsberg O, Sylvia LG, Russell SE, Dean OM, Cotton SM, et al. Nierenberg: Childhood trauma and treatment outcomes during mood-stabilising treatment with lithium or quetiapine among outpatients with bipolar disorder. *Acta Psychiatr Scand.* (2022) 145:615–27. doi: 10.1111/acps.13420

13. Wrobel AL, Jayasinghe A, Russell SE, Marx W, Alameda L, Dean OM, et al. Turner: The influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder: a systematic review and meta-analysis. *J Affect Disord.* (2022) 296:350–62. doi: 10.1016/j.jad.2021.09.103

14. Cogan CM, Paquet CB, Lee JY, Miller KE, Crowley MD, Davis LJ. Differentiating the symptoms of posttraumatic stress disorder and bipolar disorders in adults: Utilizing a trauma-informed assessment approach. *Clin Psychol Psychother.* (2021) 28:251–60. doi: 10.1002/cpp.2504

15. Schuster MP, Borkent J, Chrispijn M, Ioannou M, Doornbos B, Burger H, et al. Haarman: increased prevalence of metabolic syndrome in patients with bipolar disorder compared to a selected control group-a Northern Netherlands LifeLines population cohort study. *J Affect Disord.* (2021) 295:1161–8. doi: 10.1016/j.jad.2021.08.139

16. Grover S, Mehra A, Chakravarty R, Jagota GS. Sahoo: Change in prevalence of metabolic syndrome in patients with bipolar disorder. *Asian J Psychiatr.* (2020) 47:101876. doi: 10.1016/j.ajp.2019.101876

17. Gimenez-Palomo A, Gomes-da-Costa S, Dodd S, Pachiarotti I, Verdolini N, Vieta E, et al. Does metabolic syndrome or its component factors alter the course of bipolar disorder? A systematic review. *Neurosci Biobehav Rev.* (2022) 132:142–53. doi: 10.1016/j.neubiorev.2021.11.026

frontiers | Frontiers in Psychiatry

BRIEF RESEARCH REPORT
published: 14 April 2022
doi: 10.3389/fpsyt.2022.884217

Clinical and Genetic Correlates of Bipolar Disorder With Childhood-Onset Attention Deficit Disorder

Nicolas A. Nunez[1†], Brandon J. Coombes[2†], Francisco Romo-Nava[3], David J. Bond[4], Jennifer Vande Voort[1], Paul E. Croarkin[1], Nicole Leibman[1], Manuel Gardea Resendez[1], Marin Veldic[1], Hannah Betcher[1], Balwinder Singh[1], Colin Colby[2], Alfredo Cuellar-Barboza[5], Miguel Prieto[6], Katherine M. Moore[1], Aysegul Ozerdem[1], Susan L. McElroy[3], Mark A. Frye[1] and Joanna M. Biernacka[1,2*]*

[1] Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, United States, [2] Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, United States, [3] Lindner Center of HOPE /University of Cincinnati, Cincinnati, OH, United States, [4] Department of Psychiatry & Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, United States, [5] Department of Psychiatry, Universidad Autónoma de Nuevo León, Monterrey, Mexico, [6] Department of Psychiatry, Facultad de Medicina, Universidad de los Andes, Santiago, Chile

Background: Bipolar disorder (BD) with co-occurring attention deficit-hyperactivity disorder (ADHD) is associated with an unfavorable course of illness. We aimed to identify potential clinical and genetic correlates of BD with and without ADHD.

Methods: Among patients with BD ($N = 2,198$) enrolled in the Mayo Clinic Bipolar Biobank we identified those with ADHD diagnosed in childhood (BD+cADHD; $N = 350$), those with adult-onset attention deficit symptoms (BD+aAD; $N = 254$), and those without ADHD ($N = 1,594$). We compared the groups using linear or logistic regression adjusting for age, sex, and recruitment site. For genotyped patients ($N = 1,443$), logistic regression was used to compare ADHD and BD polygenic risk scores (PRSs) between the BD groups, as well as to non-BD controls ($N = 777$).

Results: Compared to the non-ADHD BD group, BD+cADHD patients were younger, more often men and had a greater number of co-occurring anxiety and substance use disorders (all $p < 0.001$). Additionally, BD+cADHD patients had poorer responses to lithium and lamotrigine ($p = 0.005$ and $p = 0.007$, respectively). In PRS analyses, all BD patient subsets had greater genetic risk for BD and ADHD when compared to non-BD controls ($p < 0.001$ in all comparisons). BD+cADHD patients had a higher ADHD-PRS than non-ADHD BD patients ($p = 0.012$). However, BD+aAD patients showed no evidence of higher ADHD-PRS than non-ADHD BD patients ($p = 0.38$).

Conclusions: BD+cADHD was associated with a greater number of comorbidities and reduced response to mood stabilizing treatments. The higher ADHD PRS for the BD+cADHD group may reflect a greater influence of genetic factors on early presentation of ADHD symptoms.

Keywords: ADHD, bipolar disorder, polygenic risk score, genetic, clinical features

OPEN ACCESS

Edited by:
Domenico De Berardis, Mental Health Center (CSM) and Psychiatric Service of Diagnosis and Treatment (SPDC), Italy

Reviewed by:
Michele Fornaro, University of Naples Federico II, Italy
Claudia Pisanu, University of Cagliari, Italy

***Correspondence:**
Joanna M. Biernacka
Biernacka.joanna@mayo.edu
Mark A. Frye
mfrye@mayo.edu

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

Received: *25 February 2022*
Accepted: *17 March 2022*
Published: *14 April 2022*

Citation:
Nunez NA, Coombes BJ, Romo-Nava F, Bond DJ, Vande Voort J, Croarkin PE, Leibman N, Gardea Resendez M, Veldic M, Betcher H, Singh B, Colby C, Cuellar-Barboza A, Prieto M, Moore KM, Ozerdem A, McElroy SL, Frye MA and Biernacka JM (2022) Clinical and Genetic Correlates of Bipolar Disorder With Childhood-Onset Attention Deficit Disorder. Front. Psychiatry 13:884217. doi: 10.3389/fpsyt.2022.884217

BACKGROUND

Bipolar disorder (BD) is a severe episodic mood disorder with a considerable morbidity and premature mortality due to suicide and multiple medical comorbidities (1). Lifetime prevalence rate of BD is between 2.4 and 4.4 % (2, 3) and the comorbidity with attention deficit and hyperactivity disorder (ADHD) among adults diagnosed with BD has been estimated to range from 9 to 35% (4, 5) with a higher prevalence in BD type I (BD-I) (4). Importantly, the co-occurrence of BD and ADHD is associated with a significantly increased risk of addiction and anxiety disorders, which negatively impacts BD course of illness (4, 6, 7).

Diagnostic boundaries between BD and ADHD can been clinically difficult to discern due to overlapping symptoms and a persistence of ADHD from childhood to adulthood in certain cases. Moreover, longitudinal studies have shown that ∼25% of individuals with childhood ADHD (cADHD) develop BD (8) although persistent attention deficits can also be linked to the natural course of BD illness. Although the symptomatic and syndromic overlap between BD and ADHD has been addressed extensively in the literature suggesting more of a mixed clinical presentation linked by the inattention domain, the neurobiological distinctive underpinnings of BD with and without comorbid cADHD remains unclear (9).

Both BD and ADHD have a substantial genetic component and thus many studies examining the overlap in BD and ADHD have focused on relatives of individuals with BD. Interestingly, a study on offsprings of BD patients considering high risk individuals, revealed there was no increase in ADHD diagnosis but a higher prevalence of hyperactive and mood/anxiety symptoms (10). Further, Meyer and colleagues found a higher prevalence of childhood attention and executive functions deficits and behavioral symptoms in the offsprings who developed BD compared to those with absence of a mood disorder in adulthood (11).

Polygenic risk scores (PRSs) are increasingly used in psychiatric studies because, in addition to estimating a person's genomic burden for a particular trait, they may demonstrate overlapping genetic predisposition between two traits (12). There have been previous studies that examined ADHD-PRS and its association with different psychiatric phenotypes. For example, a study examined the genetic risk for psychosis spectrum symptoms and different psychiatric phenotypes underscoring a significant association between ADHD-PRS and psychotic symptoms (13); also, a common genetic variation associated with risk for clinically diagnosed ADHD has been found to be associated with anxiety and depressive disorders amongst others (14). A recent study found that ADHD PRS was higher in BD patients diagnosed with cADHD compared to controls but was only marginally higher than in BD patients without cADHD (15). Moreover, a large Danish population study comparing genetic loci between childhood, persistent and late diagnosed patients with ADHD suggested a higher ADHD PRS was associated with persistent ADHD symptoms compared to cADHD or late ADHD (16).

Our aim in this study was to evaluate demographic, clinical, treatment, and genetic differences between BD with and without ADHD comorbidity. We extend this comparison to also consider the onset of attention deficits. Given the nosological controversies, we aimed to enhance the literature by replicating the previous findings of increased illness burden and associated sociodemographic features as well as treatment outcomes. Furthermore, we compared associations of genetic risk for ADHD and BD with the presence and time of onset of attention deficits.

MATERIALS AND METHODS

Sample Description

The Mayo Clinic BD Biobank (MCBB) was established by a collaborative network with the aim of building a repository that will facilitate studies on disease risk, pharmacogenomics and treatment outcomes (17). Enrollment sites included: Mayo Clinic (Rochester, Minnesota), Lindner Center of HOPE/University of Cincinnati College of Medicine (Cincinnati, Ohio), University of Minnesota (Minneapolis, Minnesota), Clinica Alemana (Santiago, Chile) and Universidad Autonoma de Nuevo Leon (Monterrey, Mexico). Each site had its own protocol approved by the local Institutional Review Board, and all patients consented to use of their data for future genetic studies. Diagnostic confirmation of BD was determined using the Structured Clinical Interview (SCID) for DSM-IV (18). Mood disorder psychiatrists recorded clinical characteristics and current medications by review of all available clinical materials (i.e., electronic health record, patient interviews). Using the Clinical Questionnaire, clinicians recorded the presence or absence of current and/or lifetime diagnoses of ADHD during childhood (cADHD). We also explored the phenotype of attention deficits in adulthood (aAD) in patients with no cADHD diagnoses. For the genetic analysis, controls without BD were selected from the Mayo Clinic Biobank (19). Potential controls with International Classification of Disease-9 codes for BD or schizophrenia in their electronic medical record were excluded. Patients with other psychiatric illnesses (e.g., major depression) were not excluded.

Clinical Measures

Patients were assessed for an anxiety disorder comorbidity domain (range 0–6) based on the sum of all lifetime anxiety disorders namely: post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), phobia, and panic disorder. Similarly, we calculated a mood instability domain (range 0–5) which was determined by the sum of a lifetime presence of mixed episodes, rapid cycling, ultra rapid/ultradian cycling, cycle acceleration over time, and increased episode severity over time, being coded as no = 0 and yes = 1. Data related to family history, comorbidities and pharmacological treatments were collected at time of inclusion into the MCBB by clinical interview supplemented by information extracted from the electronic health records. Treatment response to lithium, antipsychotics and antiepileptic mood stabilizers (lamotrigine and divalproex) were assessed with the Alda scale (20). This

scale was developed for retrospective evaluation of prophylactic treatment response in naturalistic conditions; it utilizes two subscales A and B. The A score is a composite measure of clinical improvement in severity, duration and frequency of illness and is rated from 0 (no change)-10 (complete response) thus a higher A score represents a greater improvement. The B score evaluates five potential confounders to determine the role of the medicine in improvement of BD: number of episodes before the treatment (B1), frequency of episode before the treatment (B2), duration of the treatment (B3), compliance during periods of stability (B4), and use of additional medications during the periods of stability (B5).

Genotyping and Imputation for Overall Sample

A subset of the clinical sample had genotype data available. Genotyping and genetic data quality control of this sample were previously described (21, 22). Briefly, the Illumina HumanOmniExpress platform was used to genotype 1,046 BD cases and 828 controls. For quality control purposes, we excluded subjects with <98% call rate and related subjects (randomly choosing one individual in pairs with kinship coefficient > 0.2). SNPs with call rate <98%, MAF < 0.01, and those not in Hardy-Weinberg Equilibrium (HWE; P<1e-06 in healthy controls) were removed. After these steps 643 011 SNPs and 920 BD cases with ADHD assessment and 777 non-BD control subjects remained. Genotypes were imputed using the Michigan Imputation Server (23) with the HRC reference sample. Dosage data was converted to best guess genotype for the well-imputed (dosage R^2 >0.8) and common (MAF >0.01) SNPs, resulting in more than 5 million SNPs.

Polygenic Risk Scores

PRSs were calculated based on genome-wide association study (GWAS) summary statistics from the largest PGC studies of BD (24) and ADHD (25) and restricted to only well-imputed variants (INFO>0.9). Summary statistics removing the MCBB sample from Mullins et al. (24) were used to avoid sample overlap. LDpred2 (26) was used to compute the ADHD and the BD-PRSs using the "auto" setting which directly learns the two LDpred2 parameters from the GWAS data and creates one PRS for a given trait. PRSs were standardized to have standard deviation equal to one and centered with respect to controls such that controls have a mean of zero.

Statistical Analysis

We used linear and logistic regression to compare demographic and clinical variables between BD+cADHD and non-ADHD (BD patients with no cADHD or aAD) groups. We also performed an exploratory analysis comparing these groups of patients to the BD+aAD group. All analyses were adjusted for age, sex and recruitment site. The PRS analyses also included comparisons with non-BD controls. For the PRS analyses logistic regression was used to predict each binary outcome (e.g., cADHD vs. non-BD controls) while adjusting for the first four principal components of ancestry (PCs) to control for population stratification. All statistical analyses were performed in R (version 3.5.1). To account for the multiple statistical tests in **Table 1**, we mainly highlight comparisons with $p < 0.001$, which approximately controls for the 30 variables compared between cADHD cases to non-ADHD BD cases.

RESULTS

Table 1 summarizes demographic and clinical information of subjects with BD+cADHD (n = 350), non-ADHD (n = 1594), BD+aAD (n = 254) and comparisons between groups. Compared to non-ADHD, BD+cADHD patients were younger (34.9 ± 13.1 vs. 43.0 ± 15.3; $p < 0.001$), more likely to be men (49.7 vs. 35.8%; $p < 0.001$) and less likely to have full time employment (21.5 vs. 27.2%; $p = 0.002$). Similarly, comparing to those with aAD, BD+cADHD cases also were younger (34.9 ± 13.1 vs. 42.5 ± 13.3; $p < 0.001$), and more likely to be men (49.7 vs. 35.2%; $p < 0.001$). In comparing those with aAD vs. those with non-ADHD, there was no significant difference in gender (35.2 vs. 35.8%; $p = 0.94$) or in age (42.5 ± 13.3 vs. 43.0 ± 15.3; $p = 0.71$).

Family History

BD+cADHD had greater prevalence of family history of mental illness: BD (52.9 vs. 44.8%, $p < 0.001$), depression (87.5 vs. 77.4%, p<0.001) and alcoholism (54.5 vs. 47.2%, $p = 0.001$) compared to non-ADHD. BD+aAD showed higher rates of BD (56.3 vs. 44.8%, $p = 0.005$) and depression (86.9 vs. 77.4%, $p < 0.001$) family history when compared to non-ADHD. There were no significant differences between BD+cADHD and BD+aAD in terms of family history.

BD-Specific Clinical Presentation

BD+cADHD, BD+aAD and non-ADHD groups were not significantly different in regard to clinical presentation. They had similar rates of BD type I (71.062.6 and 67.8%, respectively), history of psychosis (41.4, 39.3, and 39.3%, respectively), suicide attempts (35.1, 37.9, and 33.3%, respectively), and rapid cycling (71, 70, and 60%, respectively).

Anxiety Comorbidity

The BD+cADHD group exhibited a greater mean number of anxiety disorder comorbidities compared to non-ADHD (1.7 ± 1.3 vs. 1.3 ± 1.2, p <0.001) which included: greater lifetime prevalence of generalized anxiety disorder (58.3 vs. 44.5%; $p < 0.001$), social anxiety (30.9 vs. 18.4%; $p < 0.001$), panic disorder (35.7 vs. 27.0%; $p = 0.002$) and OCD (16.2 vs. 10.0%; $p = 0.005$). Similarly, the BD+aAD group had a greater overall number of anxiety disorder comorbidities compared to non-ADHD (1.8 ± 1.4 vs. 1.3 ± 1.2, $p < 0.001$) including generalized anxiety disorder (61.3 vs. 44.5%; $p < 0.001$), social anxiety (27.5 vs. 18.4%; $p < 0.001$), and OCD (25.0 vs. 10.0%; $p < 0.001$). The BD+aAD group did not differ from the BD+cADHD group with respect to anxiety comorbidity.

Substance Use Comorbidity

BD+cADHD also had higher rates of overall substance use disorder comorbidities than non-ADHD (1.2 ± 1.0 vs. 0.87 ±

TABLE 1 | Comparison of demographic and clinical variables between BD patient subgroups: BD+cADHD, BD+aAD, and no-ADHD.

	Child onset (cADHD) N=350	No ADHD *N* = 1,594	cADHD vs No ADHD p-value	Adult onset (aAD) *N* = 254	cADHD vs aAD *p*-value	aAD vs No ADHD *p*-value
Sex, Male, *N* (%)	174 (49.7%)	570 (35.8%)	<0.001*	89 (35.2%)	<0.001*	0.939
Age, Mean (SD)	34.9 (13.1)	43.0 (15.3)	<0.001*	42.5 (13.3)	<0.001*	0.707
Married (Y/N) *N* (%)	128 (37.9%)	720 (47.2%)	0.649	103 (41.7%)	0.209	0.185
Education > 12 years, *N* (%)	320 (94.7%)	1,458 (95.7%)	0.355	239 (96.8%)	0.616	0.533
Fulltime work, *N* (%)	72 (21.5%)	407 (27.2%)	0.002	56 (23.0%)	0.223	0.192
Diagnosis: BD-I vs. BD-II, *N* (%)	250 (71.4%)	1,080 (67.8%)	0.175	159 (62.6%)	0.077	0.130
Family history of bipolar disorder, *N* (%)	145 (52.9%)	541 (44.8%)	<0.001	107 (56.3%)	0.658	0.005
Family history of depression, *N* (%)	252 (87.5%)	1,043 (77.4.%)	<0.001	186 (86.9%)	0.307	0.001
Family history of alcoholism, *N* (%)	162 (54.5%)	639 (47.2%)	<0.001	119 (54.3%)	0.365	0.063
History of psychosis, *N* (%)	143 (41.4%)	621 (39.3%)	0.480	99 (39.3%)	0.736	0.910
History of suicidal attempts, *N* (%)	121 (35.1%)	528 (33.3%)	0.496	96 (37.9%)	0.536	0.171
History of rapid cycling, *N* (%)	163 (70.6%)	619 (59.7%)	0.037	114 (69.5%)	0.550	0.085
Nicotine dependence, *N* (%)	163 (47.4%)	595 (37.6%)	<0.001	106 (42.4%)	0.375	0.171
Alcohol dependence, *N* (%)	165 (48.1%)	541 (34.2%)	<0.001	104 (40.9%)	0.305	0.063
SUD (Cocaine- Methamphetamine), *N* (%)	58 (17.0%)	32 (2.0%)	0.051	39 (15.5%)	0.564	0.218
Substance use disorder comorbidity sum, Mean (SD)	1.20 (1.05)	0.87 (0.98)	<0.001	1.05 (1.02)	0.211	0.020
Anorexia, *N* (%)	23 (6.7%)	76 (4.8%)	0.044	13 (5.2%)	0.218	0.698
Bulimia, *N* (%)	25 (7.3%)	85 (5.2%)	0.055	17 (6.7%)	0.454	0.334
Binge eating disorder, *N* (%)	44 (12.8%)	188 (11.8%)	0.465	37 (14.7%)	0.823	0.101
Generalized anxiety disorder, *N* (%)	201 (58.3%)	724 (44.5%)	<0.001	152 (61.3%)	0.812	<0.001
Social anxiety disorder, *N* (%)	105 (30.9%)	300 (18.4%)	<0.001	69 (27.5%)	0.475	<0.001
Panic disorder, *N* (%)	123 (35.7%)	440 (27.0%)	0.002	91 (36.3%)	0.476	0.007
Obsessive compulsive disorder, *N* (%)	56 (16.2%)	163 (10.0%)	0.005	63 (25.0%)	0.027	<0.001
Anxiety disorder comorbidity sum, Mean (SD)	1.7 (1.35)	1.3 (1.23)	<0.001	1.8 (1.4)	0.977	<0.001
Mood instability sum, Mean (SD)	1.8 (1.33)	1.5 (1.31)	0.017	1.88(1.4)	0.321	0.005
Alda A Scores, mean (SD)						
Antipsychotics	4.1 (2.5)	5.5 (2.8)	0.020	3.6 (2.8)	0.914	0.044
Divalproex	4.9 (2.6)	5.2 (2.8)	0.466	4.6 (2.2)	0.663	0.296
Lamotrigine	4.5 (2.5)	5.6 (2.5)	0.007	4.4 (2.6)	0.922	0.005
Lithium	4.7 (2.9)	5.6 (2.8)	0.005	4.4 (3.0)	0.761	<0.001
Adherence-Alda score B4	12 (12.1%)	77 (18.0%)	0.077	9 (13.4%)	0.910	0.048

Comparisons are adjusted for age, sex, and recruitment site.

ADHD, attention deficit and hyperactivity disorder; SD, standard deviation; BD, bipolar disorder; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; SUD, stimulant use disorder; SCZ-BD, schizoaffective disorder bipolar type; Y/N, yes-no binary outcome.

**Non-adjusted by for age, sex and recruitment site.*

0.98, p<0.001) namely: alcohol dependence (48.1 vs. 34.2%, $p < 0.001$) and nicotine dependence (47.4 vs. 37.6%; $p < 0.001$). The BD+aAD cases also had slightly higher rates of overall substance use disorders than non-ADHD cases (1.05 ± 1.02 vs. 0.87 ± 0.98, $p = 0.02$) but did not differ from the BD+cADHD group.

Pharmacological Treatment and Treatment Response

BD+cADHD and BD+aAD showed greater prevalence of stimulant use compared to non-ADHD (70.2 and 75.2%, respectively vs. 53.5%; $p < 0.001$), while BD+aAD had higher antidepressant use compared to non-ADHD (85.4 vs. 78.8%; $p < 0.001$) and BD+cADHD (85.4 vs 80.6%; $p < 0.001$). Treatment response assessed by the Alda scale showed that non-ADHD cases had significantly higher mean Alda A scores (better response) for lamotrigine (5.6 ± 2.5 vs. 4.5 ± 2.5, $p = 0.007$) and lithium (5.6 ± 2.8 vs. 4.7 ± 2.9, $p = 0.005$) compared to BD+cADHD. Similarly, non-ADHD cases had significantly higher mean Alda A scores for lamotrigine (5.6 ± 2.5 vs. 4.4 ± 2.6, $p = 0.005$) and lithium (5.6 ± 2.8 vs. 4.4 ± 3.0, $p <$

TABLE 2A | Associations of ADHD PRS with BD subtypes defined by cADHD and aAD.

BD group	*N*	OR (95% CI)	R^2	*p*-value	Reference
All	1,443	1.26 (1.15, 1.38)	1.5%	9.32E-07	No BD Control (*N* = 777)
No ADHD	963	1.23 (1.10, 1.36)	1.2%	7.28E-05	
cADHD	234	1.51 (1.28, 1.77)	4.0%	4.05E-07	
aAD	178	1.32 (1.11, 1.57)	1.7%	0.002	
cADHD	234	1.20(1.04, 1.38)	0.7%	0.012	BD no ADHD (*N* = 963)
aAD	178	1.07 (0.91, 1.26)	0.0%	0.38	
cADHD	234	1.12 (0.91, 1.36)	0.2%	0.26	BD+aAD (*N* = 178)

ADHD, attention-deficit/hyperactivity disorder diagnosed during childhood (cADHD) or attention deficits diagnosed in adulthood (aAD); BD, bipolar disorder; OR, odds ratio; CI, confidence interval; PRS, polygenic risk score. R^2-Nagelkerke's pseudo-R^2.

TABLE 2B | Associations of BD PRS with BD subtypes defined by cADHD and aAD.

BD group	N	OR (95% CI)	R^2	*p*-value	Reference
All	1,443	1.65 (1.49, 1.83)	6.4%	8.7E-23	No BD Control (*N* = 777)
No ADHD	963	1.70 (1.52, 1.90)	7.5%	1.3E-21	
cADHD	234	1.51 (1.27, 1.79)	3.6%	1.5E-06	
aAD	178	1.60 (1.32, 1.94)	4.0%	1.7E-06	
cADHD	234	0.90 (0.78, 1.04)	0.1%	0.188	BD no ADHD (*N* = 963)
aAD	178	0.91 (0.77, 1.07)	0.1%	0.273	
cADHD	234	0.98 (0.79, 1.21)	0.0%	0.884	BD+aAD (*N* = 178)

ADHD, attention-deficit/hyperactivity disorder diagnosed during childhood (cADHD) or attention deficits diagnosed in adulthood (aAD); BD, bipolar disorder; OR, odds ratio; CI, confidence interval; PRS, polygenic risk score. R^2-Nagelkerke's pseudo-R^2.

0.001) compared to BD+aAD. There were no differences in mean Alda A scores between the groups of BD patients with cADHD and aAD.

Polygenic Risk Scores

Tables 2A,B summarize the associations of the ADHD and BD PRSs with groups and the proportion of variance explained by the PRSs (measured using Nagelkerke's pseudo-R^2). All BD cases had higher ADHD PRS and BD PRS than controls regardless of ADHD subgroup (OR $\geq$ 1.26 for ADHD and OR $\geq$ 1.65 for BD; $p < 0.001$ for all comparisons). Further, BD+cADHD had a higher ADHD PRS than non-ADHD cases (OR = 1.20; $p = 0.012$) while there was no significant difference between those with aAD and without ADHD (OR = 1.07; $p = 0.38$). No other within-case comparisons were significant.

DISCUSSION

This study extends on previous studies by examining clinical features and two distinct PRSs (ADHD and BD) in a cohort of patients with BD and with or without ADHD by time of symptom onset, as well as a group of controls without BD. Our results are consistent with previous literature showing that attention deficits are more prevalent in men (27) and associated with lower rates of employment (28). In line with previous studies that reported a higher prevalence of ADHD in offspring of BD patients (29), BD+ ADHD patients showed significantly higher rates of family history of affective disorders and higher prevalence of substance use disorders. Specifically, we observed increased rates of alcohol use disorder and stimulants use, which is in accordance with earlier studies that reported a higher rate (reporting up to 44%) in ADHD patients of developing substance use disorders during their lifetime (30, 31). This underscores a potential worrisome consideration for clinicians as the use of stimulants may accelerate onset of BD (32) or contribute to the development of a future substance use disorder. However, a previous study showed that the use of stimulants during cADHD (ie. methylphenidate) was not associated with an increased risk to develop a later substance use disorder (33).

Our results suggest a higher prevalence of anxiety and depression disorders in patients with attentional deficits which is consistent with previous observations (29, 34); conversely, our findings differ from an earlier study that reported higher anxiety symptoms but not anxiety disorders (35). Despite focusing on the symptomatic overlap between disorders, anxiety disorders *per se* and ADHD symptoms have been linked to an overall worse psychosocial global functioning in pediatric BD patients (36) emphasizing the need for an accurate and early diagnosis to develop successful interventions.

Overall, our data showed that in terms of treatment response to mood stabilizers, the BD+cADHD group had a significantly poorer response to lithium and lamotrigine. These findings are in accordance with previous data where BD patients with attentional deficits generally exhibit worse outcomes (35). Interestingly there were no significant differences in treatment response by time of onset of attentional deficits.

Our findings also extend the literature showing a higher ADHD PRS in BD patients compared to controls (15). Grigoroiu-Serbanescu et al. (15) reported that ADHD PRSs tend to be higher in BD patients compared to healthy controls and showed marginally significant difference between BD patients with and without ADHD comorbidity. In our study we additionally observed that ADHD PRSs were higher in BD +cADHD compared non-ADHD BD cases, but not significantly higher when we compared to BD+aAD suggesting adult symptoms of inattention, without corresponding syndromal disorder in childhood, may simply be symptoms of bipolar disorder. Although the Grigoroiu-Serbanescu study had comparable sample sizes to ours (BD +cADHD = 365 and no-cADHD = 577) they tested PRS associations under multiple p-value thresholds requiring higher multiple testing corrections. Furthermore, our PRS results align with a recent study of ADHD patients from the iPSYCH cohort, which underscored a high genetic heterogeneity in ADHD subgroups with a higher polygenic risk load for childhood ADHD compared to late-onset ADHD (16).

To our knowledge, our study is the first to examine the BD PRS association with ADHD comorbidity in BD. However, we found no evidence that the genetic risk for BD was different between the different ADHD patients' subgroups. Additionally, while those with BD+ aAD have symptoms of inattention and receive stimulants at a much higher rate and longer duration of time than non-ADHD BD patients, we found no differences between the two groups in terms of ADHD genetic risk. Interestingly a significant difference was found for the BD+cADHD from non-ADHD, which could potentially suggest a genetic and phenotypic distinctiveness of the BD+aAD group between time of onset. These concepts of an intermediate phenotype were initially described by investigations of Post and colleagues regarding the nosological separation of ADHD and BD (37) emphasizing the intricacies underlying inattention deficits in adult BD patients. Furthermore, attentional deficits in adults with BD could be far more diagnostically related to core bipolar/soft hypo/manic and/or depressive symptoms.

Our findings should be considered in the context of several limitations. First, our data is extracted from a biobank with retrospective data collection and a relatively small sample size, particularly for attentional deficits with adult onset. Thus, our findings warrant replication in larger, prospectively assessed cohorts. Secondly, we did not have data regarding different ADHD subtypes, such as the inattentive, hyperactive or combined subtypes (38). Another limitation is that a structured clinical interview was used only to confirm BD diagnosis, while presence or absence of cADHD and aAD was based on patient interviews and the present information in the electronic health record. The use of a structured clinical interview or an operationalized rating scale (such as the Adult ADHD Self-Report Scale or the Wender-Reimherr Adult ADHD Rating Scale) to assess ADHD would have been preferred. Additionally, controls were not assessed for cADHD or aAD. However, potential controls with cADHD would only reduce the power of the PRS comparisons with controls rather than inducing false positive associations. Finally, our PRS analysis was restricted to patients with European ancestries, which may limit the generalizability of our findings to other populations.

Despite the aforementioned limitations, this work has broad relevance in terms of the nature of the relationship between ADHD and BD. It strengthens the hypothesis of a unique genetic pathophysiology in patients with BD+ADHD, particularly those with BD+cADHD, and differential response to certain mood stabilizers compared to non-ADHD patients. Improving our understanding of the clinical and genetic structure of this complex comorbid phenotype should improve diagnostic accuracy and design of future genetic and other biomarker studies leading to tailored interventions.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: We used data from an existing biobank and a limited dataset is available upon request. Requests to access these datasets should be directed to frye.mark@mayo.edu; Website: https://www.mayo.edu/research/centers-programs/bipolar-disorder-biobank.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder-IRBe 08-008794. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NAN, BJC, MAF, and JMB conceptualized study design and drafted the manuscript. NAN, BJC, and CC analysis and interpretation of data. All authors critically revised the manuscript, provided critical revision, and important intellectual content to the article and approved the submitted version.

FUNDING

This research was supported by Mayo Clinic benefactors and the Mayo Clinic Center for Individualized Medicine.

ACKNOWLEDGMENTS

Establishment of the Mayo Clinic Bipolar Disorder Biobank was supported by a generous gift from the Marriott Family and the Mayo Clinic Center for Individualized Medicine. We are grateful to the patients, families, and all the medical staff from the Mayo Clinic BD Biobank.

REFERENCES

1. Calabrese JR, Hirschfeld R, Frye MA, Reed ML. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a US community-based sample. *J Clin Psychiatry.* (2004) 65:1499–504. doi: 10.4088/JCP.v65n1109
2. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry.* (2011) 68:241–51. doi: 10.1001/archgenpsychiatry.2011.12
3. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Ann Rev Public Health.* (2013) 34:119–38. doi: 10.1146/annurev-publhealth-031912-114409
4. Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry.* (2005) 57:1467–73. doi: 10.1016/j.biopsych.2005.01.036
5. Skirrow C, Hosang GM, Farmer AE, Asherson P. An update on the debated association between ADHD and bipolar disorder across the lifespan. *J Affect Disord.* (2012) 141:143–59. doi: 10.1016/j.jad.2012.04.003
6. Klassen LJ, Katzman MA, Chokka P. Adult ADHD and its comorbidities, with a focus on bipolar disorder. *J Affect Disord.* (2010) 124:1–8. doi: 10.1016/j.jad.2009.06.036
7. Karaahmet E, Konuk N, Dalkilic A, Saracli O, Atasoy N, Kurçer MA, et al. The comorbidity of adult attention-deficit/hyperactivity disorder in bipolar disorder patients. *Compr Psychiatry.* (2013) 54:549–55. doi: 10.1016/j.comppsych.2012.11.005
8. Uchida M, Spencer TJ, Faraone SV, Biederman J. Adult outcome of ADHD: an overview of results from the MGH longitudinal family studies of pediatrically and psychiatrically referred youth with and without ADHD of both sexes. *J Atten Disord.* (2018) 22:523–34. doi: 10.1177/1087054715604360
9. Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. *Am J Psychiatry.* (2012) 169:1247–55. doi: 10.1176/appi.ajp.2012.11111725
10. LaRoche C, Sheiner R, Lester E, Benierakis C, Marrache M, Engelsmann F, et al. Children of parents with manic-depressive illness: a follow-up study. *The Can J Psychiatry.* (1987) 32:563–9. doi: 10.1177/070674378703200711
11. Meyer SE, Carlson GA, Wiggs EA, Martinez PE, Ronsaville DS, Klimes–Dougan B, et al. A prospective study of the association among impaired executive functioning, childhood attentional problems, and the development of bipolar disorder. *Dev Psychopathol.* (2004) 16:461–76. doi: 10.1017/S095457940404461X
12. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet.* (2018) 19:581. doi: 10.1038/s41576-018-0018-x
13. Loohuis LO, Mennigen E, Bearden C, Ophoff R. Sa102genetic And Clinical Analyses Of Psychosis Spectrum In A Large Multi-Ethnic Youth Cohort (N> 8,000) Reveal Significant Link With Adhd. *Eur Neuropsychopharmacol.* (2019) 29:S1244. doi: 10.1016/j.euroneuro.2018.08.324
14. Du Rietz E, Coleman J, Glanville K, Choi SW, O'Reilly PF, Kuntsi J. Association of polygenic risk for attention-deficit/hyperactivity disorder with co-occurring traits and disorders. *Biol Psychiatry Cogn Neurosci Neuroimaging.* (2018) 3:635–43. doi: 10.1016/j.bpsc.2017.11.013
15. Grigoroiu-Serbanescu M, Giaroli G, Thygesen JH, Shenyan O, Bigdeli TB, Bass NJ, et al. Predictive power of the ADHD GWAS 2019 polygenic risk scores in independent samples of bipolar patients with childhood ADHD. *J Affect Disord.* (2020) 265:651–9. doi: 10.1016/j.jad.2019.11.109
16. Rajagopal VM, Duan J, Vilar-Ribó L, Grove J, Zayats T, Ramos-Quiroga JA, et al. Differences in the genetic architecture of common and rare variants in childhood, persistent and late-diagnosed attention deficit hyperactivity disorder. *medRxiv [Preprint].* (2021). doi: 10.1101/2021.08.06.21261679
17. Frye MA, McElroy SL, Fuentes M, Sutor B, Schak KM, Galardy CW, et al. Development of a bipolar disorder biobank: differential phenotyping for subsequent biomarker analyses. *Int J Bipolar Disord.* (2015) 3:14. doi: 10.1186/s40345-015-0030-4
18. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition, SCID-I/P*. New York, NY: Biometrics Research, New York State Psychiatric Institute (2002).
19. Olson JE, Ryu E, Johnson KJ, Koenig BA, Maschke KJ, Morrisette JA, et al., editors. The Mayo Clinic Biobank: a building block for individualized medicine. In: *Mayo Clinic Proceedings.* (2013). Mayo Clinic, Rochester: Elsevier.
20. Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? *J Clin Psychiatry.* (2002) 63:942–7. doi: 10.4088/JCP.v63n1013
21. Nassan M, Li Q, Croarkin PE, Chen W, Colby CL, Veldic M, et al. A genome wide association study suggests the association of muskelin with early onset bipolar disorder: Implications for a GABAergic epileptogenic neurogenesis model. *J Affect Disord.* (2017) 208:120–9. doi: 10.1016/j.jad.2016.09.049
22. Winham SJ, Cuellar-Barboza AB, McElroy SL, Oliveros A, Crow S, Colby CL, et al. Bipolar disorder with comorbid binge eating history: a genome-wide association study implicates APOB. *J Affect Disord.* (2014) 165:151–8. doi: 10.1016/j.jad.2014.04.026
23. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, et al. Next-generation genotype imputation service and methods. *Nat Genet.* (2016) 48:1284–7. doi: 10.1038/ng.3656
24. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JR, Qiao Z, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet.* (2021) 53:817–29. doi: 10.1038/s41588-021-00857-4
25. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* (2019) 51:63–75. doi: 10.1038/s41588-018-0269-7
26. Privé F, Arbel J, Vilhjálmsson BJ. LDpred2: better, faster, stronger. *Bioinformatics.* (2020) 36:5424–31. doi: 10.1093/bioinformatics/btaa1029
27. Feldman HM, Reiff MI. Attention deficit–hyperactivity disorder in children and adolescents. *N Engl J Med.* (2014) 370:838–46. doi: 10.1056/NEJMcp1307215
28. Biederman J, Petty CR, Clarke A, Lomedico A, Faraone SV. Predictors of persistent ADHD: an 11-year follow-up study. *J Psychiatr Res.* (2011) 45:150–5. doi: 10.1016/j.jpsychires.2010.06.009
29. Perugi G, Ceraudo G, Vannucchi G, Rizzato S, Toni C, Dell'Osso L. Attention deficit/hyperactivity disorder symptoms in Italian bipolar adult patients: a preliminary report. *J Affect Disord.* (2013) 149:430–4. doi: 10.1016/j.jad.2012.12.010
30. Biederman J, Wilens T, Mick E, Milberger S, Spencer TJ. Faraone SV. Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): effects of ADHD and psychiatric comorbidity. *Am J Psychiatry.* (1995) 152:1652–8. doi: 10.1176/ajp.152.11.1652
31. Shekim WO, Asarnow RF, Hess E, Zaucha K, Wheeler N. A clinical and demographic profile of a sample of adults with attention deficit hyperactivity disorder, residual state. *Compr Psychiatry.* (1990) 31:416–25. doi: 10.1016/0010-440X(90)90026-O
32. DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. *Bipolar Disord.* (2001) 3:53–7. doi: 10.1034/j.1399-5618.2001.030201.x
33. Humphreys KL, Eng T, Lee SS. Stimulant medication and substance use outcomes: a meta-analysis. *JAMA Psychiatry.* (2013) 70:740–9. doi: 10.1001/jamapsychiatry.2013.1273
34. Perroud N, Cordera P, Zimmermann J, Michalopoulos G, Bancila V, Prada P, et al. Comorbidity between attention deficit hyperactivity disorder (ADHD) and bipolar disorder in a specialized mood disorders outpatient clinic. *J Affect Disord.* (2014) 168:161–6. doi: 10.1016/j.jad.2014.06.053
35. Pinna M, Visioli C, Rago CM, Manchia M, Tondo L, Baldessarini RJ. Attention deficit-hyperactivity disorder in adult bipolar disorder patients. *J Affect Disord.* (2019) 243:391–6. doi: 10.1016/j.jad.2018.09.038
36. Frías Á, Palma C, Farriols N. Comorbidity in pediatric bipolar disorder: prevalence, clinical impact, etiology and treatment. *J Affect Disord.* (2015) 174:378–89. doi: 10.1016/j.jad.2014.12.008

37. Post RM, Chang KD, Findling RL, Geller B, Kowatch RA, Kutcher SP, et al. Prepubertal bipolar I disorder and bipolar disorder NOS are separable from ADHD. *J Clin Psychiatry.* (2004) 65:898–902. doi: 10.4088/JCP.v65n0703
38. Reimherr FW, Roesler M, Marchant BK, Gift TE, Retz W, Philipp-Wiegmann F, et al. Types of Adult Attention-Deficit/Hyperactivity Disorder: A Replication Analysis. *J Clin Psychiatry*. (2020) 81:19m13077. doi: 10.4088/JCP.19m13077

Conflict of Interest: JV reports a grant-in-kind from Assurex, unrelated to the current study. PC has received research support from Neuronetics, Inc., NeoSync, Inc., and Pfizer. He has received grant-in-kind equipment and laboratory support for research studies from Assurex Health, Neuronetics, Inc. and MagVenture, Inc. He has served as a consultant for Myriad Neuroscience and Procter & Gamble. BS received grant support from Clinical and Translational Science CCaTS Small Grants Award, and Mayo Clinic. SM is or has been a consultant to or member of the scientific advisory boards of Avanir, Allergan now AbbVie, Bracket now Signant Health, Naurex, Idorsia, Intra-Cellular Therapies, Inc., Shire now Takeda, Sunovion, and Takeda. She is or has been a principal or co-investigator on studies sponsored by the Agency for Healthcare Research & Quality AHRQ, Avenir, AstraZeneca, Cephalon, Forest, Marriott Foundation, Medibio, National Institute of Mental Health, Orexigen Therapeutics, Inc., Jazz, Shire now Takeda, Sunovian, and Takeda Pharmaceutical Company Ltd. She is also an inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent. MF has received grant support from Assurex Health, Myriad, Pfizer, National Institute of Mental Health RO1 MH079261, National Institute of Alcohol Abuse and Alcoholism P20AA017830, Mayo Foundation; has been a consultant to Janssen Global Services, LLC, Mitsubishi Tanabe Pharma Corporation, Myriad, Sunovion, and Teva Pharmaceuticals; has received CME/Travel Support/presentation from CME Outfitters Inc. and Sunovian; Mayo Clinic has a financial interest in AssureRx and OneOme.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 18 May 2022
doi: 10.3389/fpsyt.2022.825546

The Toxicity Potential of Antidepressants and Antipsychotics in Relation to Other Medication and Alcohol: A Naturalistic and Retrospective Study

Marleen M. M. Swoboda[1†], Lucie Bartova[1†], Marlene Dremel[1], Ulrich Rabl[1], Anton Laggner[2] and Richard Frey[1*]*

[1] Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria, [2] Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria

OPEN ACCESS

Edited by:
Domenico De Berardis, Mental Health Center (CSM) and Psychiatric Service of Diagnosis and Treatment (SPDC), Italy

Reviewed by:
Alessandro Cuomo, University of Siena, Italy
Carmine Tomasetti, SPDC di Giulianova, Italy

***Correspondence:**
Lucie Bartova
lucie.bartova@meduniwien.ac.at
Richard Frey
richard.frey@meduniwien.ac.at

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

Received: 30 November 2021
Accepted: 11 April 2022
Published: 18 May 2022

Citation:
Swoboda MMM, Bartova L, Dremel M, Rabl U, Laggner A and Frey R (2022) The Toxicity Potential of Antidepressants and Antipsychotics in Relation to Other Medication and Alcohol: A Naturalistic and Retrospective Study. Front. Psychiatry 13:825546. doi: 10.3389/fpsyt.2022.825546

QT interval prolongation and ventricular tachyarrhythmia are potential adverse effects of antidepressant (AD) and antipsychotic- (AP) agents, especially when overdosed. Since AD and AP agents are often prescribed to patients suffering from suicidal intentions, it is essential to estimate these risks in the context of intoxications. This retrospective and naturalistic one-year registry study included 105 patients treated for oral intoxication at the University Department of Emergency Medicine in Vienna, Austria. AD/AP intoxications were present in 26 patients, while in the control group (n = 79) non-AD/AP drugs (n = 54) and exclusively alcohol (n = 25) were the toxic agents. QT intervals, the necessity of intubation, the extent of conscious state, and the subsequent discharge management were compared. The mean age was 34.94 ± 14.6 years, 62 patients (59%) were female. There were no significant between-group differences regarding QT prolongation >470 ms using Bazett's correction (p = 0.178), or >440 ms using Fridericia's correction (p = 0.760). No significant group differences concerning the need for intubation were observed (p = 0.747). The AD/AP and the control group did not significantly differ regarding Glasgow Coma Scale scores (p = 0.439). Patients with AD/AP intoxication were significantly more often transferred to the psychiatric department, while discharge to home was more likely in the control group (p = 0.002). These results suggest that the risk of a potentially life-threatening outcome in cases of intoxication with AD/AP is not substantially higher than in other easily available toxic agents, in line with the advantageous risk/benefit ratio of newer ADs and APs.

Keywords: toxicity, electrocardiography, antidepressants, antipsychotics, alcohol, emergency psychiatry

INTRODUCTION

Antidepressants (AD) and antipsychotics (AP) administered as monotherapy or in the course of combinations/augmentations are recommended as first-line treatments for psychiatric disorders with a high risk of suicidality according to the current international treatment guidelines (1–4). In this context, it is necessary to mention that adequate psychopharmacotherapy was repeatedly

shown to decrease the risk of suicidal behavior (5–13). On the other hand, the risk of suicidality as an adverse effect of psychopharmacotherapy was discussed thoroughly, especially regarding ADs (14) but could not be ultimately confirmed (15–17). Intoxication as a method of committing suicide is often realized with accessible agents such as prescribed medications or alcohol (18). Notably, self-poisoning with psychopharmacotherapy accounted for 25% of completed suicides in men and 45% in women (19).

Although the general toxicity of ADs is expected to be relatively low (20), there is evidence for cases of fatal toxicity with risk varying substantially between the particular AD substance classes (21, 22). In this context, it is essential to systematically estimate the related risk potentials of such frequently prescribed substances. In terms of ADs and APs, cardiovascular effects seem to be most relevant (23, 24), with QT interval prolongation present in approximately 8% of patients undergoing psychopharmacotherapy (25). Increasing the risk for torsades des pointes, QT interval prolongation represents a significant risk factor for sudden cardiac death (26). Although optimal adjustments for heart rate and exact thresholds to correlate with arrhythmic risk have not been established yet (27, 28), internationally accepted formulas to measure the QT interval exist (29), whereby the Bazett (30) and Fridericia (31) QT correction formulas represent the currently recommended measures (**Figure 1**).

The present study aims to compare intoxications with ADs, APs, or both with those of other medications and alcohol to illustrate the toxicity potential of these substances in a general population treated for intoxication.

MATERIALS AND METHODS

Study Design

The naturalistic retrospective register study was approved by the Ethics Committee (EC) of the Medical University of Vienna (MUV) (EC number: 1626/2013) and conducted between 09/2013 and 09/2014. Based on the documented medical history during inpatient care at the Department of Emergency Medicine of the MUV, patients suffering from intoxications with ADs, APs, or other substances were consecutively registered.

Patients

Both male and female patients above 17 years diagnosed with and treated for oral intoxication were included. Furthermore, available electrocardiography (ECG) reports at admission were mandatory for enrollment in the present study. Exclusion criteria comprised parenteral intoxications (intravenous-, gas poisoning), acute intoxications with opioids, non-medical substances such as fungal toxins, or chronic intoxications, e.g., long-term overdosing with coumarin-type drugs.

Data Collection

QT intervals were extracted from the available ECG reports and subsequently corrected for individual heart rate using the Bazett (QTc-B) and Fridericia (QTc-F) formulas (**Figure 1**). A QTc-B above 470 ms and a QTc-F above 440 ms were considered pathologic. All ECG reports were derived from 12-lead ECGs with a 25 mm/sec feed rate.

The necessity of intubation was evaluated to estimate the severity of intoxication in a clinically pragmatic way. We differentiated between endotracheal and pharyngeal intubation employing Guedel and Wendl tubes, respectively (32, 33). Moreover, scores of the Glasgow Coma Scale (GCS) were obtained for each patient at the time of admission at the Department of Emergency Medicine. Discharge management was represented either by transfer to the Department of Psychiatry and Psychotherapy or the Department of Internal Medicine (general ward or intensive care unit) or by discharges to home corresponding with or against medical advice.

Statistical Analyses

In total, 105 patients could be included in the study and were grouped accordingly: intoxication with (1) ADs/APs, and (2) non-AD/AP substances, which were further subdivided into intoxications with non-AD/AP drugs and exclusively alcohol.

The socio-demographic (age, sex), clinical [QTc interval, intubation, and Glasgow Coma Scale (GCS)], and discharge management were displayed using descriptive statistics (means ± standard deviation, percentages). Between-group differences in categorical variables (sex, QTc-B >470 ms, QTc-F >440/470 ms, intubation, discharge management) were assessed using chi-squared tests and Fisher's/Fisher-Freeman-Halton exact tests in the case of small subsamples. Metric data were tested for Gaussian distribution *via* the Kolmogorov Smirnov test. To test for between-group differences in continuous variables (heart rate, QTc-B, QTc-F, and GCS), *t*-tests (for comparison of two groups), and analyses of variance (ANOVA) (for comparison of more than two groups) were used. Mann–Whitney-U tests (i.e., Wilcoxon signed-rank tests for comparison of two groups and Kruskal-Wallis tests for comparison of more than two groups) were performed in case of continuous non-normally distributed or ordinally scaled data. All data analyses were conducted two-sided, and p-values ≤ 0.05 were identified as statistically significant. IBM SPSS Statistics software (version 22.0, IBM Corp., Armonk, NY, United States) was employed for all statistical analyses. To better understand the comparison of QTc values between the AD/AP and control group, we conducted a *post-hoc* power analysis for a *t*-test of means of two samples with different sizes, based on the sample sizes and standard deviations found in our cohort. This analysis was performed in R (version 4.1.1[1]), using the R packages "pwr" and "ggplot2" for calculation and visualization, respectively.

RESULTS

Descriptive Data

Out of the 105 patients, 62 (59%) were female. There were no duplicates in the assessed sample. The age ranged from 17 to

[1]http://cran-r-project.org/

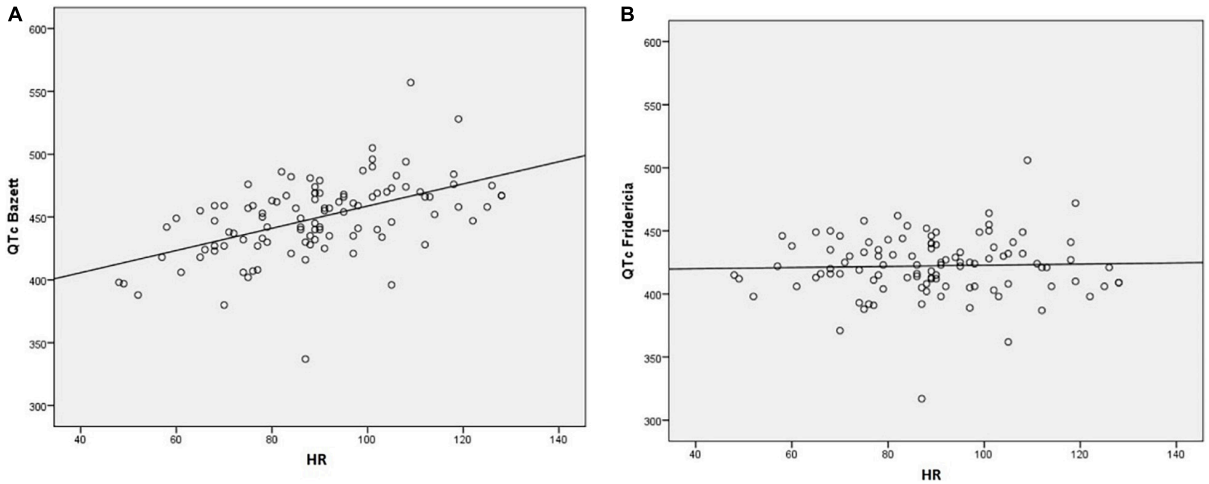


FIGURE 1 | Comparison between the QT prolongation corrected for heart rate (HR; QT-HR correlation) *via* **(A)** Bazett's correction $QTc = \frac{QT(ms)}{\sqrt{RR-\text{distance(s)}}}$ and **(B)** Fridericia's correction $QTc = \frac{QT(ms)}{\sqrt[3]{RR-\text{distance(s)}}}$. While the QTc intervals are given in milliseconds (ms) and the RR-distances in seconds (s), the heart rate is expressed as beats per minute (bpm).

TABLE 1 | Individual cases of the AD/AP group.

AD/AP category	AD/AP substance	Co-intoxication	QTc-B	QTc-F	HR
SSRI	Paroxetine, Trazodone	Oxacepam (BZD), Alprazolam (BZD)	380 ms	371 ms	70/min
SSRI	Citalopram	Lamotrigine (AC), alcohol	428 ms	402 ms	88/min
SSRI	Trazodone		421 ms	413 ms	84/min
SSRI	Trazodone	Hydroxyzine (H1RB),	437 ms	430 ms	72/min
SSRI	Trazodone		476 ms	458 ms	75/min
SSRI	Citalopram	Lorazepam (BZD)	457 ms	430 ms	85/min
SSRI	Trazodone		490 ms	450 ms	101/min
SSRI, NaSSA	Citalopram, Mirtazapine		483 ms	441 ms	106/min
SSRI, AP	Trazodone, Prothipendyl	Doxepin (AB), alcohol	468 ms	433 ms	95/min
NDRI	Bupropion		505 ms	464 ms	101/min
SNRI, AP	Venlafaxine, Tiapride		424 ms	416 ms	66/min
NaSSA	Mirtazapine	Naproxen (NSAID), Metformin (ADM), Flunarizine (CaA)	440 ms	413 ms	89/min
AP, NaSSA	Quetiapine, Mirtazapine	Dexibuprofen (NSAID), Mefenamic Acid (NSAID), Propyphenazone (NSAID)	496 ms	455 ms	101/min
AP	Prothipendyl, Risperidone	Mefenaminic Acid (NSAID)	447 ms	435 ms	68/min
AP	Olanzapine		475 ms	421 ms	126/min
AP	Quetiapine, Risperidone		446 ms	408 ms	105/min
AP	Quetiapine, Chlorprothixene	Lorazepam (BZD)	466 ms	421 ms	113/min
AP	Chlorprothixene		457 ms	427 ms	92/min
AP	Prothipendyle	Ramipril (ACE-I), Paracetamol (AN), Pantoprazole (PPI), Bezafibrate (FD), alcohol	469 ms	440 ms	89/min
AP	Quetiapine, Olanzapine, Prothipendyl	Oxazepam (BZD)	467 ms	444 ms	83/min
AP	Quetiapine, Prothipendyl		494 ms	449 ms	108/min
AP	Chlorprothixene	Nitrazepam (BZD), alcohol	462 ms	431 ms	81/min
AP	Chlorprothixene	Clonazepam (BZD)	441 ms	406 ms	98/min
AP	Levomepromazine	Zolpidem (NBZD), alcohol	428 ms	387 ms	112/min
AP	Quetiapine, Prothipendyl	Zolpidem (NBZD), alcohol	435 ms	408 ms	88/min
AP	Quetiapine		469 ms	440 ms	89/min

AD, antidepressant; AP, antipsychotic; QTc-B, QT interval – Bazett's correction; QTc-F, QT interval – Fridericia's correction; HR, heart rate; SSRI, selective serotonin reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, noradrenaline dopamine reuptake inhibitor; SNRI, (selective) serotonin norepinephrine reuptake inhibitor; BZD, benzodiazepine; AC, anticonvulsants, H1RB, H1 receptor blocker; AB, antibiotic; NSAID, nonsteroidal anti-inflammatory drug; ADM, antidiabetic medication; CaA, calcium antagonist; ACE-I, ACE inhibitor; AN, anesthetic; PPI, proton pump inhibitor; FD, fibrate drug; NBZD, non-benzodiazepine).

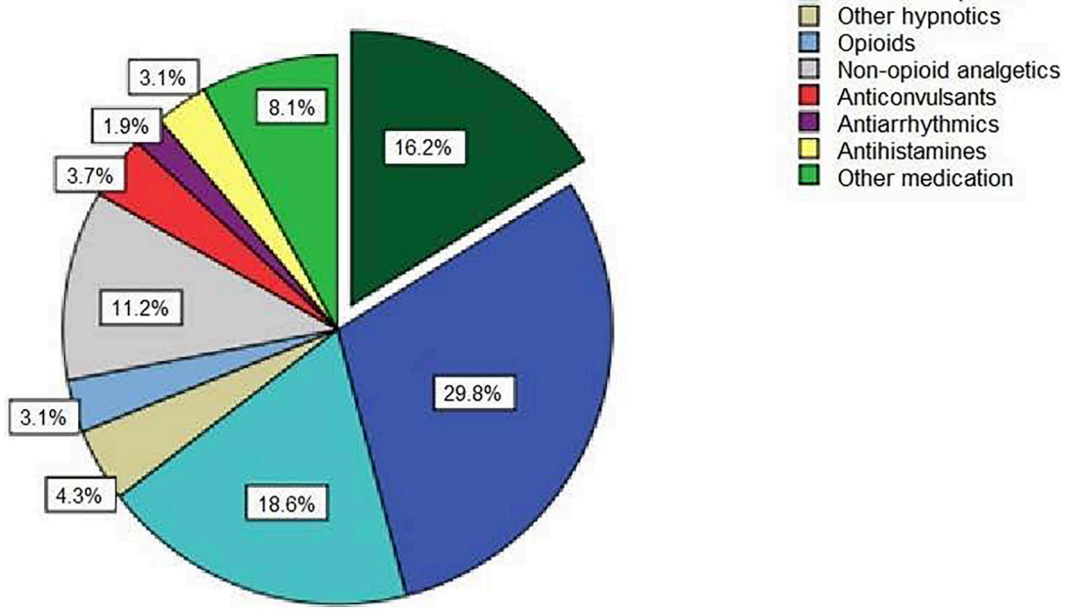


FIGURE 2 | Categories and shares of all substances utilized for overdosing. (AD/AP = antidepressants/antipsychotics).

87 years, with a mean age of 34.9 ± 14.6 years at intoxication. 26 patients (24.8 %) were intoxicated with ADs/APs, comprising sole intoxications with ADs/APs and those mixed with other substances. 13 and 16 intoxications included ADs and APs, respectively. In three cases, both ADs and APs were involved. **Table 1** shows these individual cases. Nine patients ingested selective serotonin reuptake inhibitors (SSRIs) or trazodone. In the control group (n = 79), 54 cases consisted of drug intoxications without AD/AP involvement, and 25 patients exclusively experienced mono-intoxications with alcohol. Within the non-AD/AP group, benzodiazepines (n = 30), Z-drugs (n = 7), anticonvulsants (n = 6), non-steroidal anti-inflammatory drugs (n = 18, predominantly mefenamine), antihistamines (n = 5), antiarrhythmic drugs (n = 3), and others (n = 13) including antidiabetics, amphetamines, and muscle relaxants were involved (**Figure 2**).

Single substance intoxications were present in seven patients (26.9%) in the AD/AP group (**Table 1**: 3x trazodone, 1x bupropion, 1x olanzapine, 1x chlorprothixene, 1x quetiapine) and 21 patients (38.9%) in the non-AD/AP subgroup. Co-ingestion of alcohol was observed in 6 patients (23.1%) of the AD/AP group and in 17 patients (31.5%) of the control group with other medication.

Heart Rate

The mean heart rate amounted to 91.7 ± 15.1 bpm in the AD/AP group and 88.3 ± 18.8 bpm in the control group, with no significant between-group differences [$t(102) = -0.851$, p = 0.397]. Comparing AD/AP with the control subgroups, there were also no significant differences (non-AD/AP group: 86.8 ± 19.3 bpm, $t(77) = 1.147$, p = 0.255; alcohol group: 91.4 ± 17.6 bpm, $t(49) = 0.063$, $p = 0.950$).

There was no significant difference in heart rate between male and female cases (male: 89.0 ± 18.4 bpm; female: 89.3 ± 17.7 bpm, $t(102) = -0.086$, $p = 0.932$).

QT Interval Corrected for Heart Rate (QTc)

Mean QTc-B did not significantly differ between the AD/AP (456.19 ± 28.21 ms) and the control group (446.79 ± 31.18 ms; $t(102) = -1.362$, p = 0.176), nor between the subgroups (non-AD/AP: 442.91 ± 28.48 ms; alcohol: 455.04 ± 35.46 ms; $F(2, 101) = 2.312$, $p = 0.104$), and between males and females (females: 450.21 ± 24.47 ms; males: 447.63 ± 24.41 ms; $t(102) = -0.423$, p = 0.674). 21 patients (20%) showed a pathological QTc-B >470 ms, with no significant differences between the AD/AP (seven cases, 26.9%) and the control group (14 cases, 17.7%; X^2 (1, 105) = 1.04, p = 0.309). Similarly, there were no significant differences between the three subgroups, as well as between mono- and poly-intoxications in QTc-B values >470 ms (all $p > 0.05$). High QTc-B prolongations of >500 ms were detected in 3 patients (1 case in the AD/AP group, 2 cases in the control group).

Regarding QTc-F, the mean QTc-F in the AD/AP group was 426.65 ± 22.08 ms and 420.57 ± 24.63 ms in the control group (non-AD/AP subgroup: 418.42 ± 23.10 ms; alcohol subgroup: 425.88 ± 27.39 ms). Analogous to QTc-B, there were no significant differences between the AD/AP and the control group (t (103) = −1.120, p = 0.266), respectively the subgroups

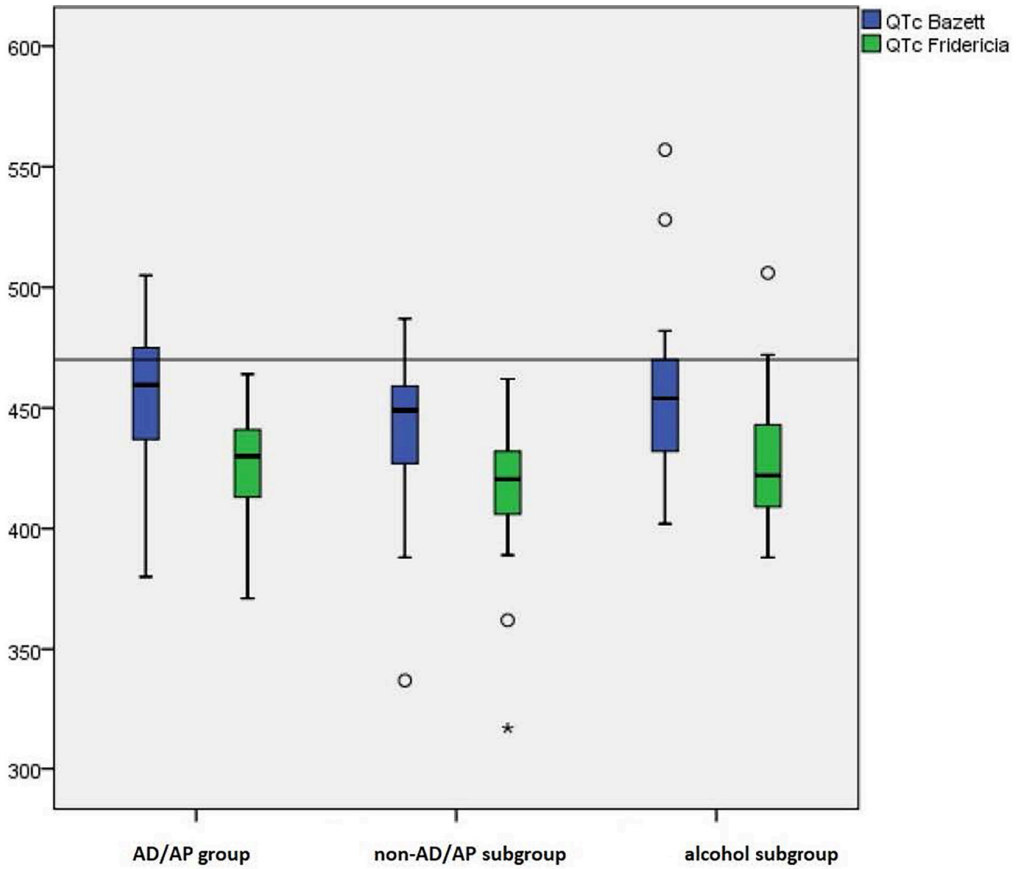


FIGURE 3 | Median values and percentiles (box plots) of the QTc-B and QTc-F data set in the AD/AP group and both control groups.

($F(2, 102) = 1.531$, $p = 0.221$), as well as between males and females (females: 422.56 ± 26.53 ms; males: 421.4 ± 20.27 ms; $t(103) = -0.249$, $p = 0.804$). **Figure 3** shows median values and percentiles (box plots) of the QTc-B and QTc-F data set in the AD/AP group and both control groups. *Post-hoc* power analysis suggested that the available sample would have been sufficiently powered (power = 0.8) to detect an effect of around 20 ms mean difference (**Supplementary Figure 1**).

A prolonged QTc-F >440 ms was measured in nine patients (34.6%) in the AD/AP group and 15 patients (19%) in the control group, without reaching significance (Exact Test, $p = 0.113$). Also, subgroup analysis did not reach significance (X^2 (2, 105) = 4.394, $p = 0.111$). However, a more stringent cut-off at QTc-F >470 ms was only present in two patients (1.9%) in the alcohol subgroup (Exact Test, $p = 0.055$).

Intubation

Intubation was necessary in 10 (9.5%) of 105 cases. While an oropharyngeal airway was applied in four patients, all from the control group, an endotracheal tube was necessary for six patients (5.7%). No significant differences in terms of the rate of endotracheal intubation were detected between the AD/AP group (1 case) and the control group (5 cases; Exact Test, $p = 1$), respectively both subgroups (non-AD/AP subgroup: 3 cases; alcohol subgroup: 2 cases; X^2 (2, 105) = 0.413, $p = 0.813$). Patients who received an endotracheal tube were not more likely to suffer from poly- versus mono-intoxication (Exact Test, $p = 0.437$).

No significant association was identified between the necessity of endotracheal intubation and QTc-B >470 ms (Exact Test, $p = 0.093$). However, the mean QTc-B of patients who received endotracheal intubation was significantly higher than that of non-intubated patients (488.20 ± 41.11 ms vs. 447.17 ± 28.87 ms; $t(102) = -3.040$, $p = 0.003$). Regarding QTc-F, the mean QTc-value of endotracheal intubated patients was also higher than that of non-intubated patients, though not significantly (439.00 ± 36.12 ms vs. 421.05 ± 23.01 ms; $t(103) = -1.793$, $p = 0.076$). The two patients in the alcohol group with QTc-F >470 ms were not intubated.

Glasgow Coma Scale

The mean score of the GCS assessed in the AD/AP group was 12.73 ± 3.69 and 12.14 ± 3.80 in the control group. However, the GCS data were not normally distributed ($D(105) = 0.253$, $p < 0.001$). The median CGS was 15 in the AD/AP group and 14 in the control group. 48.6% ($N = 51$) of all patients reached a GCS maximum score of 15. That was achieved in 57.7% ($N = 15$) in the AD/AP group and in 45.6% ($N = 36$) in the control group (non-AD/AP: $N = 28$, 51.9%; alcohol: $N = 8$, 32%).

Nine patients (8.6%) showed very low vigilance, represented by a GCS total score of 3. Out of those patients, three cases were found in the AD/AP group, five in the non-AD/AP subgroup, and one in the alcohol subgroup. No significant differences were found between the distributions of GCS scores, neither in the AD/AP group and the control group (Mann-Whitney $U = 1125.00$, $p = 0.439$) nor between the AD/AP group and the two subgroups (Kruskal-Wallis H(2) = 2.876, $p = 0.237$). Similarly, GCS scores did not significantly differ between mono- and poly-intoxications (Mann-Whitney $U = 1266.500$, $p = 0.447$).

Discharge Management

Of all 105 patients, 55 (52.4%) could be discharged after immediate care, six (5.7%) left the emergency room unplanned (two patients against medical advice and four patients without any notice of departure), five (4.8%) were transferred to a general care unit and three (2.9%) to an internal medicine intensive care unit. 36 patients were transferred to the department of psychiatry and psychotherapy. Non-psychiatric transfers were not significantly overrepresented in one of the groups (X^2 (2, 105) = 2.425, $p = 0.297$). However, significantly more patients from the AD/AP group, but no patients from the alcohol subgroup, were transferred to the psychiatric department (AD/AP: 15/26 cases, 57.7%; non-AD/AP: 21/54 cases, 38.9%; alcohol: 0/25 cases; X^2 (2, 105) = 19.874, $p < 0.001$). Similarly, more patients in the non-AD/AP group (27/54 cases, 50%) and alcohol group (20/25 cases, 80%) than in the AD/AP group (8/26 cases, 30.8%) were discharged after the initial emergency care (X^2 (2, 105) = 12.637, $p = 0.002$).

DISCUSSION

The present study retrospectively examined the toxicity potential of AD and AP agents compared to other medication and alcohol in a sample of 105 patients with rather heterogeneous clinical profiles, who were consecutively treated for oral intoxication at the emergency unit of the MUV within 1 year.

The majority of our sample was female, in line with previous studies that reported a predominance of female suicide attempters (34, 35), especially in the case of intoxication or poisoning (36, 37). Interestingly, the available evidence reported a drop in suicide rates in recent years, though this effect may be partly attributable to misclassifications and underreporting (38, 39). According to available autopsy data, suicides due to self-poisoning may be frequently interpreted as unintended or undetermined due to insufficient proof, resulting in biased suicide rates (40, 41).

We have no valid information about the severity of the patients' suicidal intent within our sample. High GCS scores and a low intubation rate in most patients may indicate an irresolute death wish. It is not unlikely that several patients, e.g., those with alcohol intoxication alone, suffered from accidental overdoses rather than from suicide attempts. Only in those patients transferred to the psychiatric department ($n = 36$) the suicide attempt and further suicidal ideation were explicitly documented. The AD/AP target group was, as expected, significantly overrepresented within this group.

We did not divide our target group into antidepressant and antipsychotic subgroups, given the small sample size and the clinically and pharmacologically overlapping effects. ADs and APs are often used in combination to treat psychiatric illnesses linked to suicidal behavior. For instance, several APs are indicated for augmentation therapy in severe or treatment-resistant depression (1, 2). Similarly, QTc prolongation has been a specific concern in developing safer drugs in both drug classes. Regarding the control group, too many different medications were used to allow for a meaningful analysis of subgroups or specific substances.

Considering that acute alcohol intoxication is quite extensively found in emergency departments, it is noteworthy that associated ECG changes are not well defined in the medical literature. A recent systematic review (42) suggests an incidence of about 50% for QTc prolongation. While we found only two patients with QTc-F values higher than 470 ms in our sample of 105 patients, both suffered from alcohol intoxication. These cases may be outliers, or the sample size might be too small since there was no significant group effect. None of the 25 patients with alcohol intoxication were transferred to the psychiatric ward, even though alcohol use disorders constitute an important challenge in psychiatry. It can be speculated that the rather stressful emergency unit setting may not be appropriate to initiate treatment of alcohol use disorders, suggesting the development of tailored interventions for this group.

A comparison between mono- and poly-intoxications did not reveal any significant findings regarding QTc intervals, rates of intubation, or GCS scores in our study. Given the relatively low number of life-threatening overdoses, a lack of power could primarily explain this counterintuitive finding. In addition, the comparison of single and multiple substance intoxications is a methodological problem due to the limited availability of chemical analyses, the overlap in different classification algorithms, and the almost unlimited number of combinations in real-world conditions. It is noteworthy in this context that no patient investigated in our study suffered from intoxication with tricyclic ADs (TCAs). This might be explained by the fact that the prescriptions of TCAs generally decreased due to the increasing use of modern ADs such as SSRIs, which are equally effective, much better tolerated, and recommended as first-line treatment (2, 43, 44).

As the present results did not reveal any significant group differences in heart rate, QTc-B, QTc-F, rate of intubation, and GCS scores, we postulate that ADs and APs generally do not show higher toxicity potential than non-AD/AP medications and alcohol. These results are in contrast to reports of overdoses of APs that, in some circumstances, were associated with a higher risk for intubation compared to other psychiatric and nonpsychiatric medications (45, 46). *Post-hoc* power analysis suggested that our sample would likely have been sufficiently powered to observe a mean difference of around 20 ms between the AD/AP and the control group. Our data, therefore, is too

small to conclude that there is no clinically significant effect of ADs/APs on QTc values. Still, the data suggests that it is smaller than commonly anticipated.

Interestingly, patients receiving intubation showed a significantly higher QTc-B, a tendency that was also trend-wise present for mean QTc-F. While mean QTc and the need for intubation are unlikely directly causally related, this result suggests that prolonged QTc and potentially higher cardiac risk are generally associated with the need for more intensive medical care, i.e., intubation. A tendency toward higher QTc-F in the alcohol subgroup further confirms previous findings (47).

Regarding the subsequent treatment, the discharge rate was the lowest, and the transfer rate to the department of psychiatry and psychotherapy was the highest within the AD/AP group. In contrast, the control group, especially the alcohol subgroup, showed an opposite pattern. Patients who already received psychopharmacotherapy were more often referred to subsequent psychiatric care. Correspondingly, international evidence shows that being diagnosed with a psychiatric disorder is associated with a higher risk for suicide attempts (1, 35). Furthermore, such associations, including rates for completed suicide, were prominent in patients treated with TCAs, representing older AD substances that were largely replaced by newer AD substances such as SSRIs and SNRIs (43, 48) due to their beneficial side effect profile (21, 49), especially in terms of QTc prolongation (25, 44). Although international treatment guidelines recommend the employment of SSRIs and SNRIs as first-line AD treatment (2), heterogeneous prescription and suicide rates identified in international samples may additionally reflect the varying quality and access of mental health care (50). Crucially, improvement of access to psychiatric care and the adequate use of ADs were repeatedly associated with a decrease in suicide rates in Austria (51) and in Europe in general (6), supporting the relevance of individualized suicide prevention strategies (52).

Several limitations need to be addressed. The retrospective cross-sectional study design does not justify causal conclusions. Furthermore, due to the applied naturalistic design that solely relied on the available case history, valid data about the included patients were not available, such as detailed socio-demographic characteristics, psychiatric and somatic diagnoses, the presence and severity of specific clinical indicators, including suicidality, and details related to the ongoing treatments. Moreover, plasma levels of the suspected toxic agents, breath-alcohol analysis, or blood electrolytes could not be analyzed due to limited availability. Additionally, sample characteristics such as the relatively low number of life-threatening overdoses, the sample size and the fact that we did not observe any significant differences between mono- and poly-intoxications in terms of mean QTc intervals, intubation rates, and GCS total scores might be critically considered. On the other hand, we are confident that these real-world data provide a valuable and generalizable perspective on oral intoxications and their management in clinical routine.

Although morbidity and mortality associated with ADs, APs, and other psychopharmacotherapeutics remain frequent subjects of scientific discourse (53), the present study corroborates the relative safety of AD/AP medication even in patients at increased risk for suicidality. It, therefore, supports the adequate use of these drugs in this vulnerable patient group, even more so since it was repeatedly shown to reduce suicidality (1, 2, 43). In emergency settings, the potential stigmatization of patients suffering from psychiatric disorders should be considered, focusing on potentially underdiagnosed psychiatric comorbidities.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author. The data were initially introduced in the course of a diploma thesis conducted in German language by MD in 2018 at the Medical University of Vienna in Austria (https://repositorium.meduniwien.ac.at/obvumwhs/content/titleinfo/2944560).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee (EC) of the Medical University of Vienna (EC number: 1626/2013). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MS: interpretation of data for the work, drafting the work, and approval of the final version of the manuscript. LB: drafting and revising the manuscript critically for important intellectual content and English language, and approval of the final version of the manuscript. MD: substantial contributions to the conception and design of the work, data acquisition, statistical analysis, diploma thesis in German language, and approval of the final version of the manuscript. UR: statistical analysis, revising the manuscript critically for important intellectual content and English language, and approval of the final version of the manuscript. AL: substantial contributions to the conception and design of the work, responsibility for data acquisition as head of the Department of Emergency Medicine at the Medical University of Vienna, and approval of the final version of the manuscript. RF: substantial contributions to the conception and design of the work, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately

investigated and resolved, supervision of the diploma thesis conducted by MD, and approval of the final version of the manuscript. All authors contributed to designing the study, implementation of the research, and critically revised and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.825546/full#supplementary-material

REFERENCES

1. Bartova L, Dold M, Kautzky A, Fabbri C, Spies M, Serretti A, et al. Results of the European group for the study of resistant depression (GSRD) – basis for further research and clinical practice. *World J Biol Psychiatry.* (2019) 20:427–48. doi: 10.1080/15622975.2019.1635270
2. Bauer M, Severus E, Möller HJ, Young AH. Pharmacological treatment of unipolar depressive disorders: summary of WFSBP guidelines. *Int J Psychiatry Clin Pract.* (2017) 21:166–76. doi: 10.1080/13651501.2017.1306082
3. Berardelli I, Rogante E, Sarubbi S, Erbuto D, Lester D, Pompili M. The importance of suicide risk formulation in schizophrenia. *Front Psychiatry.* (2021) 12:779684. doi: 10.3389/fpsyt.2021.779684
4. Kraus C, Kadriu B, Lanzenberger R, Zarate CA Jr, Kasper S. Prognosis and improved outcomes in major depression: a review. *Transl Psychiatry.* (2019) 9:127. doi: 10.1038/s41398-019-0460-3
5. Bachmann S. Epidemiology of suicide and the psychiatric perspective. *Int J Environ Res Public Health.* (2018) 15:1425. doi: 10.3390/ijerph15071425
6. Gusmão R, Quintão S, McDaid D, Arensman E, Van Audenhove C, Coffey C, et al. Antidepressant utilization and suicide in Europe: an ecological multi-national study. *PLoS One.* (2013) 8:e66455. doi: 10.1371/journal.pone.0066455
7. Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol.* (2010) 24(4 Suppl.):81–90. doi: 10.1177/1359786810385490
8. Karvonen K, Sammela HL, Rahikkala H, Hakko H, Särkioja T, Meyer-Rochow VB, et al. Sex, timing, and depression among suicide victims with schizophrenia. *Compr Psychiatry.* (2007) 48:319–22. doi: 10.1016/j.comppsych.2007.02.004
9. Morgan OW, Griffiths C, Majeed A. Association between mortality from suicide in England and antidepressant prescribing: an ecological study. *BMC Public Health.* (2004) 4:63. doi: 10.1186/1471-2458-4-63
10. Nierenberg AA. Long-term management of chronic depression. *J Clin Psychiatry.* (2001) 62(Suppl. 6):17–21.
11. Rihmer Z. Can better recognition and treatment of depression reduce suicide rates? A brief review. *Eur Psychiatry.* (2001) 16:406–9. doi: 10.1016/s0924-9338(01)00598-3
12. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29–823 patients with schizophrenia. *JAMA Psychiatry.* (2017) 74:686–93. doi: 10.1001/jamapsychiatry.2017.1322
13. van Os J, Kapur S. Schizophrenia. *Lancet.* (2009) 374:635–45. doi: 10.1016/s0140-6736(09)60995-8
14. Hall WD, Lucke J. How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality? *Aust N Z J Psychiatry.* (2006) 40:941–50. doi: 10.1080/j.1440-1614.2006.01917.x
15. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. *Am J Psychiatry.* (2003) 160:790–2. doi: 10.1176/appi.ajp.160.4.790
16. Möller HJ. Is there evidence for negative effects of antidepressants on suicidality in depressive patients? A systematic review. *Eur Arch Psychiatry Clin Neurosci.* (2006) 256:476–96. doi: 10.1007/s00406-006-0689-8
17. Rihmer Z. [Antidepressants, depression and suicide]. (Antidepresszívumok, depresszió és öngyilkosság.). *Neuropsychopharmacol Hung.* (2013) 15:157–64.
18. Currie DW, Schwab-Reese LM, Runyan CW. Psychiatric diagnoses are associated with means selection in United States suicide deaths. *Soc Psychiatry Psychiatr Epidemiol.* (2021) 56:1791–9. doi: 10.1007/s00127-020-01999-2
19. Flanagan RJ. Fatal toxicity of drugs used in psychiatry. *Hum Psychopharmacol.* (2008) 23(Suppl. 1):43–51. doi: 10.1002/hup.916
20. Brett J, Wylie CE, Raubenheimer J, Isbister GK, Buckley NA. The relative lethal toxicity of pharmaceutical and illicit substances: a 16-year study of the greater Newcastle Hunter area, Australia. *Br J Clin Pharmacol.* (2019) 85:2098–107. doi: 10.1111/bcp.14019
21. Frey R, Schreinzer D, Stimpfl T, Vycudilik W, Berzlanovich A, Kasper S. Suicide by antidepressant intoxication identified at autopsy in Vienna from 1991-1997: the favourable consequences of the increasing use of SSRIs. *Eur Neuropsychopharmacol.* (2000) 10:133–42. doi: 10.1016/s0924-977x(00)00055-9
22. Mason J, Freemantle N, Eccles M. Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract.* (2000) 50:366–70.
23. Abosi O, Lopes S, Schmitz S, Fiedorowicz JG. Cardiometabolic effects of psychotropic medications. *Horm Mol Biol Clin Investig.* (2018) 36. doi: 10.1515/hmbci-2017-0065
24. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry.* (2015) 14:119–36. doi: 10.1002/wps.20204
25. Alvarez PA, Pahissa J. QT alterations in psychopharmacology: proven candidates and suspects. *Curr Drug Saf.* (2010) 5:97–104. doi: 10.2174/157488610789869265
26. Mackin P. Cardiac side effects of psychiatric drugs. *Hum Psychopharmacol.* (2008) 23(Suppl. 1):3–14. doi: 10.1002/hup.915
27. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA.* (2003) 289:2120–7. doi: 10.1001/jama.289.16.2120
28. Glassman AH. Schizophrenia, antipsychotic drugs, and cardiovascular disease. *J Clin Psychiatry.* (2005) 66(Suppl. 6):5–10.
29. Indik JH, Pearson EC, Fried K, Woosley RL. Bazett and Fridericia QT correction formulas interfere with measurement of drug-induced changes in QT interval. *Heart Rhythm.* (2006) 3:1003–7. doi: 10.1016/j.hrthm.2006.05.023
30. Bazett HC. An analysis of the time relations of electrocardiograms. *Heart.* (1920) 7:353–70.
31. Fridericia LS. Die systolendauer im elektrokardiogramm bei normalen menschen und bei herzkranken. *Acta Med Scand.* (1920) 53:469–86. doi: 10.1111/j.0954-6820.1920.tb18266.x
32. Enk D, Palmes AM, Van Aken H, Westphal M. Nasotracheal intubation: a simple and effective technique to reduce nasopharyngeal trauma and tube contamination. *Anesth Analg.* (2002) 95:1432–6, table of contents. doi: 10.1097/00000539-200211000-00061
33. Robinson DH, Toledo AH. Historical development of modern anesthesia. *J Invest Surg.* (2012) 25:141–9. doi: 10.3109/08941939.2012.690328
34. de Araújo RM, Mazzochi L, Lara DR, Ottoni GL. Thinking about dying and trying and intending to die: results on suicidal behavior from a large web-based sample. *J Clin Psychiatry.* (2015) 76:e359–65. doi: 10.4088/JCP.13m08864
35. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry.* (2008) 192:98–105. doi: 10.1192/bjp.bp.107.040113
36. Etzersdorfer E, Klein J, Baus N, Sonneck G, Kapusta ND. Epidemiology of suicide in Austria during 2000-2010: potential years of life lost: time for the national suicide prevention program. *Wien Klin Wochenschr.* (2015) 127:308–13. doi: 10.1007/s00508-015-0729-3
37. Sulaj Z, Prifti E, Demiraj A, Strakosha A. Early clinical outcome of acute poisoning cases treated in intensive care unit. *Med Arch.* (2015) 69:400–4. doi: 10.5455/medarh.2015.69.400-404
38. Bartova L, Dold M, Fugger G, Kautzky A, Mitschek MMM, Weidenauer A, et al. Sex-related effects in major depressive disorder: results of the European group for the study of resistant depression. *Depress Anxiety.* (2021) 38:896–906. doi: 10.1002/da.23165

39. Rockett IR, Hobbs G, De Leo D, Stack S, Frost JL, Ducatman AM, et al. Suicide and unintentional poisoning mortality trends in the United States, 1987-2006: two unrelated phenomena? *BMC Public Health.* (2010) 10:705. doi: 10.1186/1471-2458-10-705
40. Kapusta ND, Tran US, Rockett IR, De Leo D, Naylor CP, Niederkrotenthaler T, et al. Declining autopsy rates and suicide misclassification: a cross-national analysis of 35 countries. *Arch Gen Psychiatry.* (2011) 68:1050–7. doi: 10.1001/archgenpsychiatry.2011.66
41. Rockett IRH, Caine ED, Stack S, Connery HS, Nolte KB, Lilly CL, et al. Method overtness, forensic autopsy, and the evidentiary suicide note: a multilevel national violent death reporting system analysis. *PLoS One.* (2018) 13:e0197805. doi: 10.1371/journal.pone.0197805
42. Raheja H, Namana V, Chopra K, Sinha A, Gupta SS, Kamholz S, et al. Electrocardiogram changes with acute alcohol intoxication: a systematic review. *Open Cardiovasc Med J.* (2018) 12:1–6. doi: 10.2174/1874192401812010001
43. Fugger G, Bartova L, Fabbri C, Fanelli G, Dold M, Swoboda MMM, et al. The sociodemographic and clinical profile of patients with major depressive disorder receiving SSRIs as first-line antidepressant treatment in European countries. *Eur Arch Psychiatry Clin Neurosci.* (2022). doi: 10.1007/s00406-021-01368-3 [Epub ahead of print].
44. Spindelegger CJ, Papageorgiou K, Grohmann R, Engel R, Greil W, Konstantinidis A, et al. Cardiovascular adverse reactions during antidepressant treatment: a drug surveillance report of German-speaking countries between 1993 and 2010. *Int J Neuropsychopharmacol.* (2014) 18:yu080. doi: 10.1093/ijnp/pyu080
45. Beauchamp GA, Giffin SL, Horowitz BZ, Laurie AL, Fu R, Hendrickson RG. Poisonings associated with intubation: US national poison data system exposures 2000-2013. *J Med Toxicol.* (2016) 12:157–64. doi: 10.1007/s13181-015-0528-2
46. Schreinzer D, Frey R, Stimpfl T, Vycudilik W, Berzlanovich A, Kasper S. Different fatal toxicity of neuroleptics identified by autopsy. *Eur Neuropsychopharmacol.* (2001) 11:117–24.
47. Lorsheyd A, de Lange DW, Hijmering ML, Cramer MJ, van de Wiel A. PR and OTc interval prolongation on the electrocardiogram after binge drinking in healthy individuals. *Neth J Med.* (2005) 63:59–63.
48. Winkler D, Kaltenboeck A, Frey R, Kasper S, Pjrek E. Changes over time of the diagnostic and therapeutic characteristics of patients of a psychiatric intensive care unit in Austria. *Compr Psychiatry.* (2019) 93:20–6. doi: 10.1016/j.comppsych.2019.06.004
49. Frey R, Kindler J, Naderi-Heiden A. Klinische Toxikologie der trizyklischen antidepressiva. moderne antidepressiva verringern suizidgefahr. *Pharmazie in unserer Zeit.* (2008) 37:250–5. doi: 10.1002/pauz.200800269
50. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry.* (2005) 62:165–72. doi: 10.1001/archpsyc.62.2.165
51. Kapusta ND, Niederkrotenthaler T, Etzersdorfer E, Voracek M, Dervic K, Jandl-Jager E, et al. Influence of psychotherapist density and antidepressant sales on suicide rates. *Acta Psychiatr Scand.* (2009) 119:236–42. doi: 10.1111/j.1600-0447.2008.01314.x
52. Blüml V, Helbich M, Mayr M, Turnwald R, Vyssoki B, Lewitzka U, et al. Antidepressant sales and regional variations of suicide mortality in Germany. *J Psychiatr Res.* (2017) 87:88–94. doi: 10.1016/j.jpsychires.2016.12.013
53. Nelson JC, Spyker DA. Morbidity and mortality associated with medications used in the treatment of depression: an analysis of cases reported to U.S. poison control centers, 2000-2014. *Am J Psychiatry.* (2017) 174:438–50. doi: 10.1176/appi.ajp.2016.16050523

Conflict of Interest: LB has received travel grants and/or consultant/speaker honoraria from AOP Orphan, Medizin Medien Austria, Universimed, Vertretungsnetz, Schwabe, Janssen, Angelini, and Lundbeck. RF has received consulting fees from Janssen-Cilag and LivaNova as well as speaker honoraria from Janssen-Cilag and Lundbeck.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 24 May 2022
doi: 10.3389/fpsyt.2022.861285

Altered Metabolomics in Bipolar Depression With Gastrointestinal Symptoms

Xiang-Jie Guo[1†], *Yan-Bing Xiong*[2,3†], *Yuan Jia*[2,3†], *Xiao-Hong Cui*[2,3], *Wen-Ze Wu*[4,5], *Jun-Sheng Tian*[4,5], *Hong Yang*[2,3*] and *Yan Ren*[2,3,6*]

[1] Department of Forensic Medicine, Shanxi Medical University, Taiyuan, China, [2] Department of Psychiatry, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China, [3] Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [4] Modern Research Center for Traditional Chinese Medicine, Shanxi University, Taiyuan, China, [5] The Key Laboratory of Chemical Biology and Molecular Engineering of Ministry of Education, Shanxi University, Taiyuan, China, [6] Shanxi Provincial Key Laboratory of Brain Science and Neuropsychiatric Diseases, Taiyuan, China

OPEN ACCESS

Edited by:
Domenico De Berardis, Mental Health Center (CSM) and Psychiatric Service of Diagnosis and Treatment (SPDC), Italy

Reviewed by:
Penghong Liu, First Hospital of Shanxi Medical University, China
Lorenza Lucidi, University of Studies G. d'Annunzio Chieti and Pescara, Italy

***Correspondence:**
Yan Ren
renyansxmu@outlook.com
Hong Yang
yhsgx@163.com

[†]These authors share first authorship

Specialty section:
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

Received: 24 January 2022
Accepted: 25 April 2022
Published: 24 May 2022

Citation:
Guo X-J, Xiong Y-B, Jia Y, Cui X-H, Wu W-Z, Tian J-S, Yang H and Ren Y (2022) Altered Metabolomics in Bipolar Depression With Gastrointestinal Symptoms. Front. Psychiatry 13:861285. doi: 10.3389/fpsyt.2022.861285

Objective: Although gastrointestinal (GI) symptoms are very common in patients with bipolar disorder (BD), Few studies have researched the pathomechanism behind these symptoms. In the present study, we aim at elucidate the pathomechanism of GI symptoms in BD through metabolomic analysis.

Method: BD patients were recruited from Shanxi Bethune Hospital that divided into two groups, each group assessed with the 24-item Hamilton Depression Rating Scale (HAMD-24) according to the presence or absence of GI symptoms. Healthy controls were recruited from the medical examination center of the same hospital. Differential metabolites were identified and further analyzed using Metabo Analyst 3.0 to identify associated metabolic pathways.

Results: There were significantly higher HAMD-24 scores in the GI symptoms group than that of non-GI symptoms group ($p = 0.007$). Based on metabolomic analysis results, we found that the common disturbances metabolic pathway of both two patients groups was ketone body metabolism, and the unique disturbances metabolic pathways of BD with GI symptoms were fatty acid biosynthesis and tyrosine metabolism, and these changes were independent of dietary habits.

Conclusion: BD patients with GI symptoms exhibited disturbances in fatty acid and tyrosine metabolism, perhaps suggesting that the GI symptoms in BD patients are related to disturbances of the gut microbiome. Both groups of patients jointly exhibit disturbances of ketone body metabolism, which may serve as a biomarker for the pathogenesis of BD patients.

Keywords: bipolar disorder, gastrointestinal symptoms, metabonomics, biomarker, gut microbiome

INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric disorder characterized by recurrent episodes of depression (bipolar depression), mania (bipolar mania), and hypomania, which affecting 1–3% of the population worldwide (1, 2). On the bipolar spectrum, bipolar depression is the leading cause of morbidity in patients with bipolar disorder, at least 50% of patients initially present with a depressive episode (3). Mood disorders or emotional symptoms, such as depression, are common among those who seek help for functional somatic symptoms. According to the studies, ∼69% of patients with major depressive disorder (MDD) experience somatic symptoms (4, 5) and over 45% of MDD seek medical attention mainly for these (6). According to a meta-analysis, the estimated prevalence of somatic symptoms in BD was 47.8%, a rate nearly double that of the healthy controls, and a rate similar to MDD (7). Studies have likewise suggested that somatic symptoms of BD may be an independent risk factor of disease severity, suicidal ideation, and rapid-cycling disease processes, implying that somatic and psychological symptoms must be co-managed in severe mental illness (8). Therefore, somatic symptoms may be key indicators of the severity and prognosis of BD.

Gastrointestinal (GI) symptoms as the most commonly reported group of somatic symptoms in affective disorders, which have a strong relationship with anxiety and depressive disorders (9). The majority of patients presenting with major depressive and anxiety also complain of GI symptoms, such as nausea, bloating, decreased appetite, etc. One study based on the general population found that 54% of those with depressive symptoms had complaints of GI discomfort, which was much higher than 29% of controls without affective disorders. In addition, the GI symptoms group had more severe affective symptoms as well as a decreased quality of life than the non-GI symptoms group (10). Another study found that there is a strong association between symptoms of affectivity and GI symptoms in BD, the findings are consistent with those reported in MDD (11).

Studying the causal connection between the onset of GI symptoms and affective symptoms is difficult because the onset of both symptoms is insidious and the course fluctuates widely (12). Previous studies have shown that there may be a common pathophysiological mechanism between depressive

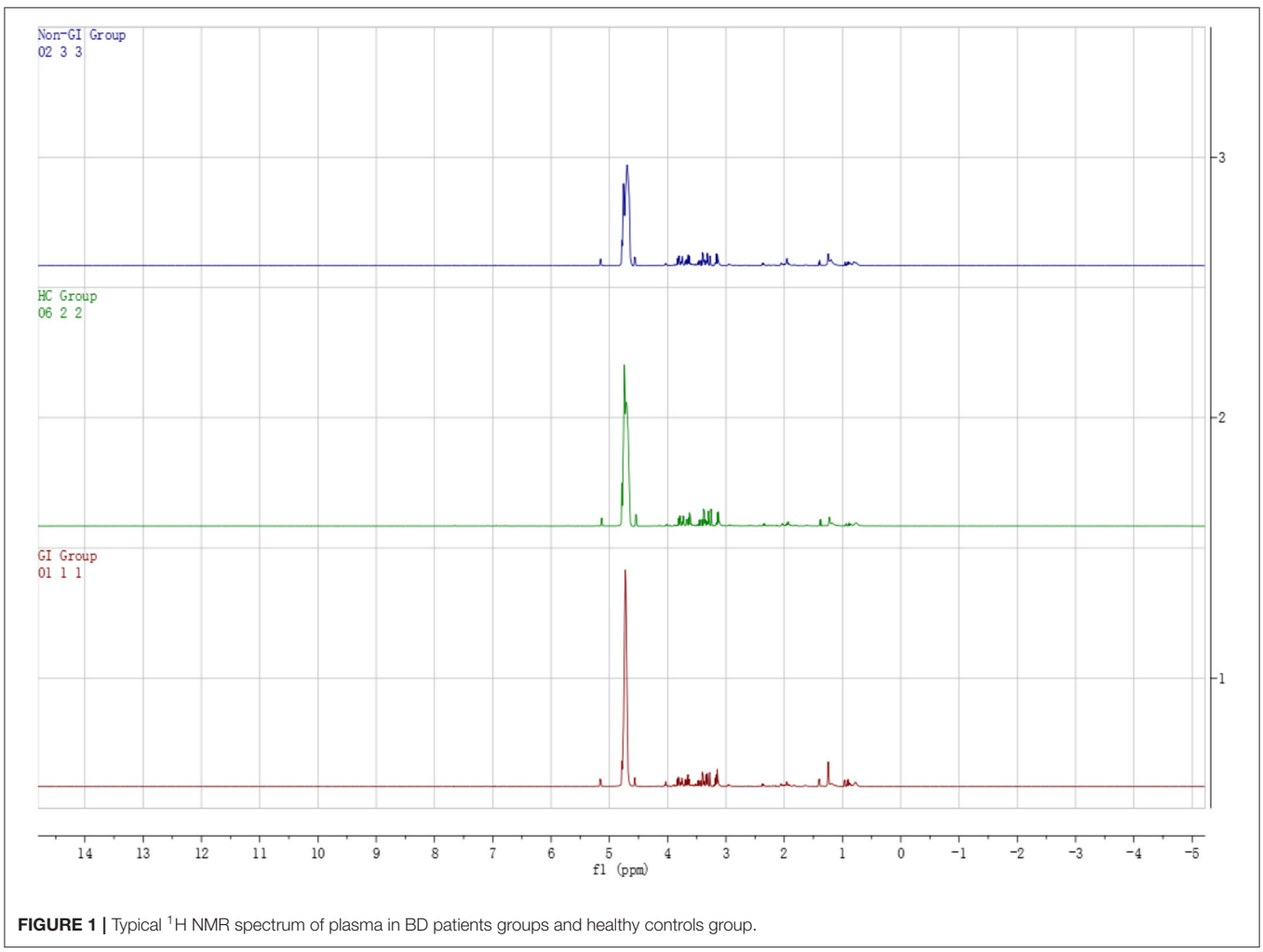


FIGURE 1 | Typical ^{1}H NMR spectrum of plasma in BD patients groups and healthy controls group.

TABLE 1 | Demographic and clinical characteristics of all participants.

Variable		Group			Analysis		
		GI ($N = 25$)	Non-GI ($N = 34$)	HC ($n = 10$)	df	F/χ2	p
Age (year)		27.16 ± 9.02	28.29 ± 12.08	28.50 ± 3.10	66	0.109	0.897
BMI		22.16 ± 2.97	22.65 ± 4.35	21.30 ± 3.68	66	0.501	0.608
Onset age (year)		21.40 ± 8.15	22.35 ± 10.58	-	57	0.141	0.709
Duration of illness (months)		37.32 ± 43.30	41.82 ± 42.52	-	57	0.159	0.691
The total scores of HAMD-24		31.68 ± 5.57	27.03 ± 6.84	-	57	7.761	0.007
Gender	Male	13	9	3	2	4.261	0.119
	Female	12	25	7			
Drink sugary drinks or eat desserts	<3 times /week	16	18	6	2	6.510	0.164
	3–6 times /week	6	6	4			
	>6 times /week	3	10	0			
kind of meat do eat	Don't eat meat	3	0	1	2	5.964	0.202
	Main lean meat	18	24	8			
	Each half	4	10	1			
	Main fat	0	0	0			
Cooking oil	Total vegetable oil	8	10	3	2	1.808	0.771
	Main vegetable oil	12	16	3			
	Each half	5	8	4			
	Main animal oil	0	0	0			

and GI symptoms, which may refer to the neuroendocrine system, neural plasticity, inflammatory response cascade and gut microbiome (13). Metabolomics, a branch of systems biology that has been widely used in many fields, can help us understand the mechanisms by which the gut microbiota could drive symptom. With the development of effective analytical techniques and methods, the discovery of specific biomarkers through the analysis of fluids and tissues has made a significant contribution to the understanding of the basis of disease (14). Four main matrixes (i.e. feces, urine, plasma and serum) have been used to analyzing the metabolites involved in the gut-brain axis by metabolomics, when focusing on plasma samples, the main goal is to remove the proteins from the sample prior to metabolomics analysis (15). We can maximize the metabolomics information of the samples by proton nuclear magnetic resonance (^{1}H NMR), gas chromatography-mass spectrometer (GC-MS), liquid chromatography-mass spectrometry (LC-MS) combined with multivariate data analysis.

GI pathologies have long been known as a common comorbidity of BD and other psychological disorders, further confirming the theory that GI pathology and psychological disorders are interrelated. A meta-analysis consisting of 177,117 irritable bowel syndrome (IBS) patients and 192,092 healthy controls showed a significant increase in the prevalence of BD in patients with IBS compared to healthy participants (16). In IBS patients, ^{1}H NMR spectroscopy showed the short-chain fatty acids (SCFAs) propionate, butyrate, and acetate to be significantly lower in the stool samples of IBS compared to healthy controls (17).

Thus, abnormal metabolic may be associated with the onset and development of GI symptoms. However, few studies have investigated the changes in metabolic in BD patients with GI symptoms. In the present study, we sought to elucidate the biochemical basis of GI symptoms by comparing metabonomics between BD patients with and without GI symptoms. We further sought to determine if these metabolic pathways were risk factors for GI symptoms in BD patients.

MATERIALS AND METHODS

Participants

Fifty-nine BD patients were recruited from Shanxi Bethune Hospital. All subjects and their guardians voluntarily participated in the study and gave informed consent. Experienced and licensed psychiatrists participated in the recruiting procedure. For inclusion in this study, the diagnoses were validated with the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). The exclusion criteria for this study included any physical or other mental disorders and drug abuse. All patients have never been treated with medication or have not been treated in the last month. A control group of 10 healthy controls were recruited by advertisement and had no DSM-IV axis I disorders. The Ethics Committee of Shanxi Bethune Hospital reviewed and approved this study and all subjects provided informed consent prior to inclusion.

Eligible patients with BD were divided into two groups based on various GI symptoms scores from the HAMD-24 (item 12) and Young Mania Rating Scale (YMRS). The scores of YMRS for all enrolled patients were <5. The severity of GI symptoms of HAMD-24 is divided into three levels from 0 to 2. Zero means no GI symptoms, 1 means the most severe GI symptoms leading to mild occasional discomfort, and 2 means the most

TABLE 2 | Peak attribution in ^{1}H-NMR spectra of differential metabolites.

No.	Metabolites	Chemical shift
1	Lipid	0.874 (m)
2	Pantothenate	0.907 (s)
3	Isoleucine	0.949 (t)
4	Leucine	0.961 (t)
5	3-hydroxybutyric acid	1.21 (d)
6	Lactate	1.33 (d)
7	Acetate	1.927 (s)
8	O-acetyl glycoproteins	2.14 (s)
9	Acetoacetate	2.28 (s), 3.44 (s)
10	Methionine	2.14 (s)
11	Guanidinoacetate	3.80 (s)
12	Uracil	5.81 (d, 7.7 Hz), 7.55 (d, 7.7 Hz)
13	Histidine	7.04 (s), 7.84 (s)
14	Dimethylglycine	2.92 (s), 3.70 (s)
15	Creatine	3.04 (s), 3.93 (s)
16	Acetylcholine	3.23 (s)
17	Taurine	3.27 (t, J = 6.6 Hz), 3.42 (t, J = 6.6 Hz)
18	Scyllo-inositol	3.36 (s)
19	3-D-hydroxybutyrate	1.20 (d)
20	Betaine	3.27 (m)
21	Glyceryl	3.67 (m), 3.78 (m)
22	Citrulline	3.73 (s)
23	N-acetyl-glycoproteins	2.05 (s)
24	Glutamate	2.06 (m), 2.14 (m), 2.36 (m)
25	Glutamine	2.14 (m)
26	Acetone	2.23 (s)
27	Acetoacetate	2.28 (s), 3.44 (s)
28	Citrate	2.53 (d, 16.1 Hz), 2.70 (d, 16.1 Hz)
29	Choline	3.20 (s), 4.06 (m)

severe symptoms leading to frequent discomfort. Among the eligible patients with BD, 34 patients reported at least one GI symptom (GI symptoms group), and 25 patients reported no GI symptoms (non-GI symptoms group). Furthermore, all of the healthy controls were free of any GI symptoms.

Sample Collection

The blood samples were collected from all subjects in the morning after 12 h of fasting by the professional staff of Shanxi Bethune Hospital. After clotting, the blood was mixed upside down and stored at room temperature for half an hour. Then centrifuged at 3,000 r/min for 15 min, and the supernatant (plasma) was taken by pipette and uniformly transferred to clean eppendorf tubes, and stored at −80°C prior to analysis.

NMR Acquisition

The samples stored at −80°C were thawed at 0°C and centrifuge at 3,000 rpm for 15 min. Four hundred and fifty μL of plasma was mixed with 900 μL of methanol and centrifuged at 13,000 rpm for 20 min at 4°C to pellet the proteins, then 1,000 μL of supernatant was transferred to a clean vial. Another 900 μL of methanol was added and the proteins were removed by centrifugation at 4°C for 20 min at 13,000 rpm. Finally, 1,800 μL of the supernatant was dried in a nitrogen stream, and 600 μL of dry-mixed samples [phosphate buffer (0.2 M Na_2HPO_4/NaH_2PO_4, pH = 7.4)] containing sodium 3-trimethylsilyl D_2O-(2, 2, 3, 3-d4) 1-propionate (TSP, 0.01%) to reduce chemical shift changes and remove any precipitates by centrifugation (13,000 rpm, 10 min at 4°C) at that time. Five hundred and fifty μL of supernatant was transferred into a 5-mm NMR tubes for NMR analysis (18).

The ^{1}H NMR spectra of the plasma samples were obtained using a Bruker 600 MHz AVANCE III NMR spectrometer (Bruker Biospin, Rheinstetten, Germany) operating at a ^{1}H frequency of 600.13 MHz and a temperature of 298 K. The broad signals with short lateral relaxation times of proteins and lipoproteins were attenuated using one-dimensional Carr-Purcell-Merboom-Gill (CPMG, RD-90-(τcp-180-τcp)-capture) and spin-spin relaxation delay of 320 ms. The ^{1}H NMR spectrum of each sample consisted of 64 scans with an acquisition time of 5 min and parameters of spectral width of 12019.2 Hz, spectral width of 65,536 points, and pulse width (PW) = 30 (12.7 ms), and relaxation delay (RD) = 1.0 s (18).

Data Processing and Statistical Analyses

All of the acquired ^{1}H NMR spectra were manually phased, and the baseline was set using MestReNova software (Mestrelab Research, Santiago de Compostella, Spain). The chemical shift of creatinine (δ3.04, -CH3) was used as a calibration standard. The region in the range of chemical shift values δ 4.7 ∼ 5.2 ppm was artificially removed to eliminate the water peak. All NMR spectra were superimposed and the δ 0.8–9.0 ppm in the spectra were integrated into the base unit of δ 0.01 ppm (19).

The processed ^{1}H NMR spectrum profile data were introduced into SIMCA-P 14.1 (Umetrics, Sweden) for multivariate analysis. Partial leastsquare-discrimination analysis (PLS-DA) and orthogonal projection to latent structure-discriminate analysis (OPLS-DA) were employed. The quality of the PLS-DA model was described by the parameters for model fitness (R^2) and predictive ability (Q^2), where a large R^2 (close to 1) and Q^2 ($Q^2 \geq 0.5$) indicate a good model. Next, the PLS-DA model was validated by the response values of the permutation test in which the class membership was randomly shuffled 200 times. The result indicated a lack of over-fitting when the new R^2 and Q^2 values were lower than the original ones (20). In the OPLS-DA model, the *p*-values of cross-validated analysis of variance (CV-ANOVA) ($p < 0.05$) was used to indicate the significance level of population separation. To further understand the underlying variables that contribute to differentiation, we performed an S-plot analysis of the OPLS-DA model, where each coordinate reflects a NMR region used to define metabolites that contribute significantly to group separation. The key metabolites needed to differentiate groups were selected from the results of the variable importance (VIP) of the items analyzed by the established OPLS-DA model (18).

To determine the pathways involved in the metabolites where the differences occurred, they were further introduced into Metabo Analyst 3.0 (http://www.metaboanalyst.ca/) to perform Pathway analysis using the human Pathway library. Pathways

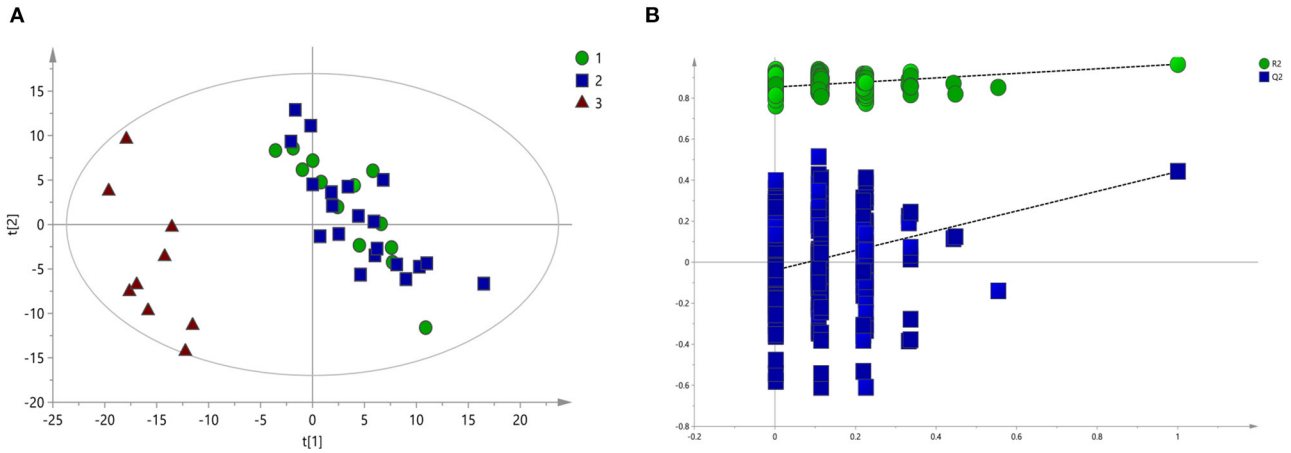


FIGURE 2 | PLS-DA of ^{1}H NMR spectra of urine samples from BD patients and HC groups. **(A)** PLS-DA score plots of ^{1}H NMR spectra in which GI group (circle), Non-GI group (square) were obviously separated from HC group (triangle). **(B)** 200-iteration permutation test map of the PLS-DA model.

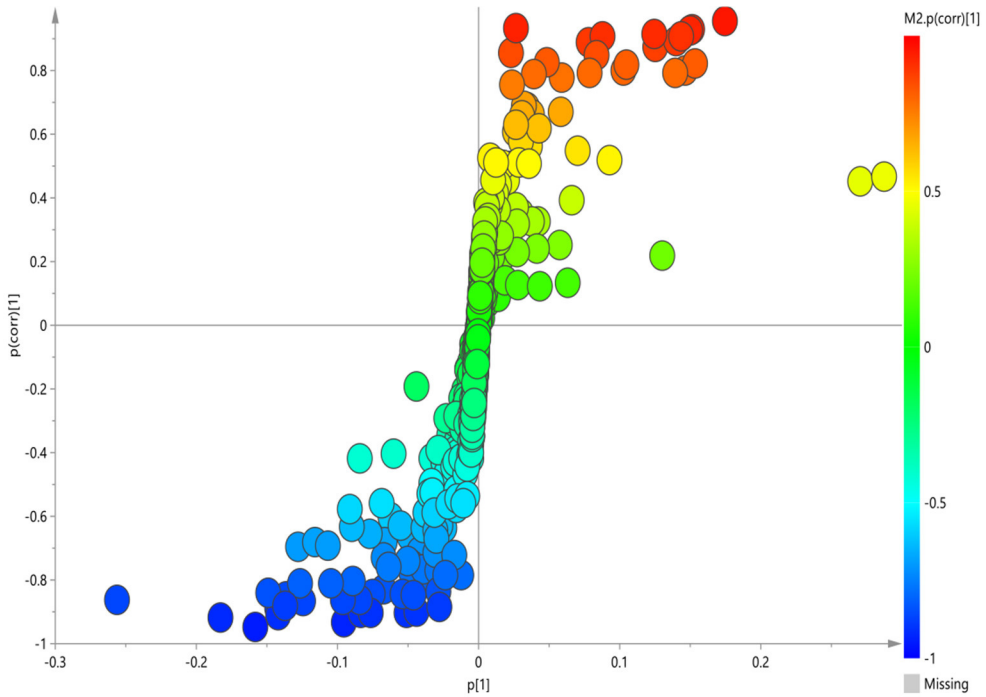


FIGURE 3 | S-plot of ^{1}H-NMR spectra between HC and GI group.

were screened based on the p value of pathway enrichment and the impact value of pathway topology analysis.

Data analyses were performed using SPSS 20.0 (IBM, Chicago, IL, United States). A t-test was used to evaluate the significant differences in the selected signals of the main metabolites that were responsible for class discrimination. All clinical scale data were expressed as the mean ± SD. Continuous variables were checked using one-way analysis of variance (ANOVA) and classified variables using the Chi-square test. A p value of 0.05 or below was considered significant for demographic analysis.

RESULTS

Demographic Data Comparisons

As shown in **Table 1**, there were no significant differences in age ($F = 0.109$, $p = 0.897$), gender ($\chi 2 = 4.261$, $p = 0.119$), or

TABLE 3 | The peak area of metabolites in serum ^{1}H-NMR spectra of HC group and GI group.

Metabolites	Peak area after normalization	
	HC	GI
Lipid	0.314 ± 0.079	0.467 ± 0.116
Pantothenate	0.245 ± 0.053	0.401 ± 0.098
3-D-hydroxybutyric acid	0.532 ± 0.192	0.127 ± 0.094
Acetate	0.717 ± 0.105	0.400 ± 0.131
N-acetyl-glycoproteins	0.120 ± 0.066	0.378 ± 0.082
Acetoacetate	0.623 ± 0.117	0.317 ± 0.132
Glyceryl	1.161 ± 0.192	0.563 ± 0.305
Ascorbic acid	0.231 ± 0.389	0.548 ± 0.116
β- glucose	10.432 ± 3.295	6.841 ± 4.178

body mass index ($F = 0.501$, $p = 0.608$) among the three groups. There were no significant differences in age of disease onset ($F = 0.141$, $p = 0.709$), duration of illness ($F = 0.159$, $p = 0.691$) between two patients group. However, the total HAMD-24 scores in the GI symptoms group were greater than that of the non-GI symptoms group ($F = 7.761$, $p = 0.007$). Furthermore, there were no significant differences in dietary habits among the three groups, include how often drink sugary drinks or eat desserts ($\chi 2 = 6.510$, $p = 0.164$), what kind of meat do eat ($\chi 2 = 5.964$, $p = 0.202$), and what kind of oil do use for cooking ($\chi 2 = 1.808$, $p = 0.771$).

^{1}H NMR Spectroscopy Data Analysis

Figure 1 shows the typical ^{1}H NMR spectrum profiles of BD with GI symptoms, BD without GI symptoms and HC groups. By looking up the human metabolome database (HMDB) (http://www.hmdb.ca/) and related articles over the years, we identified 29 small molecule compounds in the ^{1}H NMR spectrum profiles (**Table 2**).

To screen the potential differential metabolites of the three groups, the ^{1}H-NMR spectral data obtained were first subjected to PLS-DA. The score plot of the PLS-DA model showed that BD patients (whether or not with gastrointestinal symptoms) and HC could be clearly separated with little overlap (**Figure 2A**). In order to further verify the PLS-DA model, 200 iteration permutation tests were conducted (**Figure 2B**). The corresponding permuted values (bottom left) were all lower than the original R^2 and Q^2 values (top right), which meant the PLS-DA model was not over-fitted.

According to serum macro profile analysis of each group, it could be seen that HC was significantly separated from BD patients, indicating that endogenous metabolites in the BD patients group were changed compared with the HC group. However, There was no significant difference between the BD patients group with gastrointestinal symptoms and BD patients group without gastrointestinal symptoms. The above results could not observe the specific regulation of endogenous metabolites. Therefore, pairwise analysis in each group were required to find the differential metabolites.

Plasma Metabolite and Metabolic Pathways Differences Between the GI Group and HC Group

The corresponding OPLS-DA loading plot was further established between GI group and HC group to improve the classification of the different groups, as well as for biomarker screening, according to the S-plot (**Figure 3**), 10 key metabolites were especially meaningful for the distinction between two groups (VIP > 1 and $p < 0.05$; **Table 3**). Compared to HC, BD with GI symptoms were characterized by significantly higher levels of lipid, pantothenate, N-acetyl-glycoprotein, ascorbic acid, and significantly lower levels of 3-D-hydroxybutyric acid, acetate, acetoacetate, glyceryl and β- glucose.

Pathway analysis of differential metabolites was performed to reveal biological implications. Differential metabolites were analyzed using the Metabo Analyst 3.0 (http://www.metaboanalyst.ca/) platform, and the main involved metabolic pathways were identified. Among these, ketone body metabolism, fatty acid biosynthesis and tyrosine metabolism were more closely related to BD patients with GI symptoms. The analysis results are shown in **Figure 4**.

Plasma Metabolite and Metabolic Pathways Differences Between the Non-GI Group and HC Group

The corresponding S-plot was further established between Non-GI group and HC group (**Figure 5**). According to the S-plot, 10 key metabolites were especially meaningful for the distinction between two groups (VIP > 1 and $p < 0.05$; **Table 4**). Compared to HC, BD without GI symptoms were characterized by significantly higher levels of lipid, pantothenate, N-acetyl-glycoprotein, ascorbic acid, valine, 3-D-hydroxybutyric acid, dimethylglycine, and significantly lower levels of acetate, trimethylamine oxide, and guanidine acetate.

The closely related metabolic pathways between HC and BD without GI symptoms group was ketone body metabolism. The analysis results are shown in **Figure 6**.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the metabolomics characteristics of BD patients with GI symptoms. The results revealed that BD patients with GI symptoms experience more severe symptoms compared to the in metabolic pathways associated with GI symptoms that may be risk factors for gastrointestinal symptoms in BD patients.

In this study, we found that the total HAMD-24 scores in the GI symptoms group were greater than that of the non-GI symptoms group, that consistent with past research findings. Liu et al. demonstrated that the presence of GI symptoms in patients with MDD is associated with more severe symptoms of depression, especially as it pertains to patients who demonstrate no GI symptoms (21). Pinto-Sanchez et al. found a positive correlation between the prevalence and severity of depressive symptoms and the frequency and severity of GI symptoms in patients with FGIDs (22). Perera et al. studied 16,415 patients

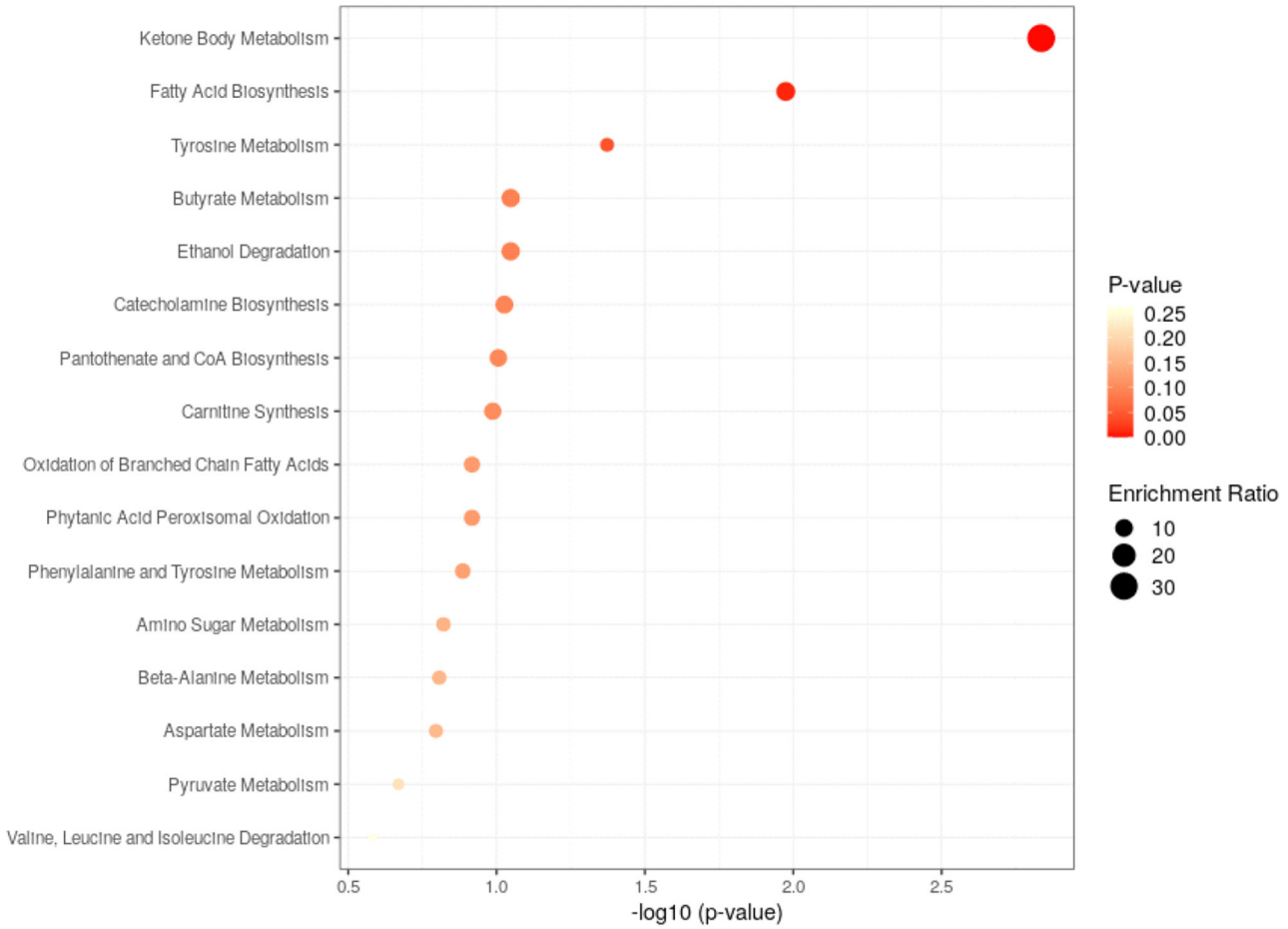


FIGURE 4 | Metabolic pathways analysis of the differential metabolites found between HC and GI group.

in the Hispanic Community Health Study and found that adults who reported multiple episodes of GI symptoms were more psychologically stressed than those who reported less frequent episodes of GI symptoms (23). Karling et al. discovered that shown that also patients with an established recurrent depression disorder report high scores on GI symptoms, but when in remission they do not differ from controls in reporting GI symptoms (24), and similarly in BD patients, they also shown that there is a strong association between symptoms of affectivity and GI symptoms (11). We believe that the present study and our previous study support that GI symptoms has an effect on the affective symptoms.

Although the exact pathological alterations in patients with BD are unknown, recent studies have demonstrated extensive alterations in very complex metabolic pathways may partially underlie the pathophysiology, and we found that these changes were independent of dietary habits. Based on metabolomic analysis results, we found that the common disturbances metabolic pathways of both groups of patients jointly exhibit disturbances of ketone body metabolism. In mammals, ketone bodies are produced predominantly in the liver from β-oxidation (FAO)-derived acetyl-CoA, and they are transported to extrahepatic tissues for terminal oxidation. Acetoacetic acid, β-hydroxybutyric acid, and acetone are eventually formed, and these three products are collectively known as ketone bodies. Apart from serving as energy fuels for extrahepatic tissues like brain, heart, or skeletal muscle, ketone bodies play pivotal roles as signaling mediators, drivers of protein post-translational modification (PTM), and modulators of inflammation and oxidative stress (25). Growing preclinical and clinical evidence that dietary ketosis lead to the mitochondrial dysfunction, amelioration of oxidative stress, and peripheral and brain inflammation in animals and humans (13, 26, 27), and research teams have reported that nutritional ketosis may reduce symptoms in patients with schizophrenia (28), BD (29), and major depressive disorder (30, 31). It is means that major depressive disorder, BD, and schizophrenia are increasingly described as neuroprogressive disorders, reflecting progressive neuroanatomical and cognitive decline caused by many common factors present in each disorder, such as peripheral and brain

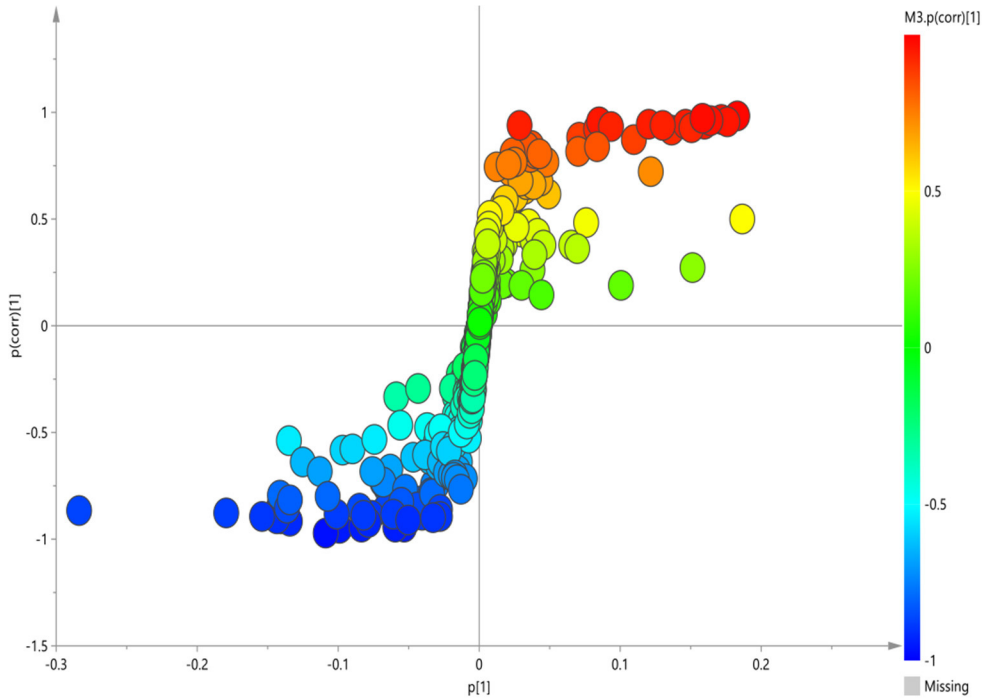


FIGURE 5 | S-plot of ^{1}H-NMR spectra between HC and non-GI group.

TABLE 4 | The peak area of metabolites in serum ^{1}H-NMR spectra of HC group and non-GI group.

Metabolites	Peak area after normalization	
	HC	Non-GI
Lipid	0.345 ± 0.069	0.442 ± 0.075
Pantothenate	0.270 ± 0.032	0.373 ± 0.061
Valine	0.015 ± 0.005	0.097 ± 0.051
3-D-hydroxybutyric acid	1.460 ± 0.385	1.808 ± 0.669
Acetate	0.749 ± 0.069	0.504 ± 0.086
N-acetyl-glycoprotein	0.107 ± 0.025	0.318 ± 0.031
Dimethylglycine	0.079 ± 0.026	0.190 ± 0.036
Trimethylamine oxide	0.813 ± 0.134	0.333 ± 0.047
Guanidine acetate	0.979 ± 0.116	0.516 ± 0.101
Ascorbic acid	0.018 ± 0.015	0.138 ± 0.061

inflammation, oxidative stress, mitochondrial dysfunction with disorders of tryptophan metabolism (32–35). In a word, ketone body metabolism be involved in the inflammation and oxidative stress may be one of the pathogeneses of BD.

What's more, we found the unique disturbances metabolic pathways of BD patients with GI symptoms were fatty acid biosynthesis and tyrosine metabolism. GI disorders pathogenesis involves changes in GI motility, intestinal secretion, visceral hypersensitivity, and intestinal permeability, all of which can be modified by the gut microbiome (36). Recent studies have shown that the composition and metabolic functions of gut microbiota have been proposed as being able to affect fatty acid biosynthesis (37). By comparing the response of germ-free and normal mice to high-fat diets, found that germ-free mice are resistant to high-fat diets, but microbial remodeling can lead to obesity in germ-free mice, thus confirming that gut microbiome are important factors affecting fatty acid biosynthesis (38, 39). Some other studies have shown that the human gut microbiota produces dozens of metabolites that accumulate in the bloodstream, where they can have systemic effects on the host (40). Dodd et al. used a combination of genetics and metabolic profiling to characterize a pathway from the gut symbiont Clostridium sporogenes that generates aromatic amino acid metabolites, and the results reveal that all three aromatic amino acids (tryptophan, phenylalanine and tyrosine) serve as substrates for the pathway, and it involves branching and alternative reductases for specific intermediates, through modulate serum levels of these metabolites in gnotobiotic mice, and show that in turn this affects intestinal permeability and systemic immunity (41). Hence, according previous studies, we found that the abnormalities of these two metabolic pathways may be related to the disturbance of the gut microbiome, and the gut microbiome has been implicated in multiple human chronic GI disorders (17).

CONCLUSION

In conclusion, we show that BD patients with GI symptoms have more severe depressive symptoms. BD patients with

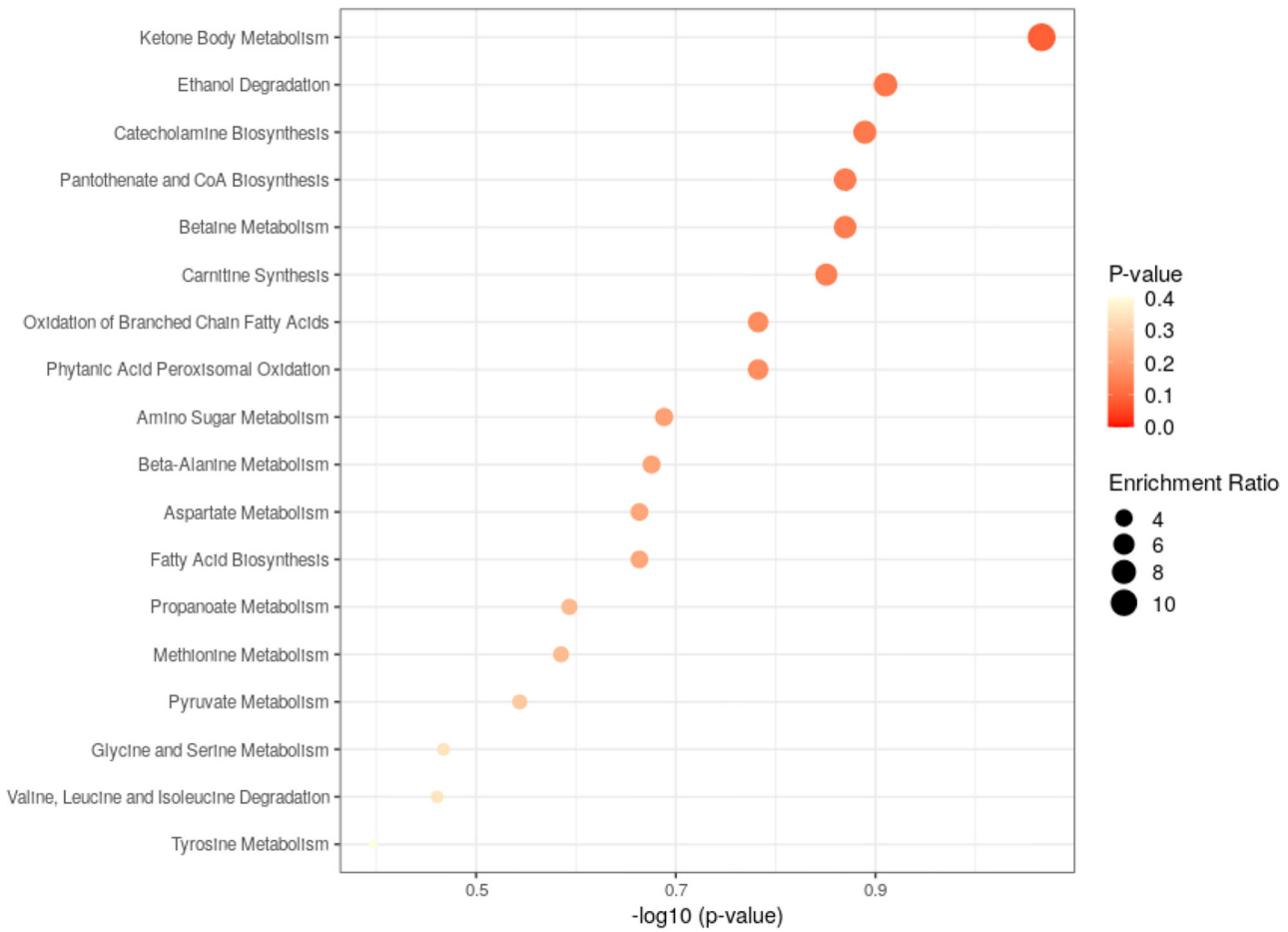


FIGURE 6 | Metabolic pathways analysis of the differential metabolites found between HC and non-GI group.

GI symptoms exhibited abnormalities in fatty acid and tyrosine metabolism, which may be associated with the disturbance of the gut microbiome. Both two patient groups exhibit abnormalities in the ketone body metabolism, which may serve as a biomarker for the pathogenesis of BD patients.

Limitations

There are two primary methodological limitation for the current study that should be considered. First, our study is a cross-sectional study that we could not continue to explore the changes in metabolomics with drug treatment. Secondly, the sample size of this study was not large. Therefore, we plan to conduct further large sample follow-up studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shanxi Bethune Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-BX and YR contributed to manuscript preparation. Y-BX, J-ST, and W-ZW performed the data analysis and statistics. YJ contributed in oversaw data/demographic data collection. X-JG, Y-BX, and YJ wrote and revised the manuscript. HY and YR was in charge of design, implementation of the study, and contributed to data interpretation. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation of China (8210053813), Research Project Supported by Shanxi Scholarship Council of China (2021-167),

Applied Basic Research Projects of Shanxi Province China (201901D111418), and Scientific Research Project of Health Commission of Shanxi Province (2019007).

ACKNOWLEDGMENTS

The authors thank all the subjects for participating in this study.

REFERENCES

1. Nierenberg AA, Kansky C, Brennan BP, Shelton RC, Perlis R, Iosifescu DV. Mitochondrial modulators for bipolar disorder: a pathophysiologically informed paradigm for new drug development. *Aust N Z J Psychiatry.* (2013) 47:26–42. doi: 10.1177/0004867412449303
2. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet.* (2013) 381:1663–71. doi: 10.1016/S0140-6736(13)60989-7
3. McIntyre RS, Calabrese JR. Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. *Curr Med Res Opin.* (2019) 35:1993–2005. doi: 10.1080/03007995.2019.1636017
4. Haj Kheder S, Heller J, Bär JK, Wutzler A, Menge BA, Juckel G. Autonomic dysfunction of gastric motility in major depression. *J Affect Disord.* (2018) 226:196–202. doi: 10.1016/j.jad.2017.09.049
5. Quick C, Kliem A, Berger S, Hocke M, Tancer M, Juckel G, et al. Gastric dysmotility in major depression. *Prog Neuropsychopharmacol Biol Psychiatry.* (2010) 34:92–7. doi: 10.1016/j.pnpbp.2009.10.003
6. Kop WJ. Somatic depressive symptoms, vital exhaustion, and fatigue: divergent validity of overlapping constructs. *Psychosom Med.* (2012) 74:442–5. doi: 10.1097/PSY.0b013e31825f30c7
7. Edgcomb JB, Tseng CH, Kerner B. Medically unexplained somatic symptoms and bipolar spectrum disorders: a systematic review and meta-analysis. *J Affect Disord.* (2016) 204:205–13. doi: 10.1016/j.jad.2016.06.029
8. Edgcomb JB, Kerner B. Predictors and outcomes of somatization in bipolar I disorder: a latent class mixture modeling approach. *J Affect Disord.* (2018) 227:681–7. doi: 10.1016/j.jad.2017.11.083
9. Haug TT, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? *Scand J Gastroenterol.* (2002) 37:294–8. doi: 10.1080/003655202317284192
10. Hillilä MT, Hämäläinen J, Heikkinen ME, Färkkilä MA. Gastrointestinal complaints among subjects with depressive symptoms in the general population. *Aliment Pharmacol Ther.* (2008) 28:648–54. doi: 10.1111/j.1365-2036.2008.03771.x
11. Karling P, Maripuu M, Wikgren M, Adolfsson R, Norrback KF. Association between gastrointestinal symptoms and affectivity in patients with bipolar disorder. *World J Gastroenterol.* (2016) 22:8540–8. doi: 10.3748/wjg.v22.i38.8540
12. Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. *J Clin Psychiatry.* (2001) 62 (Suppl 8):28–36; discussion: 37.
13. Geng J, Yan R, Shi J, Chen Y, Mo Z, Shao J, et al. Altered regional homogeneity in patients with somatic depression: a resting-state fMRI study. *J Affect Disord.* (2019) 246:498–505. doi: 10.1016/j.jad.2018.12.066
14. Zhang F, Jia Z, Gao P, Kong H, Li X, Lu X, et al. Metabonomics study of urine and plasma in depression and excess fatigue rats by ultra fast liquid chromatography coupled with ion trap-time of flight mass spectrometry. *Mol Biosyst.* (2010) 6:852–61. doi: 10.1039/b914751a
15. Konjevod M, Nikolac Perkovic M, Sáiz J, Svob Strac D, Barbas C, Rojo D. Metabolomics analysis of microbiota-gut-brain axis in neurodegenerative and psychiatric diseases. *J Pharm Biomed Anal.* (2021) 194:113681. doi: 10.1016/j.jpba.2020.113681
16. Tseng PT, Zeng BS, Chen YW, Wu MK, Wu CK, Lin PY. A meta-analysis and systematic review of the comorbidity between irritable bowel syndrome and bipolar disorder. *Medicine (Baltimore).* (2016) 95:e4617. doi: 10.1097/MD.0000000000004617
17. Mars RAT, Yang Y, Ward T, Houtti M, Priya S, Lekatz HR, et al. Longitudinal multi-omics reveals subset-specific mechanisms underlying irritable bowel syndrome. *Cell.* (2020) 182:1460–73.e1417. doi: 10.1016/j.cell.2020.08.007
18. Liu CC, Wu YF, Feng GM, Gao XX, Zhou YZ, Hou WJ, et al. Plasma-metabolite-biomarkers for the therapeutic response in depressed patients by the traditional Chinese medicine formula Xiaoyaosan: a (1)H NMR-based metabolomics approach. *J Affect Disord.* (2015) 185:156–63. doi: 10.1016/j.jad.2015.05.005
19. Ren Y, Chen ZZ, Sun XL, Duan HJ, Tian JS, Wang JY, et al. Metabolomic analysis to detect urinary molecular changes associated with bipolar depression. *Neurosci Lett.* (2021) 742:135515. doi: 10.1016/j.neulet.2020.135515
20. Chang D, Weljie A, Newton J. Leveraging latent information in NMR spectra for robust predictive models. *Pac Symp Biocomput.* (2007) 115–126.
21. Liu PH, Li Y, Zhang AX, Sun N, Li GZ, Chen X, et al. Brain structural alterations in MDD patients with gastrointestinal symptoms: evidence from the REST-meta-MDD project. *Prog Neuropsychopharmacol Biol Psychiatry.* (2021) 111:110386. doi: 10.1016/j.pnpbp.2021.110386
22. Pinto-Sanchez MI, Ford AC, Avila CA, Verdu EF, Collins SM, Morgan D, et al. Anxiety and depression increase in a stepwise manner in parallel with multiple FGIDs and symptom severity and frequency. *Am J Gastroenterol.* (2015) 110:1038–48. doi: 10.1038/ajg.2015.128
23. Perera MJ, Schneiderman N, Sotres-Alvarez D, Daviglus M, Mirabal SM, Llabre MM. Are anxious and depressive symptoms associated with gastrointestinal symptoms in the hispanic community health study/study of latinos (HCHS/SOL)? *J Racial Ethn Health Disparities.* (2021) 8:712–22. doi: 10.1007/s40615-020-00831-6
24. Karling P, Danielsson A, Adolfsson R, Norrback KF. No difference in symptoms of irritable bowel syndrome between healthy subjects and patients with recurrent depression in remission. *Neurogastroenterol Motil.* (2007) 19:896–904. doi: 10.1111/j.1365-2982.2007.00967.x
25. Puchalska P, Crawford PA. Multi-dimensional Roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab.* (2017) 25:262–84. doi: 10.1016/j.cmet.2016.12.022
26. Hasan-Olive MM, Lauritzen KH, Ali M, Rasmussen LJ, Storm-Mathisen J, Bergersen LH. A Ketogenic diet improves mitochondrial biogenesis and bioenergetics via the PGC1α-SIRT3-UCP2 Axis. *Neurochem Res.* (2019) 44:22–37. doi: 10.1007/s11064-018-2588-6
27. Kim DY, Abdelwahab MG, Lee SH, O'Neill D, Thompson RJ, Duff HJ, et al. Ketones prevent oxidative impairment of hippocampal synaptic integrity through KATP channels. *PLoS ONE.* (2015) 10:e0119316. doi: 10.1371/journal.pone.0119316
28. Włodarczyk A, Wiglusz MS, Cubała WJ. Ketogenic diet for schizophrenia: nutritional approach to antipsychotic treatment. *Med Hypotheses.* (2018) 118:74–7. doi: 10.1016/j.mehy.2018.06.022
29. Phelps JR, Siemers SV, El-Mallakh RS. The ketogenic diet for type II bipolar disorder. *Neurocase.* (2013) 19:423–6. doi: 10.1080/13554794.2012.690421
30. Bostock EC, Kirkby KC, Taylor BV. The current status of the ketogenic diet in psychiatry. *Front Psychiatry.* (2017) 8:43. doi: 10.3389/fpsyt.2017.00043
31. Brietzke E, Mansur RB, Subramaniapillai M, Balanzá-Martínez V, Vinberg M, González-Pinto A, et al. Ketogenic diet as a metabolic therapy for mood disorders: evidence and developments. *Neurosci Biobehav Rev.* (2018) 94:11–6. doi: 10.1016/j.neubiorev.2018.07.020
32. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev.* (2011) 35:804–17. doi: 10.1016/j.neubiorev.2010.10.001
33. Davis J, Moylan S, Harvey BH, Maes M, Berk M. Neuroprogression in schizophrenia: pathways underpinning clinical staging and therapeutic corollaries. *Aust N Z J Psychiatry.* (2014) 48:512–29. doi: 10.1177/0004867414533012
34. Haroon E, Miller AH. Inflammation effects on brain glutamate in depression: mechanistic considerations and treatment implications. *Curr Top Behav Neurosci.* (2017) 31:173–98. doi: 10.1007/7854_2016_40
35. Maes M, Leonard B, Fernandez A, Kubera M, Nowak G, Veerhuis R, et al. (Neuro)inflammation and neuroprogression as new pathways and drug targets in depression: from antioxidants to

kinase inhibitors. *Prog Neuropsychopharmacol Biol Psychiatry*. (2011) 35:659–63. doi: 10.1016/j.pnpbp.2011.02.019
36. Bhattarai Y, Muniz Pedrogo DA, Kashyap PC. Irritable bowel syndrome: a gut microbiota-related disorder? *Am J Physiol Gastrointest Liver Physiol*. (2017) 312:G52–g62. doi: 10.1152/ajpgi.00338.2016
37. Abenavoli L, Scarpellini E, Colica C, Boccuto L, Salehi B, Sharifi-Rad J, et al. Gut microbiota and obesity: a role for probiotics. *Nutrients*. (2019) 11:2690. doi: 10.3390/nu11112690
38. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe*. (2008) 3:213–23. doi: 10.1016/j.chom.2008.02.015
39. Velagapudi VR, Hezaveh R, Reigstad CS, Gopalacharyulu P, Yetukuri L, Islam S, et al. The gut microbiota modulates host energy and lipid metabolism in mice. *J Lipid Res*. (2010) 51:1101–12. doi: 10.1194/jlr.M002774
40. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc Natl Acad Sci U S A*. (2009) 106:3698–703. doi: 10.1073/pnas.0812874106
41. Dodd D, Spitzer MH, Van Treuren W, Merrill BD, Hryckowian AJ, Higginbottom SK, et al. A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. *Nature*. (2017) 551:648–52. doi: 10.1038/nature24661

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

MINI REVIEW
published: 26 May 2022
doi: 10.3389/fpsyt.2022.925983

Dissociative Symptoms and Disorders in Patients With Bipolar Disorders: A Scoping Review

*Ravi Philip Rajkumar**

Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India

Dissociative disorders are an important group of trauma-related disorders associated with significant disability. The co-occurrence of dissociative disorders (DD) and symptoms (DS) in bipolar disorder has been relatively understudied, but there is some evidence that this comorbidity may have significant mechanistic and clinical implications. This paper presents the results of a scoping review of the frequency and correlates of DS and DD in bipolar disorder. Based on the available evidence, DS/DD are more common in bipolar disorder than in healthy controls or in unipolar depression, are related to childhood trauma, and are associated with psychotic symptoms, suicide attempts, and a poorer response to treatment in patients with bipolar disorder. The implications of these findings, and possible mechanistic pathways underlying them, are discussed based on the current literature. Clinicians should be aware of the frequent occurrence of significant DS or DD when treating patients with bipolar disorder. A tentative future research agenda for this field, based on clinical, risk factor-related and neurobiological considerations, is outlined.

Keywords: bipolar disorders, dissociative disorders, depression, depersonalization, derealization, comorbidity

OPEN ACCESS

Edited by:
Michele Fornaro,
University of Naples Federico II, Italy

Reviewed by:
Jacopo Lisoni,
Asst Spedali Civili di Brescia, Italy

***Correspondence:**
Ravi Philip Rajkumar
ravi.psych@gmail.com

Specialty section:
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

Received: *22 April 2022*
Accepted: *03 May 2022*
Published: *26 May 2022*

Citation:
Rajkumar RP (2022) Dissociative Symptoms and Disorders in Patients With Bipolar Disorders: A Scoping Review. Front. Psychiatry 13:925983. doi: 10.3389/fpsyt.2022.925983

INTRODUCTION

Bipolar disorders are a group of mental illnesses characterized by recurrent episodes of elevated and depressed mood, associated with significant levels of morbidity and an elevated mortality risk (1). Comorbidity with other psychiatric disorders is seen in over 50% of patients with BD, particularly with anxiety, attention-deficit/hyperactivity and substance use disorders (2). The presence of comorbid diagnoses in BD is associated with poorer treatment response and a more severe illness course; patients with these diagnoses often require more intensive or complex treatment regimens (3–6).

Dissociative disorders (DD), which are characterized by disruption or discontinuity in the integration of one's consciousness, memory, identity and behavior, are associated with risks of hospitalization, self-injury and suicide comparable to BD (7). Though the comorbidity of DD and BD has been relatively under-studied (8), there is evidence from the literature of several potential clinical and mechanistic links between them. BD and DD appear to share a genetic substrate to some extent (9, 10) and the onset of symptoms of DD may be a herald of subsequent BD in adolescents (11, 12). DD may be underdiagnosed in patients with BD because of diagnostic criteria that do not allow DD to be diagnosed in the presence of depression (13), confusion arising from similar symptoms (14), or a reluctance to diagnose DD among mental health professionals (15). A further problem is posed by patients with BD who have features of dissociation that are clinically significant, but do not fulfill criteria for DD; these are referred to as "pathological dissociation" or "dissociative symptoms" (DS).

The present of DD or DS in BD raises several important questions. How frequent and severe is this comorbidity? What is the impact of DD/DS on the clinical features and prognosis of BD? Are there any specific environmental risk factors, such as childhood adversity, that are associated with the presence of DD/DS? Are DD/DS in BD associated with specific genetic factors or other biomarkers? The current scoping review aims to address these questions in a preliminary manner.

METHODOLOGY

Given the lack of a single specific question and the paucity of literature in this area, a scoping review was carried out instead of a systematic review (16). This review was carried out in accordance with the PRISMA guideline for scoping reviews (PRISMA-ScR) (17). The PubMed, Scopus and ScienceDirect databases were searched using combinations of the key words "bipolar disorder", "bipolar disorders", "bipolar spectrum", "bipolar I disorder", "bipolar II disorder" in association with "dissociative disorders", "dissociative amnesia", "dissociative identity disorder", "depersonalization", "derealization", "dissociative symptoms", "pathological dissociation". All studies published up to April 15, 2022 were included in this review. Studies were included if they measured the frequency and/or correlates of the presence of DD/DS in BD, with or without the inclusion of comparator groups. Any study that provided information on the frequency, severity, clinical impact, association with environmental risk factors, or neurobiological correlates of DS/DD in patients with bipolar disorder was included in this review. Case reports/series, editorials, commentaries and general review articles were excluded.

A total of 471 citations were retrieved; after removal of duplicates, 333 citations were screened; after exclusion of 226 unrelated abstracts, 107 citations were tabulated and their full text was examined for relevance. Of these, 27 were included in the final review (18–44). This process is illustrated through a PRISMA-ScR flow diagram in **Figure 1**.

Following tabulation, study results were sorted thematically according to the objectives of this review, as follows:

- Frequency of comorbid DD in BD or vice versa
- Frequency of significant DS in BD

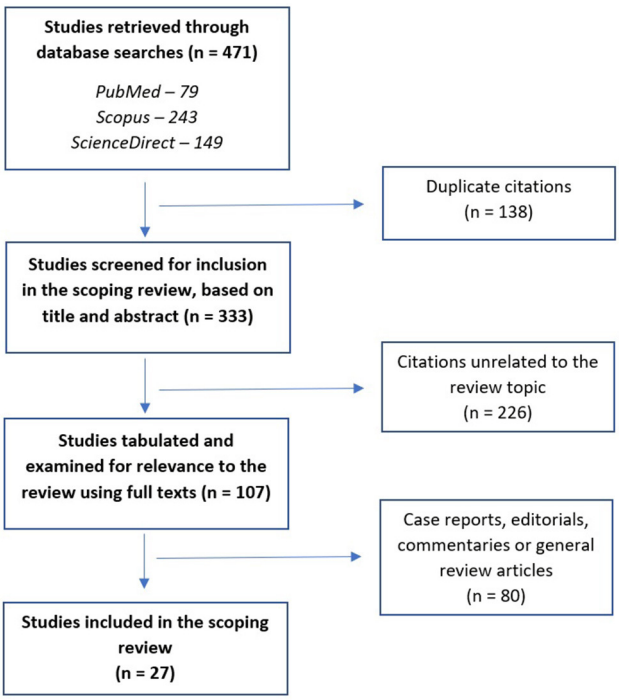


FIGURE 1 | PRISMA-ScR flow diagram for the current scoping review.

- Comparison of DD/DS in BD compared to other groups (major depression, other psychiatric diagnoses, healthy controls)
- Associations with BD subtype (e.g. type I vs type II)
- Associations with BD course (e.g., age at onset, number of episodes)
- Associations with BD symptomatology (e.g., mixed features, psychotic symptoms, suicide attempts)
- Associations with BD outcome (e.g., treatment response, disability, quality of life)
- Associations with other comorbidities in BD (e.g., anxiety disorders, substance use disorders)
- Associations with environmental factors in BD (e.g., childhood trauma, current stressors)
- Associations with other psychological variables (e.g., temperament, personality traits)
- Associations with neuropsychological deficits in BD (e.g., attention or memory deficits)
- Associations with genetic or other biological markers (e.g., specific genetic polymorphisms, levels of hormones or inflammatory markers)

The same schema was followed when reporting the results.

RESULTS

A complete description of the included studies is provided, in chronological order, in **Table 1**.

Abbreviations: AAO, age at onset; BD, bipolar disorders; BD-I, bipolar I disorder; BD-II, bipolar II disorder; BDNF, brain-derived neurotrophic factor; CADSS, Clinician-Administered Dissociative States Scale; CDS, Cambridge Depersonalization Scale; COMT, catechol O-methyltransferase; DAT, dopamine transporter; DID, dissociative identity disorder; DRD4, dopamine type 4 receptor; DD, dissociative disorders; DD-NOS, dissociative disorder not otherwise specified; DES, Dissociative Experiences Scale; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition; HAM-D, Hamilton Rating Scale for Depression; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; SCI-DER, Structured Clinical Interview for Depersonalization/Derealization Spectrum; SCL-90-R, Symptom Checkist-90 Revised; SDQ-20, Somatoform Dissociation Questionnaire-20; SERT, serotonin transporter.

TABLE 1 | Studies examining the association between dissociative symptoms or disorders and bipolar disorder, with a summary of their key findings.

References	Study population and sample size	Variables or outcomes studied	Results
Nijenhuis et al. (18)	Patients with BD ($n = 41$) and DD ($n = 51$)	DS severity across groups, rated using DES	DES scores higher in DD than in BD; significant DS in 10% of BD patients.
Nijenhuis et al. (19)	Patients with BD ($n = 23$), DD ($n = 44$), somatoform disorders ($n = 47$), eating disorders ($n = 50$), and other psychiatric diagnoses ($n = 45$)	DS severity across groups, rated using DES; somatoform DS severity across groups, rated using SDQ-20;	DES and SDQ-20 positively correlated; DES scores significantly lower in BD than in DD; DES comparable in BD and somatoform disorders; SDQ-20 significantly lower in BD than in somatoform disorders and DD.
Hlastala & McClellan (20)	Youth with psychotic BD ($n = 22$), schizophrenia ($n = 27$) and atypical psychosis ($n = 20$)	DS severity across groups, rated using DES	DES scores higher in atypical psychosis than in BD or schizophrenia.
Johnson et al. (21)	Community-dwelling adults ($n = 658$)	Prevalence and comorbidities of dissociative disorders as per DSM-IV	Diagnosis of dissociative disorder 2.4 times more likely in those with a mood disorder (unipolar depression or BD).
Oedegaard et al. (22)	In- and out-patients with BD-II ($n = 24$) and MDD ($n = 41$)	DS severity across groups, rated using DES; association with temperament and comorbid diagnoses.	DES scores higher in BD-II than in unipolar depression; cyclothymic temperament associated with higher DES scores; pathological dissociation associated with comorbid OCD
Savitz et al. (23)	Patients with BD-I ($n = 31$), BD-II ($n = 16$), and their first-degree relatives with MDD ($n = 64$), other psychiatric diagnoses ($n = 17$) or no psychiatric diagnosis ($n = 50$)	DS severity across groups, rating using DES; association with childhood trauma and polymorphisms of *BDNF, COMT*, *DAT, DRD4,* and *SERT* genes.	DES scores higher in BD-I and BD-II than in relatives with no or "other" diagnoses; significant interaction between *COMT* genotype and childhood trauma associated with DES score; additive effect of *BDNF* genotype on DES score.
Mula et al. (24)	Patients with BD-I ($n = 43$) and BD-II ($n = 48$), euthymic	DS severity rated using DES; depersonalization symptom severity using SCI-DER; association with temperament, illness course and comorbidities	DES and SCI-DER scores comparable in BD-I and BD-II; no association of DES or SCI-DER scores with temperament; DES and SCI-DER scores associated with earlier AAO; higher SCI-DER scores in BD with comorbid panic disorder.
Latalova et al. (25)	Patients with BD, euthymic ($n = 23$)	DS severity rated using DES; association with illness course, tests of attention, verbal fluency and executive function, and quality of life.	DES scores associated with higher number of manic episodes, higher mean mood stabilizer dosage, and lower quality of life in the "social activities" domain. No correlation between DES and cognition.
Mula et al. (26)	Patients with mood and anxiety disorders ($n = 258$) including BD-I ($n = 43$) and BD-II ($n = 48$)	Depersonalization symptom severity using SCI-DER; distinction between depersonalization and anhedonia	SCI-DER scores higher in BD than in unipolar depression; SCI-DER score associated with earlier AAO in BD.
Chien et al. (27)	College students ($n = 2,731$)	Psychiatric symptoms as per DSM-IV using the Adult Self Report Inventory-4	Significant positive correlation between symptoms of bipolar and dissociative disorders independent of gender.
Latalova et al. (28)	Patients with BD, euthymic ($n = 41$), healthy controls ($n = 198$)	DS severity rated using DES; association with demographic variables and illness course.	Significant dissociation (DES > 30) in 51.2% of BD patients; DES total and sub-scores significantly higher in BD than in controls; pathological dissociation associated with earlier AAO.
Weber et al. (29)	Discharge records of patients with BD ($n = 27,054$) compared to those with other diagnoses ($n = 2,325,247$)	Presence of comorbid "anxiety, dissociative and somatoform disorders" in BD; comparison of morbidity between BD and those with other diagnoses	"Anxiety, dissociative and somatoform disorders" identified in 11.4% of BD discharge records; "anxiety, dissociative and somatoform disorders" associated with 2.8 times greater morbidity in BD than in those with other diagnoses.
Souery et al. (30)	Patients with BD-I ($n = 104$), BD-II ($n = 64$), and MDD ($n = 123$; 53 with family history of BD)	Depersonalization symptom severity across groups, rated using item 19 of HAM-D	Depersonalization symptom severity greater in BD-I than in BD-II or MDD.
Macri et al. (31)	Outpatients with BD ($n = 17$), MDD ($n = 18$), anxiety disorders ($n = 32$), adjustment disorders ($n = 11$) and somatoform disorders ($n = 5$)	DS severity rated using DES; association with severity of depression and psychopathological domains on SCL-90-R	No association between DS severity and depression severity; total DES score positively correlated with all nine domains of SCL-90-R and with overall global severity of illness across diagnoses.
Dorahy et al. (32)	Patients with dissociative disorder ($n = 39$), complex PTSD ($n = 13$) and mood disorders ($n = 21$)	DS severity across groups, rated using DES	Dissociative symptoms higher in the dissociative disorder group than in the complex PTSD or mood disorder groups.
Eryilmaz et al. (33)	Patients with BD-II, euthymic ($n = 33$), healthy controls ($n = 50$)	DS severity across groups, rated using DES; association with childhood trauma and obsessive-compulsive symptoms	Significant dissociation (DES > 30) in 15.2% of BD-II patients; dissociative symptoms higher in BD-II than controls; DES correlated with scores for childhood trauma and OCD symptoms in BD-II

(Continued)

TABLE 1 | Continued

References	Study population and sample size	Variables or outcomes studied	Results
Hariri et al. (34)	Patients with BD, euthymic ($n = 200$), healthy controls ($n = 50$)	DS severity across groups, rated using DES	Significant dissociation (DES > 30) in 19.5% of BD patients; depersonalization/amnesia symptoms associated with earlier AAO and longer duration of BD; absorption/identity symptoms associated with earlier AAO.
Yayla et al. (35)	Patients with conversion disorder ($n = 54$)	Prevalence of DSM-IV DD and comorbidities	27.8% of patients with DD had comorbid BD; BD more common in patients with DD.
Bayes et al. (36)	Patients with BD or borderline personality disorder ($n = 226$)	Depersonalization symptoms (self-reported)	Depersonalization symptoms more common in borderline personality disorder than in BD.
Yilmaz et al. (37)	Patients with BD-euthymic ($n = 70$), healthy controls ($n = 70$)	DS severity across groups as rated using DES; association with childhood trauma, illness course and alexithymia	DES scores higher in BD than in healthy controls; DES score significantly associated with episode frequency and alexithymia but not with childhood trauma.
Chatterjee et al. (38)	Patients with BD-depression ($n = 35$) and recurrent MDD ($n = 36$)	DS severity as rated using DES-II	DS more severe in BD than in unipolar depression; no correlation of DES-II with AAO, illness duration or number of episodes in BD.
Kefeli et al. (39)	Patients with BD-I-euthymic ($n = 40$), healthy controls ($n = 40$)	DS severity as rated using DES-II; association with number of manic and depressive episodes	Significant dissociation (DES > 30) in 20% of BD-I as against 2.5% controls; absorption/imaginative symptoms negatively associated with BD-I; somatoform dissociation associated with number of depressive episodes.
Tekin et al. (40)	Patients with BD, euthymic ($n = 51$), healthy controls ($n = 49$)	DD diagnosis as per DSM-IV criteria; DS severity across groups as rated using DES; association with illness course	35.4% of BD patients qualified for a diagnosis of comorbid DD (depersonalization disorder 17.6%, DD-NOS 15.6%, dissociative amnesia 7.8%, DID 3.9%, dissociative fugue 1.9%); DES scores significantly higher in BD than in controls; DES total score associated with number of suicide attempts and earlier AAO in BD group.
Tuineag et al. (41)	Outpatients with BD-I ($n = 41$), BD-II ($n = 27$) or other BD ($n = 5$)	DS severity as rated using CDS; association with childhood trauma and symptoms of mania, depression and anxiety.	CDS valid for the assessment of DS in BD; CDS total score associated with childhood trauma and symptoms of depression, social anxiety, and panic disorder.
Steardo et al. (42)	Outpatients with BD-I ($n = 55$) and BD-II ($n = 45$)	DS severity as rated using DES-II; association with demographic variables, illness course and treatment response.	DES scores significantly higher in BD-I than in BD-II; DES score significantly associated with number of episodes, presence of mixed or psychotic features, history of suicide attempts or aggressive behavior, symptoms of anxiety, seasonality, antidepressant-induced mania, and poorer treatment response.
Stone et al. (43)	Patients with psychotic BD ($n = 53$) or schizophrenia ($n = 47$), healthy controls ($n = 51$), recruited during the COVID-19 pandemic	DS severity as rated using DES-II; association with childhood trauma and pandemic-related adversities.	DES scores significantly higher in BD and schizophrenia than in healthy controls; significant dissociation (DES > 30) in 17% of BD; no significant association between DES and childhood trauma or pandemic-related adversities.
Li et al. (44)	Inpatients with BD-depression ($n = 32$) and MDD ($n = 59$)	DS severity as rated using CADSS; association with parenting style, betrayal trauma and psychotic symptoms	DS of equal severity in BD and unipolar depression; DS associated with betrayal trauma and severity of psychotic symptoms.

Characteristics of the Included Studies

The majority of the studies included in this review ($n = 21$) were cross-sectional clinical studies measuring the severity or correlates of DS in patients with BD. Three studies examined the association between syndromal DD and BD (21, 29, 40), while one study each examined associations with cognitive test performance (25) and polymorphisms of specific genes considered to be related to dissociation (23).

Comorbidity Between BD and DD

Only one study directly measured the frequency of DSM-IV categorical diagnoses of DD in patients with BD. In this study, 35.4% of BD patients fulfilled criteria for one or more DD, with depersonalization disorder (17.6%) being the most frequent (40). A community-based study found that DD were 2.4 times more likely to be diagnosed in patients with mood disorders, but did not distinguish between BD and unipolar depression (21). A study of patients with conversion disorder found a significant association between comorbid diagnoses of DD and BD (35). Finally, a study of discharge records found that 11.4% of patients discharged with BD received a comorbid diagnosis of "anxiety, somatoform or dissociative disorder" as per ICD-9 criteria, but details of individual diagnoses within this group were not reported by the authors (29).

Presence of Clinically Significant DS in BD

Of the six studies providing estimates of clinically significant DS in BD, as indicated by symptom scores above a specified cut-off, five yielded very similar values in the range of 10–20% (18, 33, 34, 39, 43). A single study yielded a much higher estimate of 51%, but in this study, the control group also reported high levels of DS (24%), suggesting concerns related to methodology or sample selection (28).

Comparisons of DS Severity Between BD and Other Disorders

Five studies have compared the severity of DS in patients with BD and major depressive disorder (MDD), have measured DS during depressive episodes. In four of these studies, DS were more prominent in BD than in MDD (22, 26, 30, 38), while in the other, they were comparable (44). Studies comparing the severity of DS between BD and other, non-affective psychiatric disorders found that DS were significantly less in BD than in somatoform disorders and DD (18, 19, 32), complex post-traumatic stress disorder (PTSD) (32), atypical psychosis in adolescents (20), and borderline personality disorder (36). DS were comparable in BD and schizophrenia in a single study (43). However, DS scores were significantly higher in patients with BD than in their asymptomatic first-degree relatives (23) and were consistently higher in BD than in healthy controls (28, 33, 34, 37, 39, 43).

Relationship of DS to BD Subtype

Though some researchers have reported no difference in DS severity scores between BD-I and BD-II (23, 24), there is some evidence that DS and particularly depersonalization symptoms may be more severe in BD-I (30, 42). Only one study assessed DS in patients with other BD subtypes (BD-III and BD not otherwise specified) along with BD-I and BD-II, but the small number of cases in this subgroup precluded a meaningful comparison (41).

Relationship of DS to Symptomatology in BD

DS scores have been associated with the severity of psychotic symptoms (42, 44); both positive and null results have been reported for associations between DS and depressive symptom severity (31, 41). DS severity has also been associated with general symptom severity across psychopathological dimensions (31), with the severity of symptoms of social anxiety, panic disorder and obsessive-compulsive disorder (33, 41), with the presence of mixed symptoms (42), with suicide attempts (40, 42) and with aggression (42).

Relationship of DS/DD to Illness Course in BD

Five studies found a negative correlation between the severity of DS and the age at onset of BD (AAO), suggesting an association between dissociation and an early AAO (24, 26, 28, 34, 40). This association appeared to be more specific for depersonalization-related symptoms (24, 26, 34). Only one study reported no association between DS and AAO in BD (38). Associations between DS severity and episode frequency (37), total number of episodes (42) and frequency of manic (25) and depressive episodes (39) have been reported in individual studies. However, a lack of association with episode number has also been reported (38).

Relationship of DS to Outcome in BD

The severity of DS appears to be associated with treatment response; associations with a higher dose requirement for mood stabilizers (25), with a higher risk of antidepressant-induced mania (42) and with a poorer response to treatment (42) have all been observed. DS are also associated with a poorer quality of life in the "social activities" domain in euthymic BD patients (25).

Relationship of DS to Other Comorbidities in BD

Higher DS scores have been associated with elevated rates of comorbid obsessive-compulsive disorder (OCD) (22) and panic disorder (24) in BD; no other specific associations with any comorbid diagnosis have been reported.

Relationship of DS to Environmental Risk Factors in BD

Six studies have examined the association between childhood abuse or neglect and DS in BD; four of these found a positive association between childhood trauma and DS severity (23, 33, 41, 44), while two failed to do so (37, 43). A single study examined the relationship between DS and current stress related to the COVID-19 pandemic, but did not find any significant association between the two (43).

Relationship of DS to Temperament and Other Psychological Variables in BD

Cyclothymic temperament, considered to be a developmental precursor of BD, was associated with the presence of DS in BD patients in one study (22) but not in another (24). DS severity has also been associated with measures of alexithymia in BD (37).

Neuropsychological Correlates of DS in BD

A study examining the association between DS and performance on tests of cognition (attention, concentration, executive function and verbal fluency) found no significant association between DS severity and scores on these tests (25).

Genetic and Biomarker Studies of DS in BD

Only one study has examined the potential genetic correlates of DS in BD; in this study, an interaction between childhood trauma and a functional polymorphism of the *COMT* gene, as well as an additive effect of the *BDNF* gene, was found to predict the severity of DS (23). No other study of any specific biomarker associated with DS/DD in BD has been conducted to date.

DISCUSSION

Certain features emerge clearly from an overview of the current literature. A significant minority of patients (10–20%) with bipolar disorder experience significant DS, even during the euthymic phase. The overall severity of DS is higher in BD than in healthy controls and in major depression, but is lower

in BD when compared with "trauma spectrum disorders" such as DD, complex PTSD and borderline personality disorder. When considering the clinical profile of BD, replicated results suggest that DS are associated with psychotic symptoms, suicide attempts, and a poorer response to treatment. DS also appear to be associated with the severity of childhood trauma in patients with BD. Results related to other symptom domains, episode number and frequency, and quality of life, though of interest, require replication.

The above findings are consistent with the existing literature on DS/DD. Both pathological dissociation and DD are considered part of the "trauma spectrum" of disorders, which are related to exposure to traumatic stress, particularly in childhood (45). This group also includes PTSD and borderline personality disorder; it is perhaps significant that these conditions are also often comorbid with BD (46, 47). Given that childhood adversity is itself a risk factor for BD (48) and was associated with DS in the reviewed studies, this factor may explain a significant proportion of the co-occurrence of DD/DS and BD. Moreover, dissociation is an important mediator of the links between childhood abuse and both psychotic symptoms (49) and suicide (50), which is consistent with the findings observed in patients with BD.

Recent research has shed some light on the neurobiological correlates of dissociative symptoms (51). Some of the replicated biomarkers of pathological dissociation, such as reduced hippocampal and thalamic volumes and elevated peripheral levels of oxytocin, have also been identified in bipolar disorder (52–54), suggesting common neuroanatomical and biochemical substrates for these conditions. It should however be noted that for other biomarkers of dissociation, such as levels of tumor necrosis factor alpha, findings in bipolar disorder are in the opposite direction (55). This suggests that there may be shared mechanistic pathways, but not a complete overlap, between BD and dissociative symptoms.

Besides exposure to childhood trauma or other environmental stressors, the link between DS/DD and BD may be partly mediated through genetic vulnerability. While earlier researchers suggested that this might result from variations in single genes, such as the serotonin transporter (56), more recent results suggest that the overlap between bipolar and dissociative disorders may be polygenic in origin (10).

These findings must be interpreted in the light of important limitations in study design and methodology in the existing literature. The majority of reviewed studies are cross-sectional and focus on clinical variables, with very few studies examining neuropsychological or neurobiological correlates of DD or DS in BD. Most studies have been conducted in remitted, euthymic or clinically stable BD patients, and have measured DS using standardized scales instead diagnosing comorbid DD using standard criteria. There is also substantial heterogeneity in the measurement of DS, with some studies focusing on a subset of DS such as depersonalization/derealization or somatoform dissociation. Sample sizes for BD were generally low (mean: 61.2 $\pm$ 47.8), suggesting that some studies may have been underpowered to detect significant differences. Further, in some studies, associations between DS and clinical or environmental variables of interest were not estimated even when the data was available. These factors limit both the value of the conclusions that can be drawn from individual studies and the likelihood of their replication, and suggest the need for better designs even if the research questions are purely clinical in nature.

A further limitation arises from the fact that the link between DS/DD and BD may be non-specific. Dissociative symptoms of severity comparable to or slightly greater than those reported in BD have been observed in a wide range of psychiatric disorders, including schizophrenia, anxiety disorders, eating disorders and substance use disorders (57). These findings suggest that dissociation may be better considered from a dimensional rather than a categorical perspective, or that it may be related to a common genetic substrate that cuts across traditional psychiatric diagnoses (58).

Despite these limitations, the above review suggests that the presence of DS/DD in patients with BD may have significant clinical and research implications. From a clinical perspective, practitioners should be aware of the co-occurrence of these conditions, and maintain a high index of clinical suspicion; in cases of doubt, a standardized rating scale such as the DES can aid decision-making. Given the replicated associations with psychotic symptoms, suicidality, and poor treatment response, these patients may require more intensive clinical management. Lithium therapy, which has been shown to reverse the hippocampal and thalamic volume reductions common to bipolar disorder and dissociation (51, 52), may be a useful therapeutic option. Bipolar patients with DS/DD should be screened for other comorbid anxiety disorders as well as post-traumatic stress disorder (22, 24, 33, 41). Given the link between childhood trauma and dissociation in BD, a sensitive inquiry into possible childhood abuse or neglect should be made when patients are clinically stable. Finally, when there are significant DS or a syndromal DD, appropriate psychological interventions should be provided (59).

From a research perspective, the following areas require particular attention in the study of the links between dissociation and bipolarity:

- Replications of findings related to clinical and psychological variables of interest, such as affective temperaments, alexithymia, cycle length and the presence of mixed features
- Accurate studies of the prevalence of comorbid DD in BD, and of comorbid BD in DD, using standard diagnostic criteria
- Longitudinal studies of the impact of DS or DD on the course and outcome of BD
- Studies of high-risk youth (e.g., with a family history of BD or with a history of childhood abuse) with DS or DD, to assess their subsequent risk of BD and the possibility of early intervention (12, 60)
- Studies of structural, functional and biochemical markers of the link between BD and DD; areas that could be immediately explored include associations with peripheral levels of cytokines (61) and functional brain imaging studies focusing on key frontal and subcortical regions implicated in both disorders (49, 62)
- Assessment of the utility of a dimensional rather than a categorical approach to the study of dissociation in patients with BD, and of the correlations between DS and other symptom dimensions in BD (63)

- Genome-wide association studies using either a narrower definition of DD (i.e., without lumping them with anxiety and somatoform disorders) or a continuous measure of DS, to identify specific and shared genetic loci associated with vulnerability to pathological dissociation in patients with BD
- Evaluation of the efficacy of specific pharmacological (mood stabilizer, antipsychotic), brain stimulation (rTMS) and psychotherapeutic (trauma-focused) approaches in patients with BD and DD/DS (64, 65).

CONCLUSION

Though research on dissociative symptoms and disorders in patients with bipolar disorders is still in its infancy, existing evidence suggests that these symptoms are significantly associated with both risk factors—particularly childhood abuse—and a specific illness profile in bipolar disorder. It is hoped that the findings reviewed and summarized above will be of use to clinicians working with patients with bipolar disorder. Moreover, the tentative research agenda outlined above could improve our understanding of this specific comorbidity, leading to improved strategies for early intervention as well as treatment in subsequent stages of bipolar disorder.

AUTHOR CONTRIBUTIONS

RR selected the review topic and method, conducted the literature search and article selection, analyzed and summarized the results, and wrote and edited the manuscript.

REFERENCES

1. GBD 2019 Mental Disorders Collaborators. Global, regional and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Psychiatry.* (2022) 9:137–50. doi: 10.1016/S2215-0366(21)00395-3
2. Frías Á, Palma C, Farriols N. Comorbidity in pediatric bipolar disorder: prevalence, clinical impact, etiology and treatment. *J Affect Disord.* (2015) 174:378–89. doi: 10.1016/j.jad.2014.12.008
3. Preti A, Vrublevska J, Veroniki AA, Huedo-Medina TB, Fountoulakis KN. Prevalence, impact and treatment of generalised anxiety disorder in bipolar disorder: a systematic review and meta-analysis. *Evid Based Ment Health.* (2016) 19:73–81. doi: 10.1136/eb-2016-102412
4. Consoli A, Bouzamondo A, Guilé JM, Lechat P, Cohen D. Comorbidity with ADHD decreases response to pharmacotherapy in children and adolescents with acute mania: evidence from a metaanalysis. *Can J Psychiatry.* (2007) 52:323–8. doi: 10.1177/070674370705200507
5. Messer T, Lammers G, Müller-Siecheneder F, Schmidt RF, Latifi S. Substance abuse in patients with bipolar disorder: a systematic review and meta-analysis. *Psychiatry Res.* (2017) 253:338–50. doi: 10.1016/j.psychres.2017.02.067
6. Berk M, Ng F, Wang WV, et al. Going up in smoke: tobacco smoking is associated with worse treatment outcomes in mania. *J Affect Disord.* (2008) 110:126–34. doi: 10.1016/j.jad.2008.01.018
7. Gonzalez Vazquez AI, Seijo Ameneiros N, Díaz Del Valle JC, Lopez Fernandez E, Santed Germán MA. Revisiting the concept of severe mental illness: severity indicators and healthcare spending in psychotic, depressive and dissociative disorders. *J Ment Health.* (2020) 29:670–6. doi: 10.1080/09638237.2017.1340615
8. Mauritz MW, Goossens PJJ, Draijer N, van Achterberg T. Prevalence of interpersonal trauma exposure and trauma-related disorders in severe mental illnesses. *Eur J Psychotraumatol.* (2013) 4:19985. doi: 10.3402/ejpt.v4i0.19985
9. Palomo T, Kostrzewa RM, Beninger RJ, Archer T. Genetic variation and shared biological susceptibility underlying comorbidity in neuropsychiatry. *Neurotox Res.* (2007) 12:29–42. doi: 10.1007/BF03033899
10. Kember RL, Merikangas AK, Verma SS, Verma A, Judy R, Damrauer SM, et al. Polygenic risk of psychiatric disorders exhibits cross-trait associations in electronic health record data from European ancestry individuals. *Biol Psychiatry.* (2021) 89:236–45. doi: 10.1016/j.biopsych.2020.06.026
11. Ghosal MK, Guha P, Sinha M, Majumdar D, Sengupta P. Conversion (dissociative) symptoms as a presenting feature in early onset bipolar disorder: a case series. *BMJ Case Rep.* (2009) 2009:bcr01.2009.1448. doi: 10.1136/bcr.01.2009.1448
12. Leopold K, Ritter P, Correll CU, Marx C, Ozgurdal S, Juckel G, et al. Risk constellations prior to the development of bipolar disorders: rationale of a new risk assessment tool. *J Affect Disord.* (2012) 136:1000–10. doi: 10.1016/j.jad.2011.06.043
13. Spiegel D, Loewenstein RJ, Lewis-Fernández R, Sar V, Simeon D, Vermetten E, et al. Dissociative disorders in DSM-5. *Depress Anxiety.* (2011) 28:824–52. doi: 10.1002/da.20874
14. Savitz J, Solms M, Pietersen E, Ramesar R, Flor-Henry P. Dissociative identity disorder associated with mania and change in handedness. *Cog Behav Neurol.* (2004) 17:233–7.
15. Loewenstein RJ. Dissociation debates: everything you know is wrong. *Dialogues Clin Neurosci.* (2018) 20:229–42. doi: 10.31887/DCNS.2018.20.3/rloewenstein
16. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* (2018) 18:143. doi: 10.1186/s12874-018-0611-x
17. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med.* (2018) 169:467–73. doi: 10.7326/M18-0850
18. Nijenhuis ER, Spinhoven P, van Dyck R, van der Hart O, de Graaf A, Knoppert EAM. Dissociative pathology discriminates between bipolar mood disorder and dissociative disorder. *Br J Psychiatry.* (1997) 170:581. doi: 10.1192/S0007125000259187
19. Nijenhuis ER, van Dyck R, Spinhoven P, van der Hart O, Chatrou M, Vanderlinden J, et al. Somatoform dissociation discriminates among diagnostic categories over and above general psychopathology. *Aust N Z J Psychiatry.* (1999) 33:511–20. doi: 10.1080/j.1440-1614.1999.00601.x
20. Hlastala SA, McClellan J. Phenomenology and diagnostic stability of youths with atypical psychotic symptoms. *J Child Adolesc Psychopharmacol.* (2005) 15:497–509. doi: 10.1089/cap.2005.15.497
21. Johnson JG, Cohen P, Kasen S, Brook JS. Dissociative disorders among adults in the community, impaired functioning, and axis I and II comorbidity. *J Psychiatr Res.* (2006) 40:131–40. doi: 10.1016/j.jpsychires.2005.03.003
22. Oedegaard KJ, Neckelmann D, Benazzi F, Syrstad VE, Akiskal HS, Fasmer OB. Dissociative experiences differentiate bipolar-II from unipolar depressed patients: the mediating role of cyclothymia and the type A behaviour speed and impatience subscale. *J Affect Disord.* (2008) 108:207–16. doi: 10.1016/j.jad.2007.10.018
23. Savitz JB, van der Merwe L, Newman TK, Solms M, Stein DJ, Ramesar RS. The relationship between childhood abuse and dissociation. Is it influenced by catechol-O-methyltransferase (COMT) activity? *Int J Neuropsychopharmacol.* (2008) 11:149–61. doi: 10.1017/S1461145707007900
24. Mula M, Pini S, Preve M, Masini M, Giovannini I, Cassano GB. Clinical correlates of depersonalization symptoms in patients with bipolar disorder. *J Affect Disord.* (2009) 115:252–6. doi: 10.1016/j.jad.2008.08.001
25. Latalova K, Prasko J, Diveky T, Kamaradova D, Velartova H. Cognitive dysfunction, dissociation and quality of life in bipolar affective disorders in remission. *Psychiatr Danub.* (2010) 22:528–34.
26. Mula M, Pini S, Calugi S, Preve M, Masini M, Giovannini I, et al. Distinguishing affective depersonalization from anhedonia in

major depression and bipolar disorder. *Compr Psychiatry.* (2010) 51:187–92. doi: 10.1016/j.comppsych.2009.03.009
27. Chien YL, Gau SS, Gadow KD. Sex difference in the rates and co-occurring conditions of psychiatric symptoms in incoming college students in Taiwan. *Compr Psychiatry.* (2011) 52:195–207. doi: 10.1016/j.comppsych.2010.03.009
28. Latalova K, Prasko J, Pastucha P, Grambal A, Kamaradova D, Diveky T, et al. Bipolar affective disorder and dissociation–comparison with healthy controls. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* (2011) 155:181–6. doi: 10.5507/bp.2011.007
29. Weber NS, Fisher JA, Cowan DN, Niebuhr DW. Psychiatric and general medical conditions comorbid with bipolar disorder in the national hospital discharge survey. *Psychiatr Serv.* (2011) 62:1152–8. doi: 10.1176/ps.62.10.pss6210_1152
30. Souery D, Zaninotto L, Calati R, Linotte S, Mendlewicz J, Sentissi O, et al. Depression across mood disorders: review and analysis in a clinical sample. *Compr Psychiatry.* (2012) 53:24–38. doi: 10.1016/j.comppsych.2011.01.010
31. Macri F, Salviati M, Provenzano A, Melcore C, Terlizzi S, Campi S, et al. Psychopathological severity index and dissociative symptomatology in a group of non-psychotic outpatients. *J Psychopathol.* (2013) 19:105–8.
32. Dorahy MJ, Middleton W, Seager L, McGurrin P, Williams M, Chambers R. Dissociation, shame, complex PTSD, child maltreatment and intimate relationship self-concept in dissociative disorder, chronic PTSD and mixed psychiatric groups. *J Affect Disord.* (2015) 172:195–203. doi: 10.1016/j.jad.2014.10.008
33. Eryilmaz G, Kesebir S, Gul IG, Ozten E, Karamustafalioglu KO. Dissociative experiences in bipolar disorder II: are they related to childhood trauma and obsessive-compulsive symptoms? *Arch Clin Psychiatry.* (2015) 42:38–40. doi: 10.1590/0101-60830000000045
34. Hariri AG, Gulec MY, Orengul FFC, Sumbul EA, Elbay RY, Gulec H. Dissociation in bipolar disorder: relationships between clinical variables and childhood trauma. *J Affect Disord.* (2015) 184:104–10. doi: 10.1016/j.jad.2015.05.023
35. Yayla S, Bakim B, Tankaya O, Ozer OA, Karamustafalioglu O, Ertekin H, et al. Psychiatric comorbidity in patients with conversion disorder and presence of dissociative symptoms. *J Trauma Dissociation.* (2015) 16:29–38. doi: 10.1080/15299732.2014.938214
36. Bayes AJ, McGlure G, Fletcher K, Del Moral YERR, Hadzi-Pavlovic D, Stevenson JL, et al. Differentiating the bipolar disorders from borderline personality disorder. *Acta Psychiatr Scand.* (2016) 133:187–95. doi: 10.1111/acps.12509
37. Yilmaz O, Ates MA, Semiz UB, Tutuncu R, Bez Y, Algul A. Childhood traumas in patients with bipolar disorder: association with alexithymia and dissociative experiences. *Anatol J Psychiatry.* (2016) 17:188–95. doi: 10.5455/apd.188358
38. Chatterjee SS, Pal A, Mallik N, Ghosal M, Saha G. Dissociative experience in unipolar and bipolar depression: exploring the great divide. *Clin Psychopharmacol Neurosci.* (2018) 16:262–6. doi: 10.9758/cpn.2018.16.3.262
39. Kefeli MC, Turow RG, Yildirim A, Boysan M. Childhood maltreatment is associated with attachment insecurities, dissociation and alexithymia in bipolar disorder. *Psychiatry Res.* (2018) 260:391–9. doi: 10.1016/j.psychres.2017.12.026
40. Tekin A, Demiryürek EÖ, Güleken MD, Bakim B, Özer ÖA, Karamustafalioglu O. Investigation of the comorbidity of dissociative disorders in patients with bipolar disorder. *Eur Res J.* (2019) 5:667–72. doi: 10.18621/eurj.412272
41. Tuineag M, Therman S, Lindgren M, Rouanet M, Nahon S, Bertrand L, et al. Dissociative symptoms as measured by the Cambridge depersonalization scale in patients with a bipolar disorder. *J Affect Disord.* (2020) 263:187–92. doi: 10.1016/j.jad.2019.11.137
42. Steardo L Jr, Carbone EA, Ventura E, de Filippis R, Luciano M, Segura-Garcia C. Dissociative symptoms in bipolar disorder: impact on clinical course and treatment response. *Front Psychiatry.* (2021) 12:732843. doi: 10.3389/fpsyt.2021.732843
43. Stone LMD, Millman ZB, Öngür D, Shinn AK. The intersection between childhood trauma, the COVID-19 pandemic, and trauma-related and psychotic symptoms in people with psychotic disorders. *Schizophr Bull Open.* (2021) 2:sgab050. doi: 10.1093/schizbullopen/sgab050
44. Li D-J, Hsieh Y-C, Chiu C-D, Lin C-H, Chou L-S. The moderation of maternal parenting on the association of trauma, dissociation, and psychosis in depressive inpatients. *Eur J Psychotraumatol.* (2022) 13:2024974. doi: 10.1080/20008198.2021.2024974
45. Bremner JD, Wittbrodt MT. Stress, the brain, and trauma spectrum disorders. *Int Rev Neurobiol.* (2020) 152:1–22. doi: 10.1016/bs.irn.2020.01.004
46. Fornaro M, Orsolini L, Marini S, De Berardis D, Perna G, Valchera A, et al. The prevalence and predictors of bipolar and borderline personality disorders comorbidity: systematic review and meta-analysis. *J Affect Disord.* (2016) 195:105–18. doi: 10.1016/j.jad.2016.01.040
47. Nabavi B, Mitchell AJ, Nutt D, A. Lifetime prevalence of comorbidity between bipolar affective disorder and anxiety disorders: a meta-analysis of 52 interview-based studies of psychiatric population. *EBioMedicine.* (2015) 2:1405–19. doi: 10.1016/j.ebiom.2015.09.006
48. Palmier-Claus JE, Berry K, Bucci S, Mansell W, Varese F. Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *Br J Psychiatry.* (2016) 209:454–9. doi: 10.1192/bjp.bp.115.179655
49. Williams J, Bucci S, Berry K, Varese F. Psychological mediators of the association between childhood adversities and psychosis: a systematic review. *Clin Psychol Rev.* (2018) 65:175–96. doi: 10.1016/j.cpr.2018.05.009
50. Bertule M, Sebre SB, Kolesovs A. Childhood abuse experiences, depression and dissociation symptoms in relation to suicide attempts and suicidal ideation. *J Trauma Dissociation.* (2021) 22:598–614. doi: 10.1080/15299732.2020.1869652
51. Roydeva MI, Reinders AATS. Biomarkers of Pathological Dissociation: A Systematic Review. *Neurosci Biobehav Rev.* (2021) 123:120–202. doi: 10.1016/j.neubiorev.2020.11.019
52. Lien YJ, Chang HH, Tsai HC, Kuang Yang Y, Lu RB, See Chen P. Plasma oxytocin levels in major depressive and bipolar II disorders. *Psychiatry Res.* (2017) 258:402–6. doi: 10.1016/j.psychres.2017.08.080
53. Otten M, Meeter M. Hippocampal structure and function in individuals with bipolar disorder: a systematic review. *J Affect Disord.* (2015) 174:113–25. doi: 10.1016/j.jad.2014.11.001
54. Radenbach K, Flaig V, Schneider-Axmann T, Usher J, Reith W, Falkai P, et al. Thalamic volumes in patients with bipolar disorder. *Eur Arch Psychiatry Clin Neurosci.* (2010) 260:601–7. doi: 10.1007/s00406-010-0100-7
55. Solmi M, Suresh Sharma M, Osimo EF, Fornaro M, Bortolato B, Croatto G, et al. Peripheral levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-1β across the mood spectrum in bipolar disorder: a meta-analysis of mean differences and variability. *Brain Behav Immun.* (2021) 97:193–203. doi: 10.1016/j.bbi.2021.07.014
56. Kuzelova H, Ptacek R, Macek M Jr. The serotonin transporter gene (5-HTT) variant and psychiatric disorders. *Neuro Endocrin Lett.* (2010) 31:4–10.
57. Lyssenko L, Schmahl C, Bockhacker L, Vonderlin R, Bohus M, Kleindienst N. Dissociation in psychiatric disorders: a meta-analysis of studies using the dissociative experiences scale. *Am J Psychiatry.* (2018) 175:37–46. doi: 10.1176/appi.ajp.2017.17010025
58. Andlauer TFM, Mühleisen TW, Hoffstaedter F, Teumer A, Wiffeld K, Teuber A, et al. Genetic factors influencing a neurobiological substrate for psychiatric disorders. *Transl Psychiatry.* (2021) 11:192. doi: 10.1038/s41398-021-01317-7
59. Ganslev CA, Storebø OJ, Callesen HE, Ruddy R, Søgaard U. Psychosocial interventions for conversion and dissociative disorders in adults. *Cochrane Database Syst Rev.* (2020) 7:CD005331. doi: 10.1002/14651858.CD005331.pub3
60. Brandt JM, Hemager N, Gregersen M, Sondergaard A, Krantz MF, Ohland J, et al. Childhood trauma in children at familial high risk of schizophrenia or bipolar disorder: a longitudinal study. The Danish High Risk and Resilience Study - VIA 7 and VIA 11. *Br J Clin Psychol.* (2022). doi: 10.1111/bjc.12364
61. Bob P, Raboch J, Maes M, Susta M, Pavlat J, Jasova D, et al. Depression, traumatic stress and interleukin-6. *J Affect Disord.* (2010) 120:231–4. doi: 10.1016/j.jad.2009.03.017
62. Janiri D, Moser DA, Doucet GE, Luber MJ, Rasgon A, Lee WH et al. Shared neural phenotypes for mood and anxiety disorders: a meta-analysis of 226 task-related functional imaging studies. *JAMA Psychiatry.* (2020) 77:172–9. doi: 10.1001/jamapsychiatry.2019.3351
63. Henry C, Etain B. New ways to classify bipolar disorders: going from categorical groups to symptom clusters or dimensions. *Curr Psychiatry Rep.* (2010) 12:505–11. doi: 10.1007/s11920-010-0156-0

64. Dadomo H, Grecucci A, Giardini I, Ugolini E, Carmelita A, Panzeri M. schema therapy for emotional dysregulation: Theoretical implication and clinical applications. *Front Psychol*. (2016) 7:1987. doi: 10.3389/fpsyg.2016.01987
65. Orrú G, Bertelloni D, Cesari V, Conversano C, Gemignani A. Targeting temporal parietal junction for assessing and treating disembodiment phenomena: A systematic review of TMS effect on depersonalization and derealization disorders (DPD) and body illusions. *AIMS Neurosci*. (2021) 8:181–94. doi: 10.3934/Neuroscience.2021009

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

REVIEW
published: 15 June 2022
doi: 10.3389/fpsyt.2022.926084

Clinical Aspects of Manic Episodes After SARS-CoV-2 Contagion or COVID-19

Antonio Del Casale[1,2*], *Martina Nicole Modesti*[3], *Ludovica Rapisarda*[3], *Paolo Girardi*[1] and *Renata Tambelli*[1]

[1] Department of Dynamic and Clinical Psychology, and Health Studies, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy, [2] Unit of Psychiatry, 'Sant'Andrea' University Hospital, Rome, Italy, [3] Faculty of Medicine and Psychology, Sapienza University, Rome, Italy

As COVID-19 pandemic spread all over the world, it brought serious health consequences in every medical field, including mental health. Not only healthcare professionals were more prone to develop anxiety, depression, and stress, but the general population suffered as well. Some of those who had no prior history of a psychiatric disease developed peculiar symptoms following infection with SARS-CoV-2, mostly because of psychological and social issues triggered by the pandemic. People developed traumatic memories, and hypochondria, probably triggered by social isolation and stress. Infection with SARS-CoV-2 has influenced the mental health of psychiatric patients as well, exacerbating prior psychiatric conditions. In this review, we focus on analyzing those cases of mania in the context of bipolar disorder (BD) reported after COVID-19 disease, both in people with no prior psychiatric history and in psychiatric patients who suffered an exacerbation of the disease. Results have shown that COVID-19 may trigger a pre-existing BD or unmask an unknown BD, due to social and psychological influences (decreased social interaction, change in sleep patterns) and through biological pathways both (neuroinflammation and neuroinvasion through ACE-2 receptors expressed in the peripheral and central nervous systems (PNS and CNS respectively). No direct correlation was found between the severity of COVID-19 disease and manic symptoms. All cases presenting severe symptoms of both diseases needed specific medical treatment, meaning that they concur but are separate in the treatment strategy needed. This review highlights the importance of a now widespread viral disease as a potential agent unmasking and exacerbating bipolar mood disorder, and it can hopefully help physicians in establishing a rapid diagnosis and treatment, and pave the road for future research on neuroinflammation triggered by SARS-CoV-2.

Keywords: COVID-19, SARS-CoV-2, manic episode, bipolar disorder, neuroinflammation, neuroinvasion

OPEN ACCESS

Edited by:
Domenico De Berardis, Mental Health Center (CSM) and Psychiatric Service of Diagnosis and Treatment (SPDC), Italy

Reviewed by:
Napoleon Waszkiewicz, Medical University of Białystok, Poland
Michele De Prisco, Federico II University Hospital, Italy

***Correspondence:**
Antonio Del Casale
antonio.delcasale@uniroma1.it

Specialty section:
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

Received: *22 April 2022*
Accepted: *24 May 2022*
Published: *15 June 2022*

Citation:
Del Casale A, Modesti MN, Rapisarda L, Girardi P and Tambelli R (2022) Clinical Aspects of Manic Episodes After SARS-CoV-2 Contagion or COVID-19. Front. Psychiatry 13:926084. doi: 10.3389/fpsyt.2022.926084

INTRODUCTION

On December 31st, 2019, several cases of atypical pneumonia arose in Wuhan, China, later found as being caused by a novel coronavirus called Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) (1). The World Health Organization classified the epidemic as a global pandemic on March 11th, 2020. As the pandemic was spreading, several important consequences on the

mental health of the world population were emerging (2–4). Among these consequences, high rates of depression and anxiety among health professionals need to be highlighted (5), as well as anxiety, depression, and stress-related disorders in the general population (6, 7), psychological symptoms related to social isolation, especially in the elderly, poor, and subjects with difficulties in accessing or handling technology, such as telephone or Internet connections (7). Other symptoms that could arise in the general population are related to social isolation and quarantine (3, 8, 9), unemployment and financial difficulties (3, 9). Some of the psychological issues triggered by the pandemic are specific to infected patients and may include hypochondriac ideas, stigma-related concerns, amnesia, and traumatic memories of severe illness (4). Nevertheless, mental conditions have witnessed a change in paradigm, as the environment played a certain role in triggering some diseases, as previously stated, but the virus itself has the potential to influence the development of some neurological and psychiatric sequelae, as a direct effect of the coronavirus infection of the CNS and PNS, or an indirect effect of medical therapy or abnormal immune response, or a combination of these factors. Patients admitted to the hospital for severe SARS-CoV-2 infection can show different neurological symptoms, more commonly delirium. Different mental disorders may manifest in the subsequent months, including post-traumatic stress disorder, depression, anxiety, and fatigue. COVID-19 can be associated with delirium, agitation, and symptoms of depression, anxiety, and insomnia (4). The reason why this happens finds its roots in microbiological processes: the access of SARS-CoV-2 into human host cells is mediated by the angiotensin-converting enzyme II (ACE-2) receptor, mainly expressed in the lungs and gastrointestinal tract. This is also expressed in brain endothelial cells, which are a hypothetical route of entry into the CNS for coronaviruses (10, 11). Even if severe neurological and psychiatric direct consequences of SARS-CoV-2 appear to be rare, considering the prevalence of the pandemic, many people worldwide may have been affected (4, 12). Most of all, there is evidence of an overall increased vulnerability of patients with a primary diagnosis of bipolar disorder (BD) compared to the general population, despite some studies report a lower degree of distress in this population during the first month of the pandemic compared to a previous baseline (13, 14) Different COVID-19-related stressors can impact BD, mainly including social isolation, restrictive measures, lifestyle, biological circadian rhythms changes, and infection-related concerns (15). Furthermore, the access to mental health services among BD patients had become more difficult during some phases of the pandemic. Conversely, BD might indirectly worsen the risk of acquiring SARS-CoV-2 infection (15, 16). Neuroinvasion of the virus may represent a potential etiology for BD in absence of any other biological, psychological, and social precipitating factors. Nevertheless, some citokines appear to be involved in the development of psychiatric symptoms: it has been suggested that some may be specific for manic state (IL-2,4,6), and for depression (IL-6) (17, 18). Some authors have indeed suggested the particular need to develop standardized laboratory panels that include inflammatory markers (IL-6, TNF-α), cerebrospinal fluid (CSF) testing, and SARS-CoV-2 antibody assays to entirely understand the etiology of neuropsychiatric complications of SARS-CoV-2 infections and the pandemic itself (19). Neuroinflammation might be related to BD symptoms and is infrequently an etiological factor. An aberrant neuroglial function may be responsible for some neuronal miswiring that is consistent with psychotic symptoms frequently observed in BD (20). Manic episodes manifested during or after Covid-19 can arise both as an onset of BD and as a relapse. The main purpose of this article is to provide a review of the scientific literature focused on the clinical and biological correlates of cases of mania manifested in conjunction with or after SARS-CoV-2 infection.

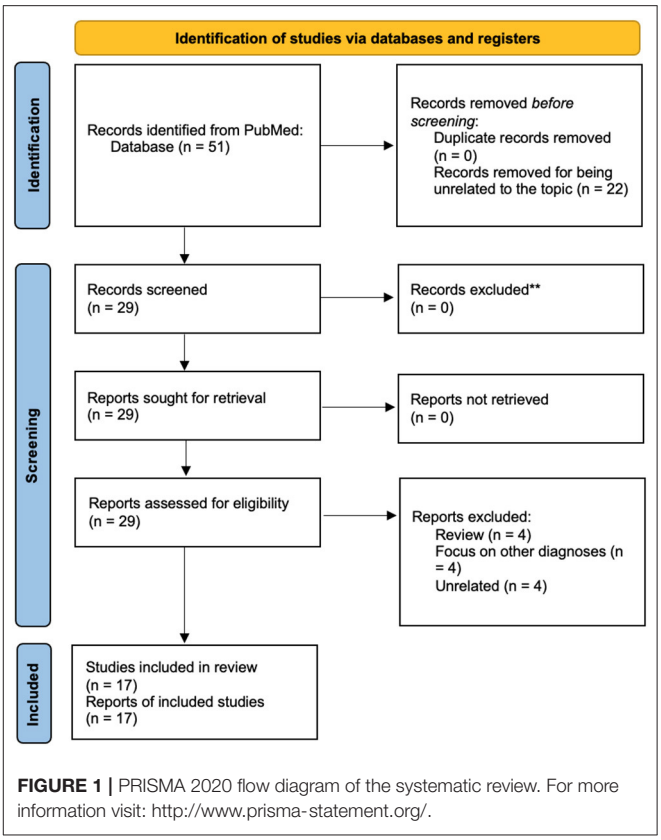


FIGURE 1 | PRISMA 2020 flow diagram of the systematic review. For more information visit: http://www.prisma-statement.org/.

METHODS

On April the 18th, 2022, we conducted a first research on PubMed with the title/abstract specification, using the terms "(mania OR manic) AND (COVID OR SARS-CoV-2)" in the search bar. For eligibility, we included randomized controlled studies, case-control studies, and case reports focused on the issue. We excluded reviews, other types of articles and other studies that did not focus on the main topic, such as BD following another medical condition. The system provided 51 articles, of which we excluded 22 for low relevance. Hence, we assessed 29 articles for eligibility, excluding 12 articles for not respecting the inclusion criteria (4 reviews, 4 unrelated to the topic, and 4

focused on other diagnoses). We finally included 17 articles in the qualitative analysis (see PRISMA flow diagram in **Figure 1**).

RESULTS

The main results are summarized as follows in **Table 1** below.

All studies are observational, being case-reports/case-series. Only traditional medical treatments were employed for the diseases. All studies regarded mania manifestations in different scenarios, and patients from cases analyzed shared a diagnosis of mania plus SARS-CoV-2 infection. Seven patients had a preexisting diagnosis of BD (21, 29); two patients had a preexisting diagnosis of major depressive disorder/unipolar depression (21, 31) 1 patient had a preexisting diagnosis of OCD (33), 2 of psychosis (21). Some cases, despite having a negative psychiatric history, had a positive psychiatric family history: 3 for BD (27, 28, 35) 1 for cognitive deficits, major depressive disorder and delirium (31). Since the aim of the review was to identify episodes of mania in the context of Covid-19, single patient outcome (resolution of the disease, remission, etc.) were not taken into consideration. Different and common clinical aspects were included in the main table in the symptoms column. Not all articles mentioned lab results of the case presented. Whenever mentioned, the mostly involved inflammatory markers were fibrinogen, ferritin, LDH, d-dimer, PCR, ESR, IL-6, IL-10.

DISCUSSION

There is increasing evidence in literature regarding patients infected with SARS-CoV-2 which developed manic symptoms, possibly correlating with the infection itself, due to a cascade triggered by SARS-CoV-2 neuroinvasion, increased neuroinflammatory and inflammatory response in general, hypoxia, iatrogenic factors including antibiotics and steroidal therapy. Results of our research raise questions regarding the possibility that SARS-CoV-2 infection can be a trigger for a manic/hypomanic episode. On the basis that COVID-19 is still under many investigations regarding all consequences of the disease, the study can be enlightening in helping clinicians to suspect a psychiatric correlate of COVID-19 when specific symptoms of mania arise.

Iqbal et al. (21) have highlighted how mania can both be caused by psychosocial stress in susceptible individuals, and by an inflammatory mechanism as well, as has been hypothesized by Park et al. (25) as well: COVID-19 infection could trigger an initial manic episode, SARS-CoV-2 could penetrate blood–brain barriers and stimulate the production of cytokines (TNF-α, IL 1 and 6, and INF-α). Nonetheless, DSM-5 (38) and ICD-10 (39) permit a diagnosis of manic episode even in the background of a medical disorder or substance use, and this could be the case with COVID-19, but knowing how widespread the virus has become, this could influence the incidence of manic episodes across all countries.

The main mania symptoms experienced in the cases analyzed include classical presentations of mania: insomnia (22, 26) abnormal behavior (23, 24, 27), delusions (30, 31), irritability (34, 36), agitation (35), aggressive behavior (33, 37), anxiety (37), impaired concentration (21), persecutory beliefs (30), auditory hallucinations (21, 25), grandiose ideas (21, 28, 29). These findings support the hypothesis that the psychiatric condition experienced is no other than a manic episode, therefore not representing a separate diagnostic entity. The fact that remission of the mood swing occurred after appropriate medical treatment (mostly thanks to Atypical and Typical Anti-psychotics) further supports this statement.

The elevated peripheral inflammatory markers support neuroinflammation as a possible mechanism for COVID-19 causing the patients' neuropsychiatric symptoms (22, 26, 29). Furthermore, the included studies showed that the severity of COVID-19 did not correlate with manic symptoms, suggesting hidden neuroinflammatory mechanisms are strongly present. A discrepancy between pro-inflammatory and anti-inflammatory cytokines has been observed in bipolar patients, the former being more elevated and the latter being less expressed, in particular during mania. (40) Inflammation may act as a triggering factor by disrupting the blood brain barrier mostly, allowing SARS-CoV-2 entrance in the CNS (41), although the neurotropism of SARS-CoV-2 is still under investigation (42). SARS-CoV-2 apparently enters human cells through ACE-2, which is mostly expressed in the respiratory and gastrointestinal system, although being present in the endothelial system as well, also in the brain (10, 11). Invasion of the Central Nervous and of the Peripheral Nervous System as well (43) may explain a potential psychiatric clinical presentation of COVID-19. More specifically, in animal models there is evidence of the expression of ACE-2 in the amygdala, i.e., a site in which the spike proteins of the virus may bind (44). Neuronal and endothelial cells are potential targets for SARS-CoV-2 infection, which may cause their dysregulation after contact with the Spike viral protein (45). Viral invasion of the CNS may occur through several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, vascular endothelium infection, and leukocyte migration across the blood-brain barrier (46). Furthermore, SARS-CoV-2 can replicate in *in-vitro* neuronal cells, although confirmatory *in vivo* studies are required (47).

Worth of mention is that behavioral and mood disorders following infectious disorders have been observed previously as far as other coronaviruses are concerned (48). Studies have shown that individuals affected by BD may show an increased inflammatory status (49), therefore neuroinvasion may act as a trigger for the disease in those with a certain predisposition, culminating with the well-known manifestations of mania. Knowing the role played by the inflammatory cascade in the development of BD (50, 51), the hypothesis that COVID-19 may be a co-protagonist in unmasking a latent BD, as has happened in some cases analyzed (27, 28, 31, 35, 36) is gaining importance, yet needing further investigation.

Regarding the hypothesis that the pandemic social consequences themselves can be triggering factors for a previously unknown BD [as happened in some case reports analyzed: Uzun et al. (36), Varsak et al. (37), Meltem et al. (32)] or an exacerbating factor for those who had already been diagnosed with BD (52, 53), this appears to be relevant,

TABLE 1 | Studies of manic episodes comorbid with ymrsSARS-CoV-2.

Article	Sample	Main SARS-CoV-2 related symptoms	Main manic symptoms	Therapy	Main clinical and pathophysiological correlates
Iqbal et al. (21) Retrospective case series	15 cases of COVID-19-associated mania or hypomania Inclusion criteria: - Patients aged ≥ 18 years - Positive real-time polymerase chain reaction test for SARS-CoV-2 during hospitalization. Mean age: 40 years (age range: 23–66) Gender: 14 men 1 woman Psychiatric history: – 6 with bipolar disorder – 2 with psychosis – 1 with unipolar depression – 6 without a past psychiatric history Significant pandemic-related psychosocial stressors prior to admission: – Present: 9 cases – Absent: 6 cases Comorbidities: 1 patient had epilepsy, which was well controlled. 1 patient with BD had brain metastases	– Asymptomatic: 10 patients – Mild COVID-19: 2 – Mild COVID-19 pneumonia: 1 – Severe COVID-19 pneumonia: 2 – Raised peripheral inflammatory markers: 7 – Mild white matter ischaemic changes: 3	Insomnia (13 subjects), elation (10), behavioral disorder (10), delusion (9), irritability (9), agitation (8), aggressive behavior (8), anxiety (7), impaired concentration (5), persecutory beliefs (5), auditory hallucinations (5). Consultation-Liaison diagnoses: – Mania: 12 patients – Hypomania 3 patients	Steroids prescribed: – Yes 3 – No 12 Psychotropic medications prescribed: – Olanzapine: 12 – Benzodiazepines (lorazepam or clonazepam): 9 – Haloperidol: 6 – Antihistamines (diphenhydramine/promethazine): 5 – Valproate: 4 – Zolpidem: 3 – Quetiapine: 2 All patients responded well to standard treatment for mania or hypomania. Upon discharge from COVID19-designated hospitals: – 5 patients were transferred to a psychiatry hospital for the treatment of ongoing manic symptoms – 10 patients were discharged to their homes.	Potential mechanisms by which SARS-CoV-2 could be a risk factor for mania or hypomania: – Psychosocial stress related to the pandemic, social isolation, and financial difficulties (9 cases). – Raised peripheral inflammatory markers (7 cases) – A history of bipolar affective disorder (6 cases, of which there was evidence of poor medication adherence in 3 cases). – Steroids were prescribed to 3 patients. Steroids can cause mania and have been implicated in some reports of COVID-19-associated mania – Hypoxia, inflammation, and a hypercoagulable state may be risk factors. – Neuroinflammation may be the most plausible correlate of manic states related to SARS-CoV-2.
Haddad et al. (22) Case report	A 30-year-old woman with no family history of mental health problems. No current or past pathologies.	A mild cough and diffuse bodily aches RT-PCR: positive Laboratory tests: elevated CRP, ferritin, LDH	The patient showed features of both delirium and mania. Manic features: elevated mood, decreased need for sleep, grandiose ideation, increased talkativeness, pressured speech, flight of ideas and distractibility. Classic features of delirium: acute disturbance of attention, awareness and cognition, misidentification of family members, brief visual hallucinations, reduced attention, disorientation to time and behaviors that implied reduced awareness, including undressing inappropriately and ingesting body wash (she denied an attempt to harm herself) → diagnosis of delirious mania	Dexamethasone, Ceftriaxone, Enoxaparin, Remdesivir, oxygen therapy Lorazepam 2 mg per day, Quetiapine 300 mg per day → at discharge: Quetiapine 500 mg per day → Reduction to quetiapine 200 mg at night → stopped 4 months after discharge (effective treatment).	Although the patient showed some symptoms consistent with hyperactive delirium, the manic symptoms were not explained by delirium. Psychiatric symptoms started soon after she developed physical symptoms of COVID-19 and received a positive PCR test. The duration of symptoms (9 days in total) was consistent with COVID-19. The raised inflammatory markers provide a plausible aetiological mechanism by which COVID-19 could cause neuropsychiatric symptoms. The association of delirious mania with COVID-19 was coincidental with the former representing the first episode of BD.

(Continued)

TABLE 1 | Continued

Article	Sample	Main SARS-CoV-2 related symptoms	Main manic symptoms	Therapy	Main clinical and pathophysiological correlates
Jiménez-Fernàndez et al. (23) Case report	A 71-year-old retired male patient with no medical history of major affective disorders	Fever, mild cough, dizziness CT: cortico-subcortical retraction pattern Blood tests: slight unspecific abnormalities PCR SARS-CoV-2 test: positive	Admitted to ED for confusion, elevated mood, logorrhoea, excessive motor activity, global insomnia, megalomaniacal delusions, sexual disinhibition, prodigality, and cognitive symptoms.	Corticosteroids 1 month back for a recurrent varicella-zoster lesion Quetiapine 75 mg per day, clonazepam 1 mg per day.	Possible conditioning factors: -infection with COVID-19 (neuroimmune response, biochemical alterations, neuroinvasion) -treatment with corticosteroids.
Kozian and Chaaban (24) Case report	85-year-old patient with no psychiatric history	COVID-19, mild symptoms	Elevated mood, increased drive, and behavior		
Kummerlowe et al. (25) Case report	A 56-year-old Caucasian male with no past personal or family psychiatric history	Mild neutrophilia, thrombocytosis, and elevated ESR and CRP SARS-CoV-2 nucleocapsid total antibody was positive (not vaccinated)	Presented to ED for new-onset odd and erratic behavior preceded by a 4-week period of decreased need for sleep, fluctuating mood, increased energy, distractibility, overvalued religious ideation that he was a prophet, conceptual disorganization, auditory hallucinations but demonstrated insight. Received a diagnosis of brief psychotic disorder → rapid improvement → discharged after 24 hours → 10 days after re-presented to the ED with labile mood, increased energy, pressured speech, talkativeness, distractibility, overvalued religious thought, and brain fog → manic episode	Not treated with corticosteroids or antibiotics Risperidone 1 mg and Lorazepam 1 mg daily: rapid response (24 h) 2° access to ED: restarted Risperidone 1 mg increased up to 2 mg daily.	Symptoms rapidly improved following treatment with atypical antipsychotics, but maintenance treatment needs to be considered even after the early remission as with typical manic episodes. Not certain whether this case may be correlated with SARS-Coronavirus-2 itself or immune response. COVID-19 infection could trigger an initial manic episode; SARS-CoV-2 could penetrate the blood-brain barrier and stimulate the production of cytokines (TNF-α, IL 1 and 6, and INF-α).
Lu et al. (26) Case report	A 51-year-old male patient without a past or family history of mental disorders	Laboratory tests: leukopenia, increased plasma levels of IL-6, IL-10, and CRP in the acute phase of the illness. Positive for SARS-CoV-2 IgG antibody in CSF. Brain MRI: small ischemic lesions located at the basal ganglia and semioval center, suggesting no major pathological changes in the brain.	On illness day 17 he showed excitement, logorrhoea, irritability, ideas of grandiosity, and decreased need for sleep. YMRS= 36	Arbidol, Moxifloxacin, Darunavir and Cobicistat Tablets, and Methylprednisolone Haloperidol, Olanzapine.	Possible risk factors for mania: – neuroinvasive potential of SARS-CoV-2 inducing CNS symptoms. – SARS-CoV-2 IgG in CSF as possible evidence of a past CNS infection – inflammation (increased IL-6, IL-10, and CRP in the acute phase of the illness) – Moxifloxacin – Methylprednisolone.

(Continued)

TABLE 1 | Continued

Article	Sample	Main SARS-CoV-2 related symptoms	Main manic symptoms	Therapy	Main clinical and pathophysiological correlates
Mahapatra and Sharma (27) Case series	A 48-year-old married man, with secondary level education, of middle socioeconomic status, with well-adjusted premorbid functioning. No history of mental disorders. Father was possibly affected by BD.	COVID-19 requiring hospitalization; meanwhile, his mother died due to COVID-19.	After 2 weeks he showed decreased need for sleep, logorrhoea, irritable mood, and ideas of grandiosity. YMRS=27	Olanzapine 15 mg per day; Clonazepam 1 mg per day optimized over 1 week → clinical response over the next 2 weeks.	Possible risk factors for mania: – bereavement (and impossibility of attending a funeral) – genetic vulnerability – COVID-19.
Mawhinney et al. (28) Case report	A 41-year-old man, with no significant medical history, reported a previous cannabis-induced severe transient mood reaction (no further use since then). Sister affected by BP.	Presented to ED with severe headache and a 10-day history of dry cough and fever. He was positive for SARS-CoV-2, chest X-ray showed pneumonitis. CRP and neutrophils were initially raised. Normal neuroimaging and lumbar puncture.	He received a diagnosis of a manic episode, showing decreased sleep, agitation, flight of ideas, hypochondriasis, sexual disinhibition, elevated mood, pressured speech, and persecutory, mystical, and grandiose ideas, needing heavy sedation and intensive care.	Antimicrobial and antiviral treatment for 48 hours; he was extubated after less than 24 hours. Clinical response of manic symptoms to olanzapine, antipsychotics and benzodiazepines.	Possible risk factors for mania: – Neuroinvasion of the virus The development of validated assays for SARS-CoV-2 in the CSF may help to determine the neuroinvasive potential of the virus.
Panda et al. (29) Case series Case report 1	A 58-year-old man affected by severe BD, diabetes.	COVID-19 pneumonia with fever, cough, and breathlessness Inflammatory markers were raised	Excessively cheerful, logorrhoea, disinhibited behavior, reduced sleep, grandiose ideas. Diagnosed as BD, current manic episode	Amoxicillin, Dexamethasone, Remdesivir Last 3 months before COVID-19: Sodium valproate 1500 mg per day, chlorpromazine 100 mg per day. After infection, chlorpromazine was stopped, and the patient was treated with haloperidol 10 mg per day, Sodium Valproate 1500 mg per day.	Possible risk factors for mania: – production of a high amount of pro-inflammatory factors. This proinflammatory state leads to relapse in patients with BD – iatrogenic factors, including corticosteroids and antibiotics – stress due to diagnosis of COVID-19, isolation, and hospitalization.
Reinfeld and Yacoub (30) Case report	A 50-year-old, married, employed man, no psychiatric history	Low fever, tachycardia, elevated blood pressure Chest CT: bilateral pneumonia Laboratory test: elevated ESR, CRP, ferritin, D-Dimer PCR SARS-CoV-2 test: negative, but 2 weeks after discharge COVID-19 IgG were positive	Delirium, mania and catatonia. Admitted to ED reporting aggressiveness, episode of staring, decrease of sleep, decreases speech, beliefs that he was responsible for pandemic, and suicidal ideation. During hospitalization continued to pace, paranoid delusion, rapid and pressured speech, incoherent behaviors, staring episode, intermittently mute, hyperactivity, fluctuating orientation.	Broad-spectrum antibiotics Lorazepam→ no response Elettroconvulsive Therapy: bifrontal treatments over 2 weeks, 0.5 ms-70 Hz (anesthetic and neuromuscular blocker used: succinylcholine and methohexital, later replaced by etomidate) → symptoms gradually improved, after 6th treatment euthymic, normal sleep-wake cycle, no excitement, normal speech, no delusion, no suicidal ideation.	Possible risk factors for mania: – Neuroinflammation (elevated acute-phase proteins and cytokines, in particular IL-6, TNF-alpha) – Not completely understood connection with SARS-CoV-2 infection.

(Continued)

TABLE 1 | Continued

Article	Sample	Main SARS-CoV-2 related symptoms	Main manic symptoms	Therapy	Main clinical and pathophysiological correlates
Russo et al. (31) Case report	A 60-year-old woman with a diagnosis of major depression. Family history was positive for cognitive deficits (maternal grandmother), delusions (mother), and major depression (two siblings).	Swab positive, asymptomatic for covid-19. Negative neurological exam Negative MRI Normal EEG Laboratory tests: mild anemia	Delusions consisting of mold growing everywhere (threw away several pieces of furniture and bought large amounts of cleaning products to deep clean her house), hallucinations (her dead mother ordered her to clean the tombstones of all her relatives to be safe from COVID-19), aggressive behavior, restless, and insomnia. Brought to a psychiatric ward, at admission she showed euphoria, accelerated speech, racing thoughts, logorrhoea, and distractibility. Diagnosed with mania with psychotic features triggered by SARS-CoV-2 infection.	Prednisone 1 mg/kg for two days. Haloperidol 8 mg per day → after 2 weeks no notable changes → switched to Clotiapine 8 months later she can recall hallucinations and delusions. Increased activity, buying sprees, engagement in goal-directed pursuits have disappeared.	Possible risk factors for mania: – SARS-CoV-2 infection – a steroid-dependent mechanism was ruled out.
Sen et al. (32) Case report	A 33-year-old high-school-graduated female patient with no previous neurological or psychiatric history and no prior alcohol or substance abuse	Sore throat and fever (37.8 C) SARS-CoV-2 IgM antibodies CT: bilateral ground-glass opacities Blood screening: increased levels of white blood cell count, C-reactive protein, fibrinogen, ferritin, and D-Dimer MRI: hyperintense signal in the splenium of the corpus callosum with decreased apparent diffusion coefficient: possibly presence of cytotoxic oedema	Admitted to ED reporting an acute onset of insomnia, irritability, and paranoid delusions; logorrhoea and increased psychomotor activity; anxiety and dysphoric mood. Hospitalized with a diagnosis of an acute manic episode. YMRS = 43	COVID-19: Hydroxychloroquine 400 mg per day; Favipiravir 1200 mg per day Haloperidol 20 mg per day; Biperiden 10 mg per day → during hospitalization switched to a daily dose of 20 mg of Olanzapine.	Structural changes of the splenium could be associated with insomnia, irritability, behavioral changes, and psychosis. No corticosteroid was administered, which supports the hypothesis that the manic symptoms may be related to the infection itself. Possible risk factors for mania: – COVID-19 related neuroinflammation and release of pro-inflammatory cytokines in the CNS (TNF-a, IL-1 and IL-6).
Uvais and Mitra (33) Case report	A 22-year-old unmarried woman, no family psychiatric history, no medical comorbidity, no significant life stressors, personal history of obsessive-compulsive symptoms	COVID-19	Admitted to a psychiatric department for a diagnosis of obsessive-compulsive disorder comorbid with moderate depressive episode treated with fluoxetine. After 2 days from COVID-19, she showed talkativeness, overactivity, sexual disinhibition, reduced need for sleep, gender incongruence, and irritability, for which she received a diagnosis of manic episode.	Sodium valproate gradually increased to 1000 mg per day; olanzapine gradually increased to 10 mg per day. Improvement in a month.	It is uncertain if the COVID-19 influenced the illness course. Gender incongruence for the past 5 years may have been covered up for social stigma.

(Continued)

TABLE 1 | Continued

Article	Sample	Main SARS-CoV-2 related symptoms	Main manic symptoms	Therapy	Main clinical and pathophysiological correlates
Uvais and Moiden (34) Case report	A 36-year-old male with type 2 diabetes, no personal or family psychiatric history, history of substance abuse	Fever, cough, and diarrhea.	Disorientation, irritability, delusion with religious contents, grandiosity, urinary incontinence, impaired appetite, decreased need for sleep, increased energy and motor activity. Diagnosed with Catatonic disorder due to a general medical condition (delirious mania associated with COVID-19 infection).	Antibiotics Olanzapine 2,5 mg/day → remained disoriented, manic symptoms exacerbated Olanzapine increased up to 5 mg → symptoms resolved in about a week.	Delirium and manic symptoms developed in middle age instead of young adulthood. Possible mechanisms could be: – SARS-CoV-2 neuroinvasion – Immunological response and the related effect on the CNS – Hyper-inflammatory state (ferritin, CRP, IL-6).
Uvais (35) Case report	A 45-year-old woman with a severe depressive episode. Family history of BD (maternal aunt).	COVID-19 pneumonia	Logorrhoea, irritability, increased energy level, reduced need for sleep; diagnosed with a current manic episode with psychotic symptoms.	Bilevel positive airway pressure, oxygen therapy and oral steroids (quetiapine was stopped) Injection of low molecular weight heparin for 5 days for pulmonary embolism Risperidone 2 mg per day; lorazepam 3 mg per day.	Possible risk factors for mania: – Steroid-induced mechanism – COVID-19 related stress (hospitalization, isolation) – Neurotropism for the virus – Immunologic response associated with COVID-19 CNS infection.
Uzun et al. (36) Case report	A 16-year-old boy with cerebral palsy and no previous psychiatric disorder nor family history	mild COVID-19 symptoms	10 days after recovery he presented excessive speaking, euphoria, irritability, increased energy and decreased sleep and appetite.	Risperidone and after 1 month Lithium was added → symptoms disappeared→ Maintenance therapy: Risperidone 3 mg/day and Lithium 1200 mg/day → manic symptoms did not recurred over 4 months.	Possible risk factors for mania: – COVID-19 related neuroinflammation and release of pro-inflammatory cytokines in the CNS – psychosocial stress due to COVID-19 – neurological disability.
Varsak et al. (37) Case report	A 64-year-old woman with no psychiatric history	Fever, myalgia, headache, diarrhea, taste and smell alterations. CT: bilateral patchy shadows and ground-glass opacity.	On day 3 of hospitalization: cheerful and irritable mood, logorrhoea, aloud singing, throwing things out of the window, and grandiose and mystic delusions. On day 7: agitation, hostile behaviors, and aggressiveness. YMRS= 43.	Hydroxychloroquine, Enoxaparin sodium, Salbutamol, Methylprednisolone Haloperidol 20 mg and Biperiden 5 mg i.m. for agitation→ Zuclopenthixol acetate, Haloperidol 10 mg i.m.→ Zuclopenthixol decanoate/2 weeks, Olanzapine 20 mg per day, Biperiden 4 mg per day → Olanzapine 10 mg per day.	The patient experienced first-episode mania during the COVID-19 treatment. The absence of psychiatric history and the first manic episode during the treatment of COVID-19 led to associating this case to the SARS-CoV-2 infection.

BD, bipolar disorder; CNS, central nervous system; COVID-19, coronavirus disease 2019; CRP, c-reactive protein; CSF, Cerebrospinal fluid; CT, computed tomography; ED, emergency department; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

as previous studies have already shown that social disasters can exacerbate BD mania symptoms but no other psychiatric disorders (54). Lockdown measures adopted to embank the pandemic influenced some of those factors which are crucial in mood maintenance in BD, such as sleep and social interactions, therefore possibly causing exacerbation of the mood disorder (55). In fact, studies have shown how the current pandemic has led to more depressive episodes in individuals affected by BD (56) compared to controls and patients affected by unipolar depression (57).

LIMITS

Our investigation was based on a low sample population and evidence mainly comes from single case reports and case series. Hence, further investigation is needed as a direct correlation between mania and SARS-CoV-2 neuroinvasion cannot be stated with certainty, although having some clue.

CONCLUSIONS

Manic episodes occurring in the context of COVID-19 are becoming more and more frequent. Knowing that biopsychological factors and environmental factors all concur in the development and/or exacerbation of BD, already well known to be of multifactorial etiology, raises alarm because of the high incidence of SARS-CoV-2 infections throughout the world. Awareness should be raised in physicians witnessing symptoms of mania in patients affected by COVID-19, even if asymptomatic from the organic point of view, and even if the patient has no prior psychiatric history. Results have shown that COVID-19 may trigger a pre-existing bipolar disorder or unmask an unknown BD, due to social and psychological influences and through biological pathways both. Further research is needed to understand the precise mechanisms of neurotropism of SARS-CoV-2 and, hopefully, prevent it at least in those patients who already received a diagnosis of BD. These, in particular, need a certain clinical focus, as they are more prone to re-exacerbation of the disease due to the stress which followed the pandemic, social isolation, difficulties in receiving appropriate medical attention and follow-up, therapy changes due to Covid-19 disease, increased inflammatory response and SARS-CoV-2 neuroinvasion of the CNS.

AUTHOR CONTRIBUTIONS

AD, RT, and MNM: conceptualization. AD and LR: data curation. AD, LR, MNM, and PG: investigation. AD: methodology. AD, PG, and RT: supervision. AD, MNM, and LR: roles/writing—original draft. AD and MNM: writing—review and editing. All authors contributed to the article and approved the submitted version.

REFERENCES

1. World Health Organization. *2019 Novel Coronavirus (2019nCoV): Strategic Preparedness and Response Plan*. (2020). Available online at: https://www.who.int/docs/default-source/coronaviruse/srp-04022020.pdf?sfvrsn=7ff55ec0_4&download=true (cited April 16, 2022).
2. World Health Organization. *Mental Health and Psychosocial Considerations During the COVID-19 Outbreak*. (2020). Available online at: https://www.who.int/docs/default-source/coronaviruse/mental-health-considerations.pdf (cited April 16, 2020).
3. Girardi P, Bonanni L, Kotzalidis GD, Fiaschè F, Del Casale A. Evolution of International Psychiatry. *Psychiatry Int.* (2020) 1:27–30. doi: 10.3390/psychiatryint1010004
4. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The lancet Psychiatry.* (2020) 7:611–27. doi: 10.1016/S2215-0366(20)30203-0
5. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw open.* (2020) 3:e203976. doi: 10.1001/jamanetworkopen.2020.3976
6. Asmundson GJG, Taylor S. Coronaphobia: Fear and the 2019-nCoV outbreak. *J Anxiety Disord.* (2020) 70:102196. doi: 10.1016/j.janxdis.2020.102196
7. Xiong J, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. *J Affect Disord.* (2020) 277:55–64. doi: 10.1016/j.jad.2020.08.001
8. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet (London, England).* (2020) 395:912–20. doi: 10.1016/S0140-6736(20)30460-8
9. Chaves C, Castellanos T, Abrams M, Vazquez C. The impact of economic recessions on depression and individual and social well-being: the case of Spain (2006-2013). *Soc Psychiatry Psychiatr Epidemiol.* (2018) 53:977–86. doi: 10.1007/s00127-018-1558-2
10. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* (2004) 203:631–7. doi: 10.1002/path.1570
11. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* (2020) 11:995–8. doi: 10.1021/acschemneuro.0c00122
12. Pleasure SJ, Green AJ, Josephson SA. The spectrum of neurologic disease in the severe acute respiratory syndrome coronavirus 2 pandemic infection: neurologists move to the frontlines. *JAMA Neurol.* (2020) 77:679–80. doi: 10.1001/jamaneurol.2020.1065
13. Orhan M, Korten N, Paans N, de Walle B, Kupka R, van Oppen P, et al. Psychiatric symptoms during the COVID-19 outbreak in older adults with bipolar disorder. *Int J Geriatr Psychiatry.* (2021) 36:892–900. doi: 10.1002/gps.5489
14. Pinkham AE, Ackerman RA, Depp CA, Harvey PD, Moore RC, A. Longitudinal Investigation of the Effects of the COVID-19 Pandemic on the Mental Health of Individuals with Pre-existing Severe Mental Illnesses. *Psychiatry Res.* (2020) 294:113493. doi: 10.1016/j.psychres.2020.113493
15. Fornaro M, De Prisco M, Billeci M, Ermini E, Young AH, Lafer B, et al. Implications of the COVID-19 pandemic for people with bipolar disorders: a scoping review. *J Affect Disord.* (2021) 295:740–51. doi: 10.1016/j.jad.2021.08.091
16. Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. *World Psychiatry.* (2021) 20:124–30. doi: 10.1002/wps.20806

17. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflamm.* (2013) 10:816. doi: 10.1186/1742-2094-10-43
18. Lorkiewicz P, Waszkiewicz N. Biomarkers of Post-COVID Depression. *J Clin Med.* (2021) 10:4142. doi: 10.3390/jcm10184142
19. Łoś K, Kulikowska J, Waszkiewicz N. The Impact of the COVID-19 Virus Pandemic on the Incidence of First Psychotic Spectrum Disorders. *Int J Environ Res Public Health*. (2022) 19:3781. doi: 10.3390/ijerph19073781
20. Kotzalidis G, Ambrosi E, Simonetti A, Cuomo I, Del Casale A, Caloro M, et al. Neuroinflammation in bipolar disorders. *Neuroimmunol Neuroinflamm.* (2015) 2:252. doi: 10.4103/2347-8659.167309
21. Iqbal Y, Alabdulla M, Latoo J, Kumar R, Albrahim S, Wadoo O, et al. Mania and hypomania associated with COVID-19: a series of 15 cases seen by the consultation-liaison psychiatry service in Qatar. *Qatar Med J.* (2021) 2021:65. doi: 10.5339/qmj.2021.65
22. Haddad PM, Alabdulla M, Latoo J, Iqbal Y. Delirious mania in a patient with COVID-19 pneumonia. *BMJ Case Rep*. (2021) 14:e243816. doi: 10.1136/bcr-2021-243816
23. Jiménez-Fernández S, Solis MO, Martínez-Reyes I, Alvarado-Dafonte A, Soldado-Rodríguez L, Rodríguez-Natal MI. Secondary Mania in an Elderly Patient during SARS-CoV-2 Infection with Complete Remission) A 1-Year Follow-Up. *Psychiatr Danub.* (2021) 33:418–20. doi: 10.24869/psyd.2021.418
24. Kozian R, Chaaban A. (Mania after COVID-19 Infection). *Psychiatr Prax.* (2022) 49:51–3. doi: 10.1055/a-1642-7701
25. Park JH, Kummerlowe M, Gardea Resendez M, Nuñez NA, Almorsy A, Frye MA. First manic episode following COVID-19 infection. *Bipolar Disord.* (2021) 23:847–9. doi: 10.1111/bdi.13123
26. Lu S, Wei N, Jiang J, Wu L, Sheng J, Zhou J, et al. First report of manic-like symptoms in a COVID-19 patient with no previous history of a psychiatric disorder. *J Affect Disord.* (2020) 277:337–40. doi: 10.1016/j.jad.2020.08.031
27. Mahapatra A, Sharma P. Case series associated with COVID-19 pandemic in causing psychiatric morbidity. *Gen psychiatry.* (2021) 34:e100343. doi: 10.1136/gpsych-2020-100343
28. Mawhinney JA, Wilcock C, Haboubi H, Roshanzamir S. Neurotropism of SARS-CoV-2: COVID-19 presenting with an acute manic episode. *BMJ Case Rep*. (2020) 13:e236123. doi: 10.1136/bcr-2020-236123
29. Panda TK, Nebhinani N, Suthar N, Choudhary S, Singhai K. Relapse in bipolar disorder in hospitalized patients with COVID-19: a case series and key recommendations. *Indian J Psychiatry*. 63:610–2. doi: 10.4103/indianjpsychiatry.indianjpsychiatry_1433_20
30. Reinfeld S, Yacoub A, A. Case of Delirious Mania Induced by COVID-19 Treated With Electroconvulsive Therapy. *J ECT*. (2021) 37:e38–9. doi: 10.1097/YCT.0000000000000789
31. Russo M, Consoli S, De Rosa MA, Calisi D, Dono F, Carrarini C, et al. A case of Sars-Cov-2-related mania with prominent psychosis. *Psychiatry Res.* (2021) 306:114266. doi: 10.1016/j.psychres.2021.114266
32. Sen M, Yesilkaya UH, Balcioglu YH. SARS-CoV-2-associated first episode of acute mania with psychotic features. *J Clin Neurosci.* (2021) 87:29–31. doi: 10.1016/j.jocn.2021.02.012
33. Uvais NA, Mitra S. Gender Incongruence Unmasked by Manic Switch During COVID-19 Infection. Prim care companion CNS Disord. (2022) 24:21cr03129. doi: 10.4088/PCC.21cr03129
34. Uvais NA, Moideen S. COVID-19 presenting with delirious mania: a case report. *Bipolar Disord*. (2022) doi: 10.1111/bdi.13180. [Epub ahead of print].
35. Uvais NA. Manic Switch in a Patient With Depression in the Setting of COVID-19 Treatment. Prim care companion CNS Disord. (2021) 23:21cr02984. doi: 10.4088/PCC.21cr02984
36. Uzun N, Kiliç AO, Akinci MA, Özgül-Katircioglu D, Erden S. Could COVID-19 be a trigger for manic attack in an adolescent? *Neurol Sci.* (2021) 42:3521–2. doi: 10.1007/s10072-021-05390-0
37. Varsak N, Topaloglu M, Özdemir E. First Manic Attack During COVID-19 Treatment: a Case Report. *Clin Psychopharmacol Neurosci.* (2021) 19:786–8. doi: 10.9758/cpn.2021.19.4.786
38. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 5th editio*. American Psychiatric Association, editor. Arlington, VA (2013).
39. World Health Organization. *The ICD-10 Classification of mental and Behavioural Disorders. 10th ed*. Geneve, Switzerland (1993).
40. Sayana P, Colpo GD, Simões LR, Giridharan VV, Teixeira AL, Quevedo J, et al. A systematic review of evidence for the role of inflammatory biomarkers in bipolar patients. *J Psychiatr Res.* (2017) 92:160–82. doi: 10.1016/j.jpsychires.2017.03.018
41. Amruta N, Chastain WH, Paz M, Solch RJ, Murray-Brown IC, Befeler JB, et al. SARS-CoV-2 mediated neuroinflammation and the impact of COVID-19 in neurological disorders. *Cytokine Growth Factor Rev.* (2021) 58:1–15. doi: 10.1016/j.cytogfr.2021.02.002
42. Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. *J Neurol.* (2020) 267:2179–84. doi: 10.1007/s00415-020-09929-7
43. Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:552–5. doi: 10.1002/jmv.25728
44. Wang L, de Kloet AD, Pati D, Hiller H, Smith JA, Pioquinto DJ, et al. Increasing brain angiotensin converting enzyme 2 activity decreases anxiety-like behavior in male mice by activating central Mas receptors. *Neuropharmacology.* (2016) 105:114–23. doi: 10.1016/j.neuropharm.2015.12.026
45. Benedetti F, Silvestri G, Mavian C, Weichseldorfer M, Munawwar A, Cash MN, et al. Comparison of SARS-CoV-2 receptors expression in primary endothelial cells and retinoic acid-differentiated human neuronal cells. *Viruses.* (2021) 13:2193. doi: 10.3390/v13112193
46. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* (2020) 77:1018–27. doi: 10.1001/jamaneurol.2020.2065
47. Chu H, Chan JF-W, Yuen TT-T, Shuai H, Yuan S, Wang Y, et al. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. *Lancet Microbe.* (2020) 1:e14–23. doi: 10.1016/S2666-5247(20)30004-5
48. Okusaga O, Yolken RH, Langenberg P, Lapidus M, Arling TA, Dickerson FB, et al. Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts. *J Affect Disord.* (2011) 130:220–5. doi: 10.1016/j.jad.2010.09.029
49. Stich O, Andres TA, Gross CM, Gerber SI, Rauer S, Langosch JM. An observational study of inflammation in the central nervous system in patients with bipolar disorder. *Bipolar Disord.* (2015) 17:291–302. doi: 10.1111/bdi.12244
50. Benros ME, Waltoft BL, Nordentoft M, Ostergaard SD, Eaton WW, Krogh J, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA psychiatry.* (2013) 70:812–20. doi: 10.1001/jamapsychiatry.2013.1111
51. Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience.* (2015) 300:141–54. doi: 10.1016/j.neuroscience.2015.05.018
52. Koenders M, Mesbah R, Spijker A, Boere E, de Leeuw M, van Hemert B, et al. Effects of the COVID-19 pandemic in a preexisting longitudinal study of patients with recently diagnosed bipolar disorder: Indications for increases in manic symptoms. *Brain Behav.* (2021) 11:e2326. doi: 10.1002/brb3.2326
53. Uvais NA. Mania Precipitated by COVID-19 Pandemic-Related Stress. *Prim Care Companion CNS Disord*. (2020) 22:20l02641. doi: 10.4088/PCC.20l02641
54. Matsumoto J, Kunii Y, Wada A, Mashiko H, Yabe H, Niwa S. Mental disorders that exacerbated due to the Fukushima disaster, a complex radioactive contamination disaster. *Psychiatry Clin Neurosci.* (2014) 68:182–7. doi: 10.1111/pcn.12112

55. Takaesu Y. Circadian rhythm in bipolar disorder: a review of the literature. *Psychiatry Clin Neurosci.* (2018) 72:673–82. doi: 10.1111/pcn.12688
56. Karantonis JA, Rossell SL, Berk M, Van Rheenen TE. The mental health and lifestyle impacts of COVID-19 on bipolar disorder. *J Affect Disord.* (2021) 282:442–7. doi: 10.1016/j.jad.2020.12.186
57. Van Rheenen TE, Meyer D, Neill E, Phillipou A, Tan EJ, Toh WL, et al. Mental health status of individuals with a mood-disorder during the COVID-19 pandemic in Australia: Initial results from the COLLATE project. *J Affect Disord.* (2020) 275:69–77. doi: 10.1016/j.jad.2020.06.037

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 15 June 2022
doi: 10.3389/fpsyt.2022.913965

Bipolar Disorder and Polysubstance Use Disorder: Sociodemographic and Clinical Correlates

Andrea Aguglia[1,2], Antimo Natale[3], Laura Fusar-Poli[3], Andrea Amerio[1,2], Edoardo Bruno[1,2], Valeria Placenti[1,2], Eleonora Vai[1,2], Alessandra Costanza[4,5], Gianluca Serafini[1,2], Eugenio Aguglia[3] and Mario Amore[1,2]*

[1] Section of Psychiatry, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy, [2] Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Policlinico San Martino, Genoa, Italy, [3] Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy, [4] Department of Psychiatry, Faculty of Medicine, University of Geneva (UNIGE), Geneva, Switzerland, [5] Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland

Introduction: Patients with bipolar disorder (BD) often show comorbidity with substance use disorder (SUD) with a negative impact on clinical course, prognosis, and functioning. The role of polysubstance use disorder (polySUD) is understudied. The aim of the present paper is to evaluate the sociodemographic and clinical characteristics associated with BD and comorbid SUD, focusing on polySUD, in order to phenotype this specific group of patients and implement adequate treatment and prevention strategies.

Methods: A cross-sectional study was conducted involving 556 patients with a primary diagnosis of BD (376 without SUD, 101 with SUD, and 79 with polySUD). A semi-structured interview was administered to collect sociodemographic variables, clinical characteristics, and pharmacological treatment. ANOVA and chi-square tests were used to compare the three groups. Significantly different variables were then inserted in multivariate logistic regression.

Results: Patients affected by BD and polySUD were younger, and more frequently males and single, than patients with SUD or without SUD. Indeed, the prevalence of patients affected by BD and polySUD living in residential facilities was higher than in the other groups. Moreover, earlier age at onset, higher prevalence of psychotic and residual symptoms, involuntary hospitalization, and a family history of psychiatric disorders were associated with polySUD in patients suffering from BD. Lastly, patients with BD and polySUD were more likely to take four or more medications, particularly benzodiazepines and other drugs. At the multinomial regression, younger age, male gender, early age at onset, psychotic and residual symptoms, positive family history of psychiatric disorders, and use of benzodiazepines remained significantly associated with polySUD in patients with BD.

Conclusion: Our findings show a specific profile of patients with BD and polySUD. It is important to conduct research on this topic in order to adopt specific therapeutic strategies, minimize the use of polypharmacy, and aim at full remission and mood stabilization.

Keywords: bipolar disorder, substance use disorder, treatment, psychotic symptoms, polypharmacy

OPEN ACCESS

Edited by:
Domenico De Berardis, Mental Health Center (CSM) and Psychiatric Service of Diagnosis and Treatment (SPDC), Italy

Reviewed by:
Renato de Filippis, Magna Græcia University, Italy
Xenia Gonda, Semmelweis University, Hungary

****Correspondence:***
Andrea Aguglia
andrea.aguglia@unige.it

Specialty section:
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

Received: *06 April 2022*
Accepted: *11 May 2022*
Published: *15 June 2022*

Citation:
Aguglia A, Natale A, Fusar-Poli L, Amerio A, Bruno E, Placenti V, Vai E, Costanza A, Serafini G, Aguglia E and Amore M (2022) Bipolar Disorder and Polysubstance Use Disorder: Sociodemographic and Clinical Correlates. Front. Psychiatry 13:913965. doi: 10.3389/fpsyt.2022.913965

INTRODUCTION

Bipolar disorder (BD) is a severe, recurrent, and multifactorial psychiatric condition, characterized by the alternation of different phases, specifically hypomanic/manic and major depressive episodes (1). BD affects at least 2–3% of the general population and its onset typically occurs during adolescence or early adulthood (2), influenced often by seasonality and sunlight (3, 4). BD is often associated with several medical conditions, such as cardiovascular and endocrine-metabolic diseases (5–10) and higher inflammatory status (11, 12), leading to a worsening of the quality of life and functioning (13).

Substance use disorder (SUD), which is defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) criteria as "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems" (1), is a common issue in patients with BD. It has a negative impact on the illness course, including more difficulties to achieve intraepisodic remission and stabilization and maintaining adequate and full adherence to therapeutic strategies (14, 15).

The comorbidity between BD and SUD is frequent, as confirmed by several epidemiological studies. For example, the Epidemiologic Catchment Area (ECA) study found a higher prevalence of substance abuse in subjects diagnosed with BD type I (40.7%) than in the general population (16). In the National Epidemiologic Survey on Alcohol and Related Conditions (NERSAC) studies, patients with BD showed high rates of SUD (17–20), as well as in other epidemiological studies, with a prevalence ranging from 26 to 43% (21–23). In general, patients with BD tend to use illicit substances with a strong statistical association [odds ratio (OR): 4.96] with the following prevalence: alcohol (42%), cannabis (20%), and cocaine and amphetamine (17%) (24). However, the use of novel psychoactive substances has been also associated with young patients with BD more than controls and subjects with other psychiatric disorders (25, 26).

The reasons why patients with BD use illicit substances are different, including seeking relief by self-medication, improving psychic status, relieving tension and boredom, escaping from reality, achieving and/or maintaining elevated mood, and increasing energy (27). Furthermore, common genetic (i.e., polymorphism of the aldehyde hydrogenase and alcohol dehydrogenase, or $5HT_{2C}$ gene), socioeconomic, and environmental factors (i.e., access and availability of illicit drugs in the community, poverty), stressful events (i.e., trauma, physical, and sexual abuse), temperamental traits (i.e., a sensation of seeking behavior), lifetime suicide attempts, and psychiatric comorbidities (i.e., conduct disorder, cluster B personality disorder, and post-traumatic stress disorder) have been associated with SUD in patients with BD (24, 28, 29).

The comorbidity between BD and SUD is associated with several detrimental clinical characteristics, such as an earlier onset of illness, greater severity of the disorder, more rapid cycling with a higher risk of switching into (hypo)manic or mixed phases and frequent affective relapses, increased risk of suicide attempts or suicide, and accelerated progression of BD with higher prevalence of negative and cognitive symptomatology. Furthermore, patients affected by BD and SUD are characterized by treatment delay due to possible misdiagnosis, reduced response to lithium and other pharmacological treatments with worsening of adherence, presence of medical comorbidities (hepatitis C, acquired immune deficiency syndrome, and others), increased psychosocial problems, and poorer social support (27, 28, 30). Finally, illicit substances, particularly cannabis, are considered risk factors for the onset of BD (31, 32).

Although previous studies have recognized the negative impact of concurrent SUD in patients with BD, to the best of our knowledge, no studies have specifically focused on the factors associated with BD and polysubstance use disorder (polySUD). The present study aimed to evaluate the sociodemographic and clinical characteristics associated with BD and comorbid SUD, focusing specifically on polySUD. In fact, a detailed characterization of the phenotype of patients with BD and polySUD may help the identification and prevention of risk factors for multidrug abuse. This may in turn improve the clinical course and outcomes of BD and may help the building of a meaningful therapeutic relationship and the choice of the most effective treatments (28).

MATERIALS AND METHODS

Sample and Assessment

A cross-sectional study was conducted involving 556 patients with a primary diagnosis of BD, consecutively admitted to the Section of Psychiatry, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), IRCCS Ospedale Policlinico San Martino, University of Genoa (Italy), during a period of 5 years (January 2017–December 2021).

The inclusion criteria consisted of the following: (a) inpatient status; (b) ongoing major depressive or (hypo)manic episode into a primary diagnosis of BD type I and II, according to the DSM-5 criteria (1); (c) 18 years of age or older; and (d) written informed consent to participate in the study.

The exclusion criteria were as follows: (a) primary diagnosis of schizophrenia and related disorders; (b) pregnancy or recent childbirth; (c) any condition affecting the ability to fill out the assessment, such as major neurocognitive disorders; (d) any severe neurological disorder or positive history of acute neurological injury, including an intellectual disability; and (e) the inability or refusal to provide written informed consent to participate in the study.

A semi-structured interview was administered to collect both sociodemographic and clinical characteristics. Sociodemographic characteristics included age, gender, marital and working status, education level in years, and living status, while the clinical characteristics included family history for psychiatric disorders, age of BD onset, duration of illness, presence of lifetime involuntary hospitalization, psychotic and residual symptoms, suicide attempts and non-suicidal self-injury (NSSI), lifetime SUD, and pharmacological treatment grouped as antidepressants, antipsychotics, mood stabilizers (i.e., lithium, valproate, lamotrigine, and carbamazepine), benzodiazepines,

and others (i.e., gabapentin, pregabalin, and oxcarbazepine). Moreover, according to the existing literature, the presence of at least two or four medications was defined as polypharmacy simplex and complex, respectively (33).

Potential participants were provided with an in-depth explanation of the study objectives and procedures and an opportunity to ask questions. The study was designed in agreement with the guidelines from the Declaration of Helsinki (34) and was approved by the Research Ethical Committees.

Statistical Analysis

Continuous and categorical variables were presented as means and standard deviations (SD) or frequency and percentage, respectively.

First, the sample was divided into three subgroups: (a) patients with BD and absence of lifetime SUD; (b) patients with BD and lifetime SUD (use of one illicit drug); and (c) patients with BD and polySUD (at least two concomitant illicit drugs). For the sociodemographic and clinical comparison, ANOVA with Bonferroni's *post hoc* correction was used for continuous variables and Pearson's chi-square test (χ^2) for categorical variables. Subsequently, a multinomial regression analysis was used to explore the relationship between patients with BD and polySUD and each of the significant independent variables found in univariate analysis, correcting for age and gender.

The Statistical Package for Social Sciences (SPSS) for Windows 25.0 (IBM Corp., Armonk, NY, United States) was used to carry out all the mentioned statistical analyses, and the value of statistical significance was set at $p < 0.05$ (two-tailed).

RESULTS

General Characteristics of the Sample

The total sample included 556 patients with a primary diagnosis of BD, of which 43.7% were men ($N = 243$). The mean ($\pm$ *SD*) age was 49.17 ($\pm$ 14.14) years, and 239 patients (43.0%) were single. Moreover, 198 patients (35.6%) were living alone, and 190 (34.2%) were employed. A total of 277 patients were affected by BD type I, the age of onset was 29.07 ($\pm$ 13.26) years, while the duration of illness was 19.79 ($\pm$ 13.10) years. Finally, about half of the patients ($N = 225$, 40.5%) were taking at least four medications.

All sociodemographic and clinical characteristics are displayed in **Tables 1**, **2**.

Comparison of Sociodemographic and Clinical Parameters Between Three Groups of the Sample

Comparing the sociodemographic characteristics, patients with BD and polySUD were more frequently males (65.8% vs. 55.4% vs. 35.9%, $p < 0.001$), younger (38.90 $\pm$ 11.99 vs. 47.98 $\pm$ 13.02 vs. 51.64 $\pm$ 13.87 years, $p < 0.001$), single (69.6% vs. 46.5% vs. 36.4%, $p < 0.001$), and living in a residential facility (11.4% vs. 3.0% vs. 1.3%, $p < 0.001$) than both participants without SUD or using only one illicit substance.

Regarding the clinical characteristics, patients suffering from BD and polySUD had an earlier age onset (21.25 $\pm$ 9.78 vs. 27.29 $\pm$ 10.56 vs. 31.20 $\pm$ 13.88 years, $p < 0.001$), a higher prevalence of psychotic (44.3% vs. 22.8% vs. 26.1%, $p = 0.002$) and residual (31.6% vs. 15.8% vs. 13.6%, $p < 0.001$) symptoms, and involuntary hospitalization (31.6% vs. 20.8% vs. 18.4%, $p < 0.001$) than the other subgroups. Finally, a family history for psychiatric disorders was significantly associated with a primary diagnosis of BD and polySUD comorbid (57.0% vs. 53.5% vs. 42.0%, $p = 0.015$).

Lastly, patients suffering from BD and polySUD showed more polypharmacy complex (53.2% vs. 45.5% vs. 36.4%, $p = 0.012$) than the other subgroups and the assumption of benzodiazepines (81.0% vs. 68.3% vs. 66.4%, $p = 0.007$) and other drugs (34.2% vs. 32.7% vs. 19.9%, $p = 0.003$). All findings are reported in **Tables 1**, **2**.

Multinomial Regression

When the multinomial regression was performed with BD without any SUD as the reference category, male gender [OR: 2.411; 95% confidence interval (CI): 1.50–3.87; $p < 0.001$] and use of other drugs (OR: 1.819; 95% CI: 1.09–3.04; $p = 0.023$) were associated with SUD in patients affected by BD.

Furthermore, younger age (OR: 0.938; 95% CI: 0.91–0.97; $p < 0.001$), male gender (OR: 3.464; 95% CI: 1.88–6.40; $p < 0.001$), earlier age at onset (OR: 0.956; 95% CI: 0.92–0.99; $p = 0.014$), presence of psychotic (OR: 4.254; 95% CI: 1.87–6.49; $p = 0.001$), and residual (OR: 7.815; 95% CI: 3.62–16.89; $p < 0.001$) symptoms, positive family history for psychiatric disorders (OR: 1.830; 95% CI: 1.02–3.28; $p = 0.042$), and use of benzodiazepines (OR: 3.481; 95% CI: 1.61–7.53; $p = 0.002$) resulted associated with polySUD in patients with BD, compared to the reference category. All findings are displayed in **Table 3**.

DISCUSSION

The present paper aimed to evaluate the factors associated with SUD and polySUD in a cohort of patients with BD. Evidence from epidemiological, clinical, and review studies has shown that the comorbidity between patients with a primary diagnosis of BD and SUD is frequent (23, 27, 28, 35). This has also been confirmed in our sample. Moreover, our results showed that while SUD was significantly associated only with the male gender and the category "other drugs," several sociodemographic and clinical factors were significantly associated with polySUD compared to non-users among patients with BD. Overall, our findings underline that the presence of polySUD should be carefully considered in the pharmacological and non-pharmacological approaches to BD patients for personalized treatment.

According to the existing data literature (26, 36, 37), sociodemographic characteristics such as being male, single, and younger are associated with polySUD. These findings are quite expected, due to the increasing early use of illicit substances in young males in the current society and their well-known negative consequences on neurostructural patterns and functioning, which may impair the building of meaningful

TABLE 1 | Sociodemographic characteristics of the total sample and comparison between the three subgroups.

	Total sample (*N* = 556)	BD without SUD (*N* = 376)	BD with SUD (*N* = 101)	BD with polySUD (*N* = 79)	*F*	*p*
Gender (male), *N* (%)	243 (43.7)	135 (35.9)	56 (55.4)	52 (65.8)	30.666	<0.001
Age (years), mean ± *SD*	49.17 ± 14.14	51.64 ± 13.87	47.98 ± 13.02	38.90 ± 11.99	29.718	<0.001*
Marital Status, *N* (%)						
Single	239 (43.0)	137 (36.4)	47 (46.5)	55 (69.6)	44.642	<0.001
Married	180 (32.4)	140 (37.2)	30 (29.7)	10 (12.7)		
Separated/divorced	108 (19.4)	70 (18.6)	24 (23.8)	14 (17.7)		
Widowed	29 (5.2)	29 (7.7)	0 (0)	0 (0)		
Educational level (years), mean ± *SD*	11.62 ± 3.62	11.83 ± 3.74	11.07 ± 3.21	11.33 ± 3.44	2.052	0.129
Occupational status, *N* (%)	190 (34.2)	136 (36.2)	30 (29.7)	24 (30.4)	2.069	0.355
Living with, *N* (%)					23.670	<0.001
Alone	198 (35.6)	141 (37.5)	31 (30.7)	26 (32.9)		
Family	341 (61.3)	230 (61.2)	67 (66.3)	44 (55.7)		
Residential facility	17 (3.1)	5 (1.3)	3 (3.0)	9 (11.4)		

**Post hoc (Bonferroni) BD without SUD > BD with SUD > BD with polySUD.*
BD, bipolar disorder; SUD, substance use disorder.

TABLE 2 | Clinical characteristics of the total sample and comparison between the three subgroups.

	Total sample (*N* = 556)	BD without SUD (*N* = 376)	BD with SUD (*N* = 101)	BD with polySUD (*N* = 79)	*F*	*p*
Psychiatric family history, *N* (%)	257 (46.2)	158 (42.0)	54 (53.5)	45 (57.0)	8.467	0.015
Age at onset, mean ± *SD*	29.07 ± 13.26	31.20 ± 13.88	27.29 ± 10.46	21.25 ± 9.78	20.878	<0.001*
Duration of illness (years), mean ± *SD*	19.79 ± 13.10	19.98 ± 13.41	20.99 ± 13.71	17.38 ± 10.41	1.802	0.166
Diagnosis, *N* (%)						
Bipolar disorder I	277 (49.8)	187 (49.7)	45 (44.6)	45 (57.0)	2.733	0.255
Bipolar disorder II	279 (50.2)	189 (50.3)	56 (55.4)	34 (43.0)		
Psychotic symptoms, *N* (%)	156 (28.1)	98 (26.1)	23 (22.8)	35 (44.3)	12.468	0.002
Residual symptoms, *N* (%)	92 (16.5)	51 (13.6)	16 (15.8)	25 (31.6)	15.502	<0.001
Involuntary hospitalization, *N* (%)	115 (20.7)	69 (18.4)	21 (20.8)	25 (31.6)	7.034	0.030
Lifetime suicide attempts, *N* (%)	181 (32.6)	124 (33.0)	32 (31.7)	25 (31.6)	0.095	0.953
Non-suicidal self-injuries, *N* (%)	92 (16.5)	55 (14.6)	21 (20.8)	16 (20.3)	3.107	0.212
Polypharmacy simplex, *N* (%)	101 (18.2)	75 (19.9)	18 (17.8)	8 (10.1)	4.245	0.120
Polypharmacy complex ≥ 4, *N* (%)	225 (40.5)	137 (36.4)	46 (45.5)	42 (53.2)	8.904	0.012
Antidepressants, *N* (%)	224 (40.3)	152 (40.4)	46 (45.5)	26 (32.9)	2.950	0.229
Antipsychotics, *N* (%)	423 (76.1)	291 (77.4)	70 (69.3)	62 (78.5)	3.153	0.207
Mood Stabilizers, *N* (%)	470 (84.5)	310 (82.4)	87 (86.1)	73 (92.4)	5.195	0.074
Benzodiazepines, *N* (%)	369 (66.4)	236 (62.8)	69 (68.3)	64 (81.0)	9.948	0.007
Others, *N* (%)	135 (24.3)	75 (19.9)	33 (32.7)	27 (34.2)	11.919	0.003

**Post hoc (Bonferroni) BD without SUD > BD with SUD > BD with polySUD.*
BD, bipolar disorder; SUD, substance use disorder.

social relationships, including marital ones (38–40). However, a difference in marital status emerged only in the univariate but not in the multinomial regression analysis. Furthermore, although our findings showed that patients affected by BD and polySUD lived mainly with family members, the prevalence of patients living in residential facilities was significantly higher than in the other two subgroups. In fact, as indicated by recent guidelines, patients with BD and SUD often need to be addressed toward specific and tailored therapeutic pathways in residential facilities, especially when no familial and social support is present (41). On the one hand, this clinical indication contributes to avoid the use of illicit substances, because patients are placed in a protected context, away from the pathological environment; on the other hand, it allows to follow specific psychological and pharmacological therapeutic strategies, aimed at maintaining the mood stabilization and correcting the unhealthy lifestyles for a better social and familial functioning. Thus, the high rates of comorbidity between severe mental illness and SUD need an integrated approach in psychiatric services with specialized clinicians to encourage early

TABLE 3 | Multinomial logistic regression.

	BD with SUD			BD with polySUD		
	Odds Ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Gender (male)	2.411	1.50–3.87	<0.001	3.464	1.88–6.40	<0.001
Age	0.990	0.97–1.01	0.345	0.938	0.91–0.97	<0.001
Marital status (single)	0.954	0.54–1.68	0.870	0.796	0.38–1.66	0.543
Living with (residential facility)	1.500	0.33–6.87	0.601	2.241	0.59–8.51	0.236
Psychiatric family history	0.058	0.99–2.50	0.058	1.830	1.02–3.28	0.042
Age at onset	0.983	0.96–1.00	0.115	0.956	0.92–0.99	0.014
Psychotic symptoms	0.719	0.41–1.28	0.261	4.254	1.87–6.49	0.001
Residual symptoms	1.699	0.86–3.36	0.127	7.815	3.62–16.89	<0.001
Involuntary hospitalization	0.976	0.52–1.80	0.939	0.955	0.47–1.94	0.898
Polypharmacy complex ≥ 4	1.288	0.77–2.16	0.338	1.570	0.83–2.98	0.168
Benzodiazepines	1.154	0.67–1.98	0.608	3.481	1.61–7.53	0.002
Others	1.819	1.09–3.04	0.023	1.450	0.63–2.78	0.158

The reference category is: bipolar patients without substance use disorder.
BD, bipolar disorder; CI, confidence interval; SUD, substance use disorder.

assessment and intervention with active and careful monitoring (42, 43).

Regarding clinical variables, earlier age at onset, the presence of psychotic and residual symptoms, and a family history positive for psychiatric disorders were found to be significantly associated with polySUD in patients with BD. These findings are in line with other studies (35, 37, 44). Illicit substances are considered to be one of the main risk factors and triggers for bipolar illness, as defined by the new diagnostic category named "substance-induced bipolar and related disorder" in the DSM-5 (1). The use of drugs, such as cocaine, amphetamines, or cannabis, is often associated with the first manifestation of an affective episode (31, 32, 45). The earlier age at onset in people with polySUD is not surprising. A timely diagnosis of BD in individuals with SUD may represent a challenge for clinicians, as both the acute and long-term clinical effects of drug abuse and BD symptoms may overlap. Thus, the clinical picture may initially be attributed only to drug use without an accurate assessment for bipolarity, with a consequent misdiagnosis and treatment delay. The actual recognition of an underlying BD may thus be performed only during subsequent hospitalizations.

It is very important to emphasize the association between polySUD and psychotic and residual symptoms. These clinical characteristics were found to be associated with polySUD not only in the univariate but also in the multinomial regression analysis. It is well-known that psychotic and residual symptoms exert a negative impact on the functioning, quality of life, and adherence to treatment in patients with BD (46–49). The relationship between psychotic symptoms and illicit substances in BD could be bidirectional. On the one hand, as mentioned above, illicit substances may induce psychotic symptoms, especially at the onset of BD; moreover, they may determine a switch to a (hypo)manic or mixed episode and the persistence of psychotic symptoms even after the interruption of the pathological use, being potentially related to a gradual and progressive worsening of cognitive functions (50–53). On the other hand, patients suffering from BD may use drugs due to the disinhibition and exaltation typical of manic phases, or to regulate, in the short-term, the negative emotional states typical of major depressive episodes (54). The presence of residual symptoms, intra- or inter- affective episodes, are strongly associated with chronic bipolar illness course, incomplete mood stabilization and frequent affective recurrences, poor sleep quality, as well as social, occupational, and cognitive deterioration with increased subjective stigma and reduced adherence to treatment (46, 55, 56). However, data about the association between residual symptoms and SUD in patients with BD are still controversial and this relationship needs to be explored in depth (44, 57).

Family history of psychiatric disorders has been reported to be a predictor of polySUD in patients with a primary diagnosis of BD, suggesting a vulnerability for this comorbidity (35, 58, 59). Indeed, our results have shown an increase in inpatient involuntary admissions of BD patients with SUD, in line with previous studies (60, 61).

Lastly, our data revealed no difference in SUD between BD type I and II. This is in contrast with previous clinical (26, 35, 62) and epidemiological studies, reporting an increased prevalence of SUD in BD type I (20, 24). No association between polySUD and current or lifetime suicidal behaviors was found in the multinomial regression analysis, although this significant relationship has been reported in a recent meta-analysis (28). Clinicians should always monitor the bipolar illness course in patients with polySUD, focusing mainly on full clinical remission, providing more attention to psychotic symptoms, reducing involuntary admissions, and avoiding the pathological use of illicit substances to decrease suicidality, which should be addressed and evaluated with specific psychometric tools (63, 64).

Finally, with regard to pharmacological treatment, patients with BD and polySUD were more likely to be treated with a complex pharmacological approach, defined as four or more medications (33), compared to the other two subgroups. Even if some level of evidence about the efficacy of polypharmacy exists for BD with comorbid cannabis and cocaine use, unfortunately, a

very low grade of evidence is available for heroin, amphetamine, and methamphetamine (41). To our knowledge, this is the first paper that analyzes this particular aspect, and to date, there is no evidence about a possible role of SUD in determining a multiple pharmacological prescriptions in patients affected by BD (33, 65). Our results may underline the necessity to develop more specific guidelines for the treatment of this peculiar subgroup of patients with BD to guide clinicians and avoid the prescription of too many medications with a poor efficacy/side effects balance.

Looking specifically at the pharmacological categories, benzodiazepines and the category of "other drugs" (i.e., gabapentin, pregabalin, oxcarbazepine) were more frequently prescribed among polySUD than the other categories. Several studies showed higher rates of use of benzodiazepines in patients with SUD than in the general population, with a risk of abuse of these drugs (66–68). On the contrary, evidence regarding factors associated with benzodiazepines prescription in patients with BD and comorbid SUD are scarce and inconclusive (69, 70). A recent review explored the use of gabapentin and pregabalin in the treatment of patients with BD, indicating a potential role of these medications in the management of SUD comorbidity (71). Similarly, oxcarbazepine has been proposed as an alternative treatment for SUD during pregnancy (72), but with scarce evidence for the treatment of SUD in comorbidity with BD (73). The increased prevalence of polypharmacy, particularly benzodiazepines and other drugs, in patients suffering from BD and polySUD should be framed as an attempt to reduce abstinence, treat residual symptoms as sleep or anxiety derived from potential subsyndromal psychotic symptoms, or recognize the need for better mood stabilization. However, these hypotheses need to be confirmed by further studies.

Despite the clinical relevance of our findings, several limitations should be discussed. First, our study has a cross-sectional design; therefore, it is not possible to make any inferences on the temporal or causal relationship between the considered variables. Second, several clinical variables (i.e., number of affective episodes, type of bipolar cycle, adherence to treatment, substance switch, and psychiatric comorbidity with personality disorders or anxiety disorders) that could affect the illness course and impact the use of specific drugs were not included in the analyses due to the high number of missing values. Third, no assessment with psychometric tools was made to investigate the potential clinical dimension such as impulsivity, hostility, and aggressiveness. Finally, our data are limited to those derived from a single research center and inpatient unit; therefore, patients with BD in a euthymic phase were not considered.

CONCLUSION

Our study highlighted that several sociodemograhic and clinical characteristics may be associated with polySUD in patients with a primary diagnosis of BD. Given the significant impact of polySUD on the course and outcome of BD and the need for polypharmacy to guarantee adequate mood stabilization, further research on this topic is needed. Focusing the attention on this specific subtype of patients with BD may help implement personalized pharmacological and psychosocial therapies integrating the different professional roles.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the IRCCS Ospedale Policlinico San Martino. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AAg and AN: statistical analyses and writing the original draft. EB, VP, and EV: data collection and revision of data literature. AAm and AC: supervision of data collection, writing the protocol, review, and editing of the original draft. LF-P: methodology, conceptualization, review, and editing of the original draft. GS, EA, and MA: scientific advisor of the project. All authors approved the final draft of the manuscript before submission.

ACKNOWLEDGMENTS

This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018–2022 (Law 232/2016).

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association (2013). doi: 10.1176/appi.books.978089042559
2. Silva Ribeiro J, Pereira D, Salagre E, Coroa M, Santos Oliveira P, Santos V, et al. Risk calculators in bipolar disorder: a systematic review. *Brain Sci.* (2020) 10:525. doi: 10.3390/brainsci10080525
3. Geoffroy PA, Bellivier F, Scott J, Etain B. Seasonality and bipolar disorder: a systematic review, from admission rates to seasonality of symptoms. *J Affect Disord.* (2014) 168:210–23. doi: 10.1016/j.jad.2014.07.002
4. Aguglia A, Borsotti A, Maina G. Bipolar disorders: is there an influence of seasonality or photoperiod? *Braz J Psychiatry.* (2018) 40:6–11. doi: 10.1590/1516-4446-2016-2144
5. Maina G, D'Ambrosio V, Aguglia A, Paschetta E, Salvi V, Bogetto F. Bipolar disorders and metabolic syndrome: a clinical study in 185 patients. *Riv Psichiatr.* (2010) 45:34–40.
6. Fusar-Poli L, Amerio A, Cimpoesu P, Natale A, Salvi V, Zappa G, et al. Lipid and glycemic profiles in patients with bipolar disorder: cholesterol levels are reduced in mania. *Medicina (Kaunas).* (2020) 57:28. doi: 10.3390/medicina57010028

7. Salvi V, Aguglia A, Barone-Adesi F, Bianchi D, Donfrancesco C, Dragogna F, et al. Cardiovascular risk in patients with severe mental illness in Italy. *Eur Psychiatry.* (2020) 63:e96. doi: 10.1192/j.eurpsy.2020.94
8. Aguglia A, Salvi V, Amerio A, Gari M, Dragogna F, Mencacci C, et al. Number of episodes and duration of illness associated with hypertension and 10-year cardiovascular risk in patients with bipolar disorder type I. *Psychiatry Res.* (2022) 308:114344. doi: 10.1016/j.psychres.2021.114344
9. Foroughi M, Medina Inojosa JR, Lopez-Jimenez F, Saeidifard F, Suarez L, Stokin GB, et al. Association of bipolar disorder with major adverse cardiovascular events: a population-based historical cohort study. *Psychosom Med.* (2022) 84:97–103. doi: 10.1097/PSY.0000000000001017
10. Liu YK, Ling S, Lui LMW, Ceban F, Vinberg M, Kessing LV, et al. Prevalence of type 2 diabetes mellitus, impaired fasting glucose, general obesity, and abdominal obesity in patients with bipolar disorder: a systematic review and meta-analysis. *J Affect Disord.* (2022) 300:449–61. doi: 10.1016/j.jad.2021.12.110
11. Fusar-Poli L, Natale A, Amerio A, Cimpoesu P, Grimaldi Filioli P, Aguglia E, et al. Neutrophil-to-lymphocyte, Platelet-to-lymphocyte and monocyte-to-lymphocyte ratio in bipolar disorder. *Brain Sci.* (2021) 11:58. doi: 10.3390/brainsci11010058
12. Solmi M, Sharma MS, Osimo EF, Fornaro M, Bortolato B, Croatto G, et al. Peripheral levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-1β across the mood spectrum in bipolar disorder: a meta-analysis of mean differences and variability. *Brain Behav Immun.* (2021) 97:193–203. doi: 10.1016/j.bbi.2021.07.014
13. Khafif TC, Belizario GO, Silva M, Gomes BC, Lafer B. Quality of life and clinical outcomes in bipolar disorder: an 8-year longitudinal study. *J Affect Disord.* (2021) 278:239–43. doi: 10.1016/j.jad.2020.09.061
14. Kirchner SK, Lauseker M, Adorjan K, Anderson-Schmidt H, Anghelescu IG, Baune BT. Medication adherence in a cross-diagnostic sample of patients from the affective-to-psychotic spectrum: results from the PsyCourse study. *Front Psychiatry.* (2022) 12:713060. doi: 10.3389/fpsyt.2021.713060
15. Oladunjoye AF, Kaleem SZ, Suresh A, Sahni V, Thoonkuzhy MJ, Anugwom G, et al. Cannabis use and medication nonadherence in bipolar disorder: a nationwide inpatient sample database analysis. *J Affect Disord.* (2022) 299:174–9. doi: 10.1016/j.jad.2021.11.067
16. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. results from de epidemiologic catchment area (ECA) study. *JAMA.* (1990) 264:2511–8. doi: 10.1016/0376-8716(93)90010-n
17. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. *JAMA Psychiatry.* (2015) 72:757–66. doi: 10.1001/jamapsychiatry.2015.0584
18. Grant BF, Saha TD, Ruan WJ, Goldstein RB, Chou SP, Jung J, et al. Epidemiology of DSM-5 drug use disorder: results from the national epidemiologic survey on alcohol and related conditions-III. *JAMA Psychiatry.* (2016) 73:39–47. doi: 10.1001/jamapsychiatry.2015.2132
19. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry.* (2004) 61:807–16. doi: 10.1001/archpsyc.61.8.807
20. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry.* (2005) 66:1205–15. doi: 10.4088/jcp.v66n1001
21. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. . Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry.* (2007) 64:543–52. doi: 10.1001/archpsyc.64.5.543
22. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry.* (2011) 68:241–51. doi: 10.1001/archgenpsychiatry.2011.12
23. Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990-2015: systematic review and meta-analysis. *J Affect Disord.* (2016) 206:321–30. doi: 10.1016/j.jad.2016.06.051
24. Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: systematic review and meta-analysis. *J Affect Disord.* (2016) 206:331–49. doi: 10.1016/j.jad.2016.07.011
25. Acciavatti T, Lupi M, Santacroce R, Aguglia A, Attademo L, Bandini L, et al. Novel psychoactive substance consumption is more represented in bipolar disorder than in psychotic disorders: a multicenter-observational study. *Hum Psychopharmacol.* (2017) 32:e2578. doi: 10.1002/hup.2578
26. Zamora-Rodríguez FJ, Sánchez-Waisen-Hernández MR, Guisado-Macías JA, Vaz-Leal FJ. Substance use and course of bipolar disorder in an inpatient sample. *Actas Esp Psiquiatr.* (2018) 46:183–91.
27. Preuss UW, Schaefer M, Born C, Grunze H. Bipolar disorder and comorbid use of illicit substances. *Medicina (Kaunas).* (2021) 57:1256. doi: 10.3390/medicina57111256
28. Messer T, Lammers G, Müller-Siecheneder F, Schmidt RF, Latifi S. Substance abuse in patients with bipolar disorder: a systematic review and meta-analysis. *Psychiatry Res.* (2017) 253:338–50. doi: 10.1016/j.psychres.2017.02.067
29. Grunze H, Schaefer M, Scherk H, Born C, Preuss UW. Comorbid bipolar and alcohol use disorder-a therapeutic challenge. *Front Psychiatry.* (2021) 12:660432. doi: 10.3389/fpsyt.2021.660432
30. Tsuboi T, Suzuki T, Azekawa T, Adachi N, Ueda H, Edagawa K, et al. Factors associated with non-remission in bipolar disorder: the multicenter treatment survey for bipolar disorder in psychiatric outpatient clinics (MUSUBI). *Neuropsychiatr Dis Treat.* (2020) 16:881–90. doi: 10.2147/NDT.S246136
31. Bach SL, Cardoso TA, Moreira FP, Mondin TC, Simjanoski M, Kapczinski FP, et al. Risk factors for new-onset bipolar disorder in a community cohort: a five-year follow up study. *Psychiatry Res.* (2021) 303:114109. doi: 10.1016/j.psychres.2021.114109
32. Lalli M, Brouillette K, Kapczinski F, de Azevedo Cardoso T. Substance use as a risk factor for bipolar disorder: a systematic review. *J Psychiatr Res.* (2021) 144:285–95. doi: 10.1016/j.jpsychires.2021.10.012
33. Kim AM, Salstein L, Goldberg JF. A systematic review of complex polypharmacy in bipolar disorder: prevalence, clinical features, adherence, and preliminary recommendations for practitioners. *J Clin Psychiatry.* (2021) 82:20r13263. doi: 10.4088/JCP.20r13263
34. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* (2013) 310:2191–4.
35. Menculini G, Steardo L Jr., Verdolini N, Cirimbilli F, Moretti P, Tortorella A. Substance use disorders in bipolar disorders: clinical correlates and treatment response to mood stabilizers. *J Affect Disord.* (2022) 300:326–33. doi: 10.1016/j.jad.2022.01.001
36. Simhandl C, Radua J, König B, Amann BL. Prevalence and impact of comorbid alcohol use disorder in bipolar disorder: a prospective follow-up study. *Aust N Z J Psychiatry.* (2016) 50:345–51. doi: 10.1177/0004867415585855
37. Pinto JV, Medeiros LS, Santana da Rosa G, Santana de Oliveira CE, Crippa JAS, Passos IC, et al. The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: a systematic review with meta-analysis and meta-regression. *Neurosci Biobehav Rev.* (2019) 101:78–84. doi: 10.1016/j.neubiorev.2019.04.004
38. Szmulewicz AG, Valerio MP, Lomastro J, Smith JM, Chiappe V, Martino DJ, et al. Neurocognitive functioning in first-episode bipolar disorder: relationship with functional status. *J Affect Disord.* (2018) 228:97–100. doi: 10.1016/j.jad.2017.12.015
39. Prisciandaro JJ, Mellick W, Mitaro E, Tolliver BK. An evaluation of the impact of co-occurring anxiety and substance use disorder on bipolar disorder illness outcomes in STEP-BD. *J Affect Disord.* (2019) 246:794–9. doi: 10.1016/j.jad.2018.12.070
40. Sultan AA, Kennedy KG, Fiksenbaum L, MacIntosh BJ, Goldstein BI. Neurostructural correlates of cannabis use in adolescent bipolar disorder. *Int J Neuropsychopharmacol.* (2021) 24:181–90. doi: 10.1093/ijnp/pyaa077
41. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* (2018) 20:97–170. doi: 10.1111/bdi.12609

42. Vieta E, Salagre E, Grande I, Carvalho AF, Fernandes BS, Berk M, et al. Early intervention in bipolar disorder. *Am J Psychiatry.* (2018) 175:411–26. doi: 10.1176/appi.ajp.2017.17090972
43. Fantuzzi C, Mezzina R. Dual diagnosis: a systematic review of the organization of community health services. *Int J Soc Psychiatry.* (2020) 66:300–10. doi: 10.1177/0020764019899975
44. Grover S, Chakrabarti S, Sahoo S. Prevalence and clinical correlates of residual symptoms in remitted patients with bipolar disorder: an exploratory study. *Indian J Psychiatry.* (2020) 62:295–305. doi: 10.4103/psychiatry.IndianJPsychiatry_760_19
45. van Laar M, van Dorsselaer S, Monshouwer K, de Graaf R. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction.* (2007) 102:1251–60. doi: 10.1111/j.1360-0443.2007.01875.x
46. Samalin L, de Chazeron I, Vieta E, Bellivier F, Llorca PM. Residual symptoms and specific functional impairments in euthymic patients with bipolar disorder. *Bipolar Disord.* (2016) 18:164–73. doi: 10.1111/bdi.12376
47. Morton E, Murray G, Michalak EE, Lam RW, Beaulieu S, Sharma V, et al. Quality of life in bipolar disorder: towards a dynamic understanding. *Psychol Med.* (2018) 48:1111–8. doi: 10.1017/S0033291717002495
48. Bonnín CM, Jiménez E, Solé B, Torrent C, Radua J, Reinares M, et al. Lifetime psychotic symptoms, subthreshold depression and cognitive impairment as barriers to functional recovery in patients with bipolar disorder. *J Clin Med.* (2019) 8:1046. doi: 10.3390/jcm8071046
49. Consoloni JL, M'Bailara K, Perchec C, Aouizerate B, Aubin V, Azorin JM, et al. Trajectories of medication adherence in patients with bipolar disorder along 2 years-follow-up. *J Affect Disord.* (2021) 282:812–9. doi: 10.1016/j.jad.2020.12.192
50. Dell'Osso B, Camuri G, Cremaschi L, Dobrea C, Buoli M, Ketter TA, et al. Lifetime presence of psychotic symptoms in bipolar disorder is associated with less favorable socio-demographic and certain clinical features. *Compr Psychiatry.* (2017) 76:169–76. doi: 10.1016/j.comppsych.2017.04.005
51. Inchausti L, Gorostiza I, Torres G, Oraa R. Diagnostic stability in substance-induced psychosis. *Rev Psiquiatr Salud Ment (Engl Ed).* (2020): [Epub ahead of print], doi: 10.1016/j.rpsm.2019.10.005
52. Fiorentini A, Cantù F, Crisanti C, Cereda G, Oldani L, Brambilla P. Substance-induced psychoses: an updated literature review. *Front Psychiatry.* (2021) 12:694863. doi: 10.3389/fpsyt.2021.694863
53. Gogia M, Shah AQ, Kapczinski F, de Azevedo Cardoso T. The impact of substance use disorder comorbidity on cognition of individuals with bipolar disorder: a systematic review. *Psychiatr Res.* (2022) 311:114525. doi: 10.1016/j.psychres.2022.114525
54. Arias F, Szerman N, Vega P, Mesïas B, Basurte I, Rentero D. Bipolar disorder and substance use disorders. Madrid study on the prevalence of dual disorders/pathology. *Adicciones.* (2017) 29:186–94. doi: 10.20882/adicciones.782
55. Cretu JB, Culver JL, Goffin KC, Shah S, Ketter TA. Sleep, residual mood symptoms, and time to relapse in recovered patients with bipolar disorder. *J Affect Disord.* (2016) 190:162–6. doi: 10.1016/j.jad.2015.09.076
56. Samalin L, Boyer L, Murru A, Pacchiarotti I, Reinares M, Bonnin CM, et al. Residual depressive symptoms, sleep disturbance and perceived cognitive impairment as determinants of functioning in patients with bipolar disorder. *J Affect Disord.* (2017) 210:280–6. doi: 10.1016/j.jad.2016.12.054
57. Serafini G, Vazquez GH, Gonda X, Pompili M, Rihmer Z, Amore M. Depressive residual symptoms are associated with illness course characteristics in a sample of outpatients with bipolar disorder. *Eur Arch Psychiatry Clin Neurosci.* (2018) 268:757–68. doi: 10.1007/s00406-018-0875-5
58. Duffy A, Horrocks J, Milin R, Doucette S, Persson G, Grof P. Adolescent substance use disorder during the early stages of bipolar disorder: a prospective high- risk study. *J Affect Disord.* (2012) 142:57–64. doi: 10.1016/j.jad.2012.04.010
59. Hulvershorn LA, King J, Monahan PO, Wilcox HC, Mitchell PB, Fullerton JM, et al. Substance use disorders in adolescent and young adult relatives of probands with bipolar disorder: what drives the increased risk? *Compr Psychiatry.* (2017) 78:130–9. doi: 10.1016/j.comppsych.2017.07.010
60. Schuepbach D, Goetz I, Boeker H, Hell D. Voluntary vs. involuntary hospital admission in acute mania of bipolar disorder: results from the Swiss sample of the EMBLEM study. *J Affect Disord.* (2006) 90:57–61. doi: 10.1016/j.jad.2005.09.012
61. Schuepbach D, Novick D, Haro JM, Reed C, Boeker H, Noda S, et al. Determinants of voluntary vs. involuntary admission in bipolar disorder and the impact of adherence. *Pharmacopsychiatry.* (2008) 41:29–36. doi: 10.1055/s-2007-993213
62. Serafini G, Gonda X, Aguglia A, Amerio A, Santi F, Pompili M, et al. Bipolar subtypes and their clinical correlates in a sample of 391 bipolar individuals. *Psychiatry Res.* (2019) 281:112528. doi: 10.1016/j.psychres.2019.112528
63. Baertschi M, Costanza A, Canuto A, Weber K. The dimensionality of suicidal ideation and its clinical implications. *Int J Methods Psychiatr Res.* (2019) 28:e1755. doi: 10.1002/mpr.1755
64. Levola J, Laine R, Pitkanen T. In-patient psychiatric care and non-substance-related psychiatric diagnoses among individuals seeking treatment for alcohol and substance use disorders: associations with all-cause mortality and suicide. *Br J Psychiatry.* (2022):1–8. doi: 10.1192/bjp.2022.20 [Epub ahead of print].
65. Golden JC, Goethe JW, Woolley SB. Complex psychotropic polypharmacy in bipolar disorder across varying mood polarities: a prospective cohort study of 2712 inpatients. *J Affect Disord.* (2017) 221:6–10. doi: 10.1016/j.jad.2017.06.005
66. Maust DT, Lin LA, Blow FC. Benzodiazepine use and misuse among adults in the United States. *Psychiatr Serv.* (2019) 70:97–106. doi: 10.1176/appi.ps.201800321
67. Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: a systematic review. *Drug Alcohol Depend.* (2019) 200:95–114. doi: 10.1016/j.drugalcdep.2019.02.033
68. McHugh RK, Geyer RB, Chase AR, Griffin ML, Bogunovic O, Weiss RD. Sex differences in benzodiazepine misuse among adults with substance use disorders. *Addict Behav.* (2021) 112:106608. doi: 10.1016/j.addbeh.2020.106608
69. Bobo WV, Reilly-Harrington NA, Ketter TA, Brody BD, Kinrys G, Kemp DE, et al. Complexity of illness and adjunctive benzodiazepine use in outpatients with bipolar I or II disorder: results from the bipolar CHOICE study. *J Clin Psychopharmacol.* (2015) 35:68–74. doi: 10.1097/JCP.0000000000000257
70. Wingård L, Taipale H, Reutfors J, Westerlund A, Bodén R, Tiihonen J, et al. Initiation and long-term use of benzodiazepines and Z-drugs in bipolar disorder. *Bipolar Disord.* (2018) 20:634–46. doi: 10.1111/bdi.12626
71. Ng QX, Han MX, Teoh SE, Yaow CYL, Lim YL, Chee KTA. Systematic review of the clinical use of gabapentin and pregabalin in bipolar disorder. *Pharmaceuticals (Basel).* (2021) 14:834. doi: 10.3390/ph14090834
72. Johnson KD, Miller LN, Pouliot JD, Martin PR. Retrospective analysis of oxcarbazepine in pregnant women with substance use disorders: focus on safety. *J Pharm Pract.* (2021) 34:28–34. doi: 10.1177/0897190019850700
73. Altinbas K, Evren C. Comorbid substance use disorder in bipolar disorder: a hard rock to roll on the treatment road. *Dusunen Adam.* (2021) 34:111–3. doi: 10.14744/DAJPNS.2021.00128

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

TYPE Perspective
PUBLISHED 11 August 2022
DOI 10.3389/fpsyt.2022.949375

OPEN ACCESS

EDITED BY
Michele Fornaro,
University of Naples Federico II, Italy

REVIEWED BY
Claudio Caiazza,
University of Naples Federico II, Italy
Xenia Gonda,
Semmelweis University, Hungary

*CORRESPONDENCE
Anna Comparelli
anna.comparelli@uniroma1.it

SPECIALTY SECTION
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

RECEIVED 20 May 2022
ACCEPTED 19 July 2022
PUBLISHED 11 August 2022

CITATION
Comparelli A, Polidori L, Sarli G, Pistollato A and Pompili M (2022) Differentiation and comorbidity of bipolar disorder and attention deficit and hyperactivity disorder in children, adolescents, and adults: A clinical and nosological perspective. *Front. Psychiatry* 13:949375. doi: 10.3389/fpsyt.2022.949375

Differentiation and comorbidity of bipolar disorder and attention deficit and hyperactivity disorder in children, adolescents, and adults: A clinical and nosological perspective

Anna Comparelli[1]*, Lorenzo Polidori[2], Giuseppe Sarli[2], Andrea Pistollato[2] and Maurizio Pompili[3]

[1]Department of Psychiatry, Sant'Andrea Hospital of Rome, Rome, Italy, [2]Psychiatry Residency Training Program, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy, [3]Department of Neurosciences, Mental Health and Sensory Organs, Faculty of Medicine and Psychology, Suicide Prevention Centre, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

Bipolar Disorder (BD) and Attention Deficit and Hyperactivity Disorder (ADHD) are mental disorders with high degree of lifetime comorbidity. Both BD and ADHD are disorders with onset in childhood and early adolescence. Both disorders are often undiagnosed, misdiagnosed, and sometimes overdiagnosed, leading to high rates of morbidity and disability. The psychiatric and behavioral symptoms associated with ADHD and BD have significant overlap. Albeit the existence of a large body of literature, it is far from being clear whether comorbidity can be explained by the confounding overlap of operationally defined criteria or whether it reflects a genuine comorbidity of two biologically distinct disorders. The aim of this paper is to recognize and/or differentiate the pattern of ADHD across the course of BD from a nosological point of view, focusing on specific clinical and neurobiological dimensions. We found that some critical issues may help to fulfill the purpose of our perspective. We suggest that the relationship between ADHD and BD, based on clinical, developmental, and epidemiological commonalities, can be better clarified using four different scenarios.

KEYWORDS

bipolar disorder, ADHD, comorbidity, nosology and classification of mental disorders, neurodevelopment

Introduction

Bipolar Disorder (BD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are often recognized as mental disorders with a high degree of comorbidity (1–4). Bipolar disorders are chronic diseases characterized by the alternance of episodes of mania or hypomania and depression. Bipolar disorders have an early mean age of onset and are a major cause for disability in young people. Early recognition of the disease leads to more effective treatment and prevents greater disability (5). The definition of bipolar disorder

in pre-pubertal children (pediatric bipolar disorder, PBD) is still the object of an ongoing debate. There is a controversy concerning what is the definition of a pre-pubertal bipolar disorder, if there is a continuity of pediatric BD with adult BD, and if symptoms explained by a diagnosis of PBD could be better explained by other diagnoses, such as ADHD (6, 7).

ADHD is defined by the DSM-5 as an early-onset "neurodevelopmental disorder defined by impairing levels of inattention, disorganization and/or hyperactivity-impulsivity" (8). ADHD is a common childhood mental health disorder, even if its prevalence varies widely across different clinical settings and countries, partly due to differences in classifications and methods to diagnose it (9). About 50–65% of children with ADHD will continue to meet diagnostic criteria for ADHD in adulthood (4, 10).

There is an overlap between symptoms of ADHD and BD, and in particular (hypo) manic mood episodes features, such as hyperactivity, distractibility, lack of inhibition, restlessness, racing thoughts, rapid speech, talkativeness, and irritability. The overlap of symptoms and diagnostic criteria could make the distinction between the two disorders difficult, even if ADHD is a disorder with persistent symptoms, whereas symptoms in BD are episodic (4, 11, 12).

Many children are diagnosed with comorbid ADHD and PBD; comorbidity rates are estimated to be around 20% (1, 4), and children with ADHD are more likely to be diagnosed with BD later in life (4). BD with comorbid ADHD presents a more severe course of illness, with earlier onset, a shorter interval between episodes, and a shorter time of euthymia (11).

In this perspective paper, we focused on specific clinical and developmental dimensions in order to recognize and/or differentiate the pattern of ADHD across the course of BD in a nosological perspective. We found that some issues may help to fulfill the purpose of our perspective; we described the results in sections according to the crucial points raised.

Shared background between BD and ADHD

There is a well-established psychopathological bond between ADHD and BD, even if some studies show controversial results regarding their longitudinal relationship. Rates of comorbidity are very heterogeneous; this is influenced by several aspects. Interestingly, a difference can be detected between continents. For BD, it was suggested that the prevalence may be higher in the Americas compared with Asia and European nations (13, 14); this is not the same for ADHD. Geographic factors only seem to play a marginal role, while all the important differences between countries might be better explained by the adoption of different methodological approaches (9). A high proportion of ADHD patients, about 10%, receive a BD diagnosis throughout their life (2). One out of 13 patients with ADHD have BD, and nearly 1 in 6 patients with BD are diagnosed with ADHD. The prevalence of ADHD in BD patients differs when comparing distinct age groups: 73% in childhood, 43% in adolescence, and 17% in adulthood (3). The lifetime prevalence of ADHD is around 6.5%, while that of BD reaches 1–2% (9, 15, 16). All these data suggest that comorbid BD and ADHD can occur in around 0.12% of the general population, or up to 0.38% if considering smaller studies; this would correspond to nearly 4 million persons affected in US and Europe (16), representing a large burden as a comorbid nosological entity.

There are genetic implications involved in ADHD and BD comorbidity. Relatives of patients with BD had a significantly higher chance of having ADHD, and among relatives of ADHD patients BD occurred more frequently (17); the relative risk was about 2-fold higher for both situations. The existence of a familiarity suggests a genetic vulnerability for both the diseases. In fact, up to 33 loci were found to be involved in both ADHD and BD (18–21).

Shared additional risk factors are related to the prenatal, perinatal, and childhood periods. Maternal substance abuse exposes children to both conditions, and one study showed that this risk factor can be associated with the symptoms of ADHD, but not with a clinical diagnosis (22, 23). Maternal stress exposure during the first trimester was found to correlate with an increased risk of BD (22); the same association emerged with ADHD (24). However, this finding can be also attributed to genetic factors. Mothers suffering from BD or ADHD might experience more maternal stress; genetic background could indirectly impact the offspring (25). Individuals with childhood adversities and trauma were found more likely to develop ADHD and BD (26); regarding the latter, this risk factor may also lead to worse clinical outcomes (27).

ADHD: Developmental trajectories

The clinical course of ADHD to adulthood is characterized by the development of several psychiatric comorbidities during the transition from childhood/adolescence, impairment of social functioning, and deviant or rule-breaking behaviors. In adolescence, distinct cognitive profiles may emerge both reflecting continuation or potential recovery of ADHD, with or without an emotional dysregulation profile (28). Five different neurobiological developmental models explain the highly variable course of the symptomatology of ADHD during the transition from childhood to adolescence have been supposed (29). These models try to disentangle the reasons that define remission or persistence of symptoms. The first—"convergence"—posits that improvement follows the convergence of atypical neural features toward more typical brain features. The second—"compensation"—views symptomatic improvement as a consequence of the recruitment of new brain systems, compensating the core symptoms

of ADHD. The third model—"carried forward"—postulates different adolescent neural trajectories that take origin during childhood. Adolescents showing improvement or remission appear to have more typical neural features, while those showing persistence had more childhood anomalies. The fourth model—"cascading anomalies"—holds that early symptoms of ADHD may worsen neural anomalies and generate neural dysfunction. The last model—"fixed anomalies"—hypothesizes that the presence of childhood ADHD may be seen as a neural imprint that will persist regardless of the clinical course during the transition toward adolescence.

Several clinically informed factors such as gender, pre-mature birth, maternal education, school readiness, peer and conduct problems, cognitive and temperamental factors, early comorbidities, social context and medication could differentiate individuals following different ADHD symptom trajectories (29, 30). Genetic factors are major drivers for ADHD symptoms persistence during adolescence (31); conduct problems and comorbidities seems to play a major role for the future development of Bipolar Disorder (32).

Clinical trajectories from childhood ADHD to adult ADHD: Syndromatic and symptomatic ADHD

A large body of literature (28–30) suggests that ADHD tends to persist from childhood to adulthood in many cases. Some questions have been raised about the need for a proper definition of "persistence." According to Faraone et al. (29), syndromatic persistence is the permanence of a full diagnostic status, referring to individuals continuing to meet ADHD diagnostic criteria, even after the adulthood transition. On the other hand, symptomatic persistence is the presence of a partial diagnostic status along with impairment, referring to individuals who fail to meet full blown diagnostic criteria for ADHD, but who continue to have impairing symptoms.

A 10-year follow-up study by Biederman et al. (28) demonstrated that the majority of ADHD individuals continue to experience symptoms and functional impairment when moving into adulthood. Persistence at follow-up was associated with psychiatric comorbidity, functional impairments, familiarity, comorbid Conduct Disorder (CD), Major Depressive Disorder (MDD), treatment for ADHD and Oppositional-Defiant Disorder (33, 34).

A recent global systematic review and meta-analysis (30) estimated the prevalence of persistent adult ADHD (considering a childhood onset) and symptomatic adult ADHD (not considering childhood onset). Both measures showed a decrease with advancing age. Prevalence of persistent adult ADHD was 2.58%; prevalence of symptomatic adult ADHD was 6.76% globally.

Bipolar disorder developmental trajectory: "Homotypic trajectory" and "heterotypic trajectory"

Many studies, including systematic reviews, meta-analyses, prospective and retrospective studies, have evaluated the developmental trajectory ADHD-BD (2, 11, 32, 35–38).

A recent systematic meta-analytic review (2) estimated that about 10–12% of individuals with ADHD will be later diagnosed with BD; this transition mostly occurs during development. According to another follow-up study including a total of 17,285 subjects with ADHD conducted in Taiwan (35) the progression rate from ADHD to BD was 5.12%. Interestingly, among all participants, 62.16% progressed within the first 3 years, following the ADHD onset. Geographical features and sample sizes could explain progression rates differences. From a retrospective view Nierenberg et al. (11) estimated a 9.5% overall lifetime prevalence of comorbid ADHD in adults with BD.

Predictors of BD, considering the psychopathological characteristics that forewent the disorder, could be evaluated following the model proposed by Faedda et al. (32). More specifically, this involved a "homotypic trajectory" moving from affective psychopathology toward BDI/II, and an "heterotypic trajectory" moving from non-affective psychopathology. Evidence from the aforementioned paper showed a heterotypic developmental trajectory from prodromal sub-syndromal and syndromal Disruptive Behavior Disorders (ADHD, Conduct Disorder) and Anxiety Disorders (early-onset panic attacks, separation anxiety, and social phobia) toward BD. ADHD or anxiety increased the risk of developing BD in adulthood by 10-fold, while the combination of ADHD and anxiety increased the risk by 30-fold (38). This suggests that early manifestations of both externalizing and internalizing psychopathology could be related with the risk of future BD, considering internalizing psychopathology as an expression of conditions associated with negative emotions and externalizing psychopathology as an expression of conditions characterized by disinhibition (39). This dysregulation profile is characterized by a combination of externalizing (inattention and hyperactivity) and internalizing (anxiety) psychopathology that may indicate youth with propensity to BD. Dysregulation profile is currently conceptualized as a broad syndrome of difficulties in regulating affect, behavior, and cognition (40, 41). According to Brancati et al. (2), moving from this pattern of prodromal features emotional dysregulation can be considered as a trans-nosographic psychopathological dimension that facilitates the progression from ADHD to BD.

Several conditions and psychiatric comorbidities elevate the risk of progression from ADHD to BD. Among these are family history of BD, older age, Major Depressive Disorder (MDD), Anxiety Disorder, Autism Spectrum Disorder (ASD), Intelligence Disability (ID), Disruptive Behavior Disorder

(DBD), Oppositional-Defiant Disorder (ODD), Conduct Disorder (CD), criminal behavior, Alcohol Use Disorder (AUD), and Cluster A or B Personality Disorder (32, 35, 36, 38).

Comorbidity between BD and ADHD

There are significant clinical differences between patients diagnosed with both ADHD and BD and patients with BD without comorbid ADHD. Compared with the "pure" BD counterpart, patients with BD and ADHD have shorter period of wellness and stability (37), are younger when experiencing their first psychiatric symptoms (2, 11), show earlier treatment implementation (2) and are less successful at school and more unemployed (42). Talking about behavioral and properly ADHD features, patients with comorbid ADHD-BD exhibit a younger age of ADHD onset (2, 11), more externalizing problems (2, 43), a higher severity of hyperactive/impulsive and inattentive symptoms (2), more reactivity and verbal aggressiveness (44) and a history of violence, legal troubles, and rule-breaking behaviors (2, 37). Moreover, referring only to affective episodes, individuals with comorbid ADHD-BD experience significantly more depressive, mixed, hypo-manic, and total number of mood episodes (2, 37, 45), shorter euthymic intervals (2), earlier age of onset of mood disorder, more severe and chronic mood disorder, poorer response to mood stabilizer, and are more irritable (2, 37, 45, 46); the psychotic features are, however, less likely compared to "pure" bipolar patients (37). At last, for these patients more suicide attempts, more additional psychopathology (Anxiety, Disruptive Behavior Disorders, Substance Use Disorder and Alcohol Abuse) and more psychiatric hospitalizations are documented (2, 3, 11, 47).

A recent systematic review and meta-analysis (16) reported that there is no difference in comorbidity between ADHD and BD type I or BD type II. Nevertheless, differential diagnosis between ADHD and BD type II appears to be challenging due to the presence of sub-syndromal phenomena and mood states such as hypomania, rapid cycling, mixed episodes, and high-frequency mood swings, which are particularly common in BD type II. The trait-like nature of ADHD must be considered when comparing with state-like features of BD. A positive history of childhood ADHD can impact both the phenotype and the onset of depressive disorder, increasing the risk of bipolar spectrum features. Screening for lifetime ADHD in depressed individuals with treatment refractoriness and mixed features should be mandatory; on the other hand, young adults with ADHD along with a familiar load for mood disorder or with anxiety disorders should be candidates for depressive disorder prevention (36).

Discussion

Herein, we aimed to focus on specific clinical, developmental and neurobiological dimensions to recognize and/or differentiate the pattern of ADHD across the course of BD from a nosological perspective.

We are inclined to propose four scenarios that aim to clarify possible different relationships in clinical and research settings:

1) Overestimated comorbidity of ADHD or BD due to overlap of symptoms (especially in childhood and youth);
2) ADHD can be a prodrome of BD;
3) Comorbidity of syndromatic ADHD with strictly defined BD;
4) ADHD-BD is a full entity.

Regarding the first point, some authors (48, 49) have highlighted the possibility of a diagnostic artifact rather than a genuine finding when considering BD and ADHD in comorbidity. The adoption of a categorical approach instead of a dimensional one, over-splitting of symptoms (artificial subdivision of syndromes), and the overlapping symptoms such as impulsivity, irritable mood, and poor concentration might contribute to the development of a "false" comorbidity. In childhood and youth, differential diagnosis is clinically the most difficult due to the large overlap of the symptomatic and family patterns of both disorders; currently, there is substantial consensus that episodes are one of the hallmarks of BD and that phenotypes characterized by chronic irritability and lack of episodicity, are not consistent with a diagnosis of BD (50). In adulthood, a correct differential diagnosis between BD and ADHD, is pivotal, because irritability, inattention and hyperactivity improve with specific medications, and patients often do not need a mood stabilizer (that might be given with an overestimated comorbidity of BD) (51). A wrong BD diagnosis in adults with ADHD can lead to mood stabilizers that do not usually improve attention and memory, whilst the stimulant therapy can improve overall symptomatology, including irritability and hyperactivity (52).

Considering the second scenario, misleading comorbidity may be also related to developmental sequencing, which is an example of "heterotypic continuity" in which the same developmental process has different phenotypes at different stages of life. In this case, ADHD may represent a BD precursor in a heterotypic trajectory. Unfortunately, we are not currently able to accurately predict which patients with ADHD are prone to subsequent development of BD. In fact, on one hand, a specifically increased risk of BD can be confirmed in ADHD patients compared to healthy controls, which is higher than what expected based on the general predisposing effect on other kinds of psychopathology. On the other hand, BD following ADHD may be a specific, pediatric-onset, neurodevelopmentally-based, form of BD, different from adult-onset or older-age (neurodegenerative)-onset BD, despite phenotypical similarities. Early neurodevelopmental disorders, such as co-occurring

ADHD and emotional dysregulation, may be considered a precursor in the pathway to neurodevelopmental, early-onset, bipolarity (2).

As regard to the third scenario, although the higher known rates of ADHD and BD comorbidity is in childhood (3), we suggest that further studies are needed to establish the timing of emergence of different forms of BD in ADHD patients and *vice-versa*. Lower but still rather high comorbidity rates have been reported at later ages. Therefore, in adult patients with a recent diagnosis of BD, but with an unknown history of ADHD, an accurate assessment for a previous or current diagnosis of ADHD appears mandatory (3); if a history of childhood or adolescent ADHD emerges, clinicians should carefully ascertain whether the ADHD persists in a symptomatic or syndromatic form; only in the latter should a diagnosis of comorbidity be made (32).

The hypothesis of a full entity ADHD-BD, different from both ADHD and BD, is supported by several familial (53, 54) and genetic (55) studies. These findings suggest a mixed BD-ADHD disorder, with its own evolution, continuous rather than cyclic (56), earlier onset, male predominance, more frequent episodes with mixed states, irritability as a main feature, more severe manic symptoms, increased psychosocial problems, and necessitating a sequential treatment. Interestingly, this hypothesis is also in line with recent dimensional approaches to nosology, such as the Hierarchical Taxonomy of Psychopathology (HiTOP), which aims to identify psychopathology constructs based on patterns of co-variation among signs and symptoms (57), in contrast to the DSM/ICD nosography. In a dimensional perspective, in fact, ADHD and bipolar disorder may fall on a genetic continuum of severity, with patients with ADHD but not bipolar disorder being at the mild end, patients with bipolar disorder but not ADHD having greater severity and patients with both ADHD and bipolar disorder having the greatest severity (58).

Apart from theoretical and nosological issues, therapeutic implications may arise from perspective paper such as the present one.

Treatment of concurrent ADHD and BD, regardless of the phase of illness, remains an unresolved challenge; in a developmental perspective view, treatment may require a staged approach. By staging the introduction of treatments, one can reduce the risk of overmedicating patients and better assess the effect of each individual treatment (59). On the other hand, in case of real comorbidity, a hierarchical approach to treatment should be followed. At present, data on treatment response of comorbid ADHD-BD are very limited. In clinical practice, most adult patients presenting with symptoms of both ADHD and BD tend to be treated only for the mood disorder (60). The use of BD medications in ADHD-BD patients may be problematic, with high rates of non-response and residual functional impairment. Patients should be treated hierarchically: BD should be treated first, while ADHD should be treated combining ADHD medications and mood stabilizers after mood stabilization (61). A proper mood stabilizing therapy can reduce the chance of positive mood episodes that might arise if we only use ADHD specific medications and that is why we actually follow a hierarchical approach.

Our perspective is focused on the clinical and developmental aspects of ADHD and BD; genetic, neurobiological, neurocognitive and therapeutic aspects were not part of the aims of this perspective paper. We hope that better clinical and developmental characterization is coming and that parallel efforts through nosology can be useful.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AC: conception, original draft, and revision. LP, GS, and AP: drafting and collecting data. MP: final revision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Franke B, Michelini G, Asherson P, Banaschewski T, Bilbow A, Buitelaar JK, et al. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. *Eur Neuropsychopharmacol.* (2018) 28:1059–88. doi: 10.1016/j.euroneuro.2018.08.001

2. Brancati GE, Perugi G, Milone A, Masi G, Sesso G. Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis of prospective studies. *J Affect Disord.* (2021) 293:186–96. doi: 10.1016/j.jad.2021.06.033

3. Sandstrom A, Perroud N, Alda M, Uher R, Pavlova B. Prevalence of attention-deficit/hyperactivity disorder in people with mood disorders: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica.* (2021) 143:380–91. doi: 10.1111/acps.13283

4. Edinoff AN, Apgar TL, Rogers JJ, Harper JD, Cornett EM, Kaye AM, et al. Attention deficit hyperactivity disorder and bipolar disorder: diagnosis, treatments, and clinical considerations: a narrative review. *Psychiatry Int.* (2021) 3:17–28. doi: 10.3390/psychiatryint3010002

5. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. *Nat Rev Dis Prim.* (2018) 4:18008. doi: 10.1038/nrdp.2018.8

6. Duffy A, Carlson G, Dubicka B, Hillegers MHJ. Pre-pubertal bipolar disorder: origins and current status of the controversy. *Int J Bipolar Disord.* (2020) 8:18. doi: 10.1186/s40345-020-00185-2

7. Carlson GA, Klein DN. How to understand divergent views on bipolar disorder in youth. *Ann Rev Clin Psychol.* (2014) 10:529–51. doi: 10.1146/annurev-clinpsy-032813-153702

8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5 (R))*, 5th Edn. Arlington, TX: American Psychiatric Association (2013).

9. Polanczyk G v, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol.* (2014) 43:434–42. doi: 10.1093/ije/dyt261

10. Asherson P, Buitelaar J, Faraone SV, Rohde LA. Adult attention-deficit hyperactivity disorder: key conceptual issues. *Lancet Psychiatry.* (2016) 3:568–78. doi: 10.1016/S2215-0366(16)30032-3

11. Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, et al. Clinical and diagnostic implications of lifetime attention-deficit/ hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry.* (2005) 57:1467–73. doi: 10.1016/j.biopsych.2005.01.036

12. Zaravinos-Tsakos F, Kolaitis G. Disentangling pediatric bipolar disorder and attention deficit-hyperactivity disorder: a neuropsychological approach. *Psychiatriki*. (2020) 31:332–40. doi: 10.22365/jpsych.2020.314.332

13. Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry.* (2011) 68:241–51. doi: 10.1001/archgenpsychiatry.2011.12

14. Rehm J, Shield KD. Global burden of disease and the impact of mental and addictive disorders. *Curr Psychiatry Rep.* (2019) 21:10. doi: 10.1007/s11920-019-0997-0

15. Fayyad J, Sampson NA, Hwang I, Adamowski T, Aguilar-Gaxiola S, Al-Hamzawi A, et al. The descriptive epidemiology of DSM-IV adult ADHD in the world health organization world mental health surveys. *Attent Deficit Hyperact Disord.* (2017) 9:47–65. doi: 10.1007/s12402-016-0208-3

16. Schiweck C, Arteaga-Henriquez G, Aichholzer M, Edwin Thanarajah S, Vargas-Cáceres S, Matura S, et al. Comorbidity of ADHD and adult bipolar disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* (2021) 124:100–23. doi: 10.1016/j.neubiorev.2021.01.017

17. Faraone S v., Biederman J, Wozniak J. Examining the comorbidity between attention deficit hyperactivity disorder and bipolar i disorder: a meta-analysis of family genetic studies. *Am J Psychiatry.* (2012) 169:1256–66. doi: 10.1176/appi.ajp.2012.12010087

18. O'Connell KS, Shadrin A, Bahrami S, Smeland OB, Bettella F, Frei O, et al. Identification of genetic overlap and novel risk loci for attention-deficit/hyperactivity disorder and bipolar disorder. *Mol Psychiatry.* (2021) 26:4055–65. doi: 10.1038/s41380-019-0613-z

19. Fahira A, Li Z, Liu N, Shi Y. Prediction of causal genes and gene expression analysis of attention-deficit hyperactivity disorder in the different brain region, a comprehensive integrative analysis of ADHD. *Behav Brain Res.* (2019) 364:183–92. doi: 10.1016/j.bbr.2019.02.010

20. Hitomi Y, Nakatani K, Kojima K, Nishida N, Kawai Y, Kawashima M, et al. NFKB1 and MANBA confer disease susceptibility to primary biliary cholangitis via independent putative primary functional variants. *Cell Mol Gastroenterol Hepatol.* (2019) 7:515–32. doi: 10.1016/j.jcmgh.2018.11.006

21. MacArthur J, Bowler E, Cerezo M, Gil L, Hall P, Hastings E, et al. The new NHGRI-EBI catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res.* (2017) 45:D896–901. doi: 10.1093/nar/gkw1133

22. Marangoni C, Hernandez M, Faedda GL. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. *J Affect Disord.* (2016) 193:165–74. doi: 10.1016/j.jad.2015.12.055

23. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal risk factors and the etiology of ADHD—review of existing evidence. *Curr Psychiatry Rep.* (2017) 19:1. doi: 10.1007/s11920-017-0753-2

24. Manzari N, Matvienko-Sikar K, Baldoni F, O'Keeffe GW, Khashan AS. Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis. *Soc Psychiatry Psychiatric Epidemiol.* (2019) 54:1299–309. doi: 10.1007/s00127-019-01745-3

25. Perez Algorta G, Kragh CA, Arnold LE, Molina BSG, Hinshaw SP, Swanson JM, et al. Maternal ADHD symptoms, personality, and parenting stress: differences between mothers of children with ADHD and mothers of comparison children. *J Attent Disord.* (2018) 22:1266–77. doi: 10.1177/1087054714561290

26. Brown NM, Brown SN, Briggs RD, Germán M, Belamarich PF, Oyeku SO. Associations between adverse childhood experiences and ADHD diagnosis and severity. *Acad Pediatr.* (2017) 17:349–55. doi: 10.1016/j.acap.2016.08.013

27. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry.* (2016) 3:342–9. doi: 10.1016/S2215-0366(15)00544-1

28. Biederman J, Petty CR, Evans M, Small J, Faraone SV. How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. *Psychiatry Res.* (2010) 177:299–304. doi: 10.1016/j.psychres.2009.12.010

29. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med.* (2006) 36:159–65. doi: 10.1017/S003329170500471X

30. Song P, Zha M, Yang Q, Zhang Y, Li X, Rudan I. The prevalence of adult attention-deficit hyperactivity disorder: a global systematic review and meta-analysis. *J Global Health.* (2021) 11:1–9. doi: 10.7189/jogh.11.04009

31. Shaw P, Sudre G. Adolescent attention-deficit/hyperactivity disorder: understanding teenage symptom trajectories. *Biol Psychiatry.* (2021) 89:152–161. doi: 10.1016/j.biopsych.2020.06.004

32. Faedda GL, Serra G, Marangoni C, Salvatore P, Sani G, Vázquez GH, et al. Clinical risk factors for bipolar disorders: a systematic review of prospective studies. *J Affect Disord.* (2014) 168:314–21. doi: 10.1016/j.jad.2014.07.013

33. Caye A, Swanson J, Thapar A, Sibley M, Arseneault L, Hechtman L, et al. Life span studies of ADHD—conceptual challenges and predictors of persistence and outcome. *Curr Psychiatry Rep.* (2016) 18:111. doi: 10.1007/s11920-016-0750-x

34. Tandon M, Tillman R, Agrawal A, Luby J. Trajectories of ADHD severity over 10 years from childhood into adulthood. *ADHD Attent Deficit Hyperact Disord.* (2016) 8:121–30. doi: 10.1007/s12402-016-0191-8

35. Chu CS, Tsai SJ, Hsu JW, Huang KL, Cheng CM, Su TP, et al. Diagnostic progression to bipolar disorder in 17,285 adolescents and young adults with attention deficit hyperactivity disorder: a longitudinal follow-up study. *J Affect Disord.* (2021) 295:1072–8. doi: 10.1016/j.jad.2021.08.097

36. Purper-Ouakil D, Porfirio MC, le Strat Y, Falissard B, Gorwood P, Masi G. What do childhood attention deficit/hyperactivity symptoms in depressed adults tell us about the bipolar spectrum? *Psychiatry Res.* (2017) 249:244–51. doi: 10.1016/j.psychres.2016.12.055

37. Rydén E, Thase ME, Stråht D, Åberg-Wistedt A, Bejerot S, Landén M. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. *Acta Psychiatrica Scandinavica.* (2009) 120:239–46. doi: 10.1111/j.1600-0447.2009.01399.x

38. Meier SM, Pavlova B, Dalsgaard S, Nordentoft M, Mors O, Mortensen PB, et al. Attention-deficit hyperactivity disorder and anxiety disorders as precursors of bipolar disorder onset in adulthood. *Brit J Psychiatry.* (2018) 213:555–60. doi: 10.1192/bjp.2018.111

39. Krueger RF, Markon KE. Understanding psychopathology: melding behavior genetics, personality, and quantitative psychology to develop an empirically based model. *Curr Dir Psychol Sci.* (2006) 15:113. doi: 10.1111/j.0963-7214.2006.00418.x

40. Althoff RR, Verhulst FC, Rettew DC, Hudziak JJ, van der Ende J. Adult outcomes of childhood dysregulation: a 14-year follow-up study. *J Am Acad Child Adolesc Psychiatry.* (2010) 49:1105–16. doi: 10.1016/j.jaac.2010.08.006

41. Deutz MHF, Geeraerts SB, Belsky J, Deković M, van Baar AL, Prinzie P, et al. General psychopathology and dysregulation profile in a longitudinal community sample: stability, antecedents and outcomes. *Child Psychiatry Hum Dev.* (2020) 51:114–26. doi: 10.1007/s10578-019-00916-2

42. Pinna M, Visioli C, Rago CM, Manchia M, Tondo L, Baldessarini RJ. Attention deficit-hyperactivity disorder in adult bipolar disorder patients. *J Affect Disord.* (2019) 243:391–6. doi: 10.1016/j.jad.2018.09.038

43. Serrano E, Ezpeleta L, Castro-Fornieles J. Comorbidity and phenomenology of bipolar disorder in children with ADHD. *J Attent Disord.* (2013) 17:330–8. doi: 10.1177/1087054711427553

44. Doerfler LA, Connor DF, Toscano PF. Aggression, ADHD symptoms, and dysphoria in children and adolescents diagnosed with bipolar disorder and ADHD. *J Affect Disord.* (2011) 131:312–9. doi: 10.1016/j.jad.2010.11.029

45. Bernardi S, Cortese S, Solanto M, Hollander E, Pallanti S. Bipolar disorder and comorbid attention deficit hyperactivity disorder. A distinct clinical phenotype? Clinical characteristics and temperamental traits. *World J Biol Psychiatry.* (2010) 11:656–66. doi: 10.3109/15622971003653238

46. Perugi G, Ceraudo G, Vannucchi G, Rizzato S, Toni C, Dell'Osso L. Attention deficit/hyperactivity disorder symptoms in italian bipolar adult patients: a preliminary report. *J Affect Disord.* (2013) 149:430–4. doi: 10.1016/j.jad.2012.12.010

47. Karaahmet E, Konuk N, Dalkilic A, Saracli O, Atasoy N, Kurçer MA, et al. The comorbidity of adult attention-deficit/hyperactivity disorder in bipolar disorder patients. *Comp Psychiatry.* (2013) 54:549–55. doi: 10.1016/j.comppsych.2012.11.005

48. Youngstrom EA, Arnold LE, Frazier TW. Bipolar and ADHD comorbidity: both artifact and outgrowth of shared mechanisms. *Clin Psychol Sci Pract.* (2010) 17:350–9. doi: 10.1111/j.1468-2850.2010.01226.x

49. Lus G, Mukaddes NM. Co-morbidity of bipolar disorder in children and adolescents with attention deficit/hyperactivity disorder (ADHD) in an outpatient Turkish sample. *World J Biol Psychiatry.* (2009) 10:488–94. doi: 10.1080/15622970902929876

50. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry.* (2011) 168:129–42. doi: 10.1176/appi.ajp.2010.10050766

51. Perugi G, Pallucchini A, Rizzato S, Pinzone V, De Rossi P. Current and emerging pharmacotherapy for the treatment of adult attention deficit hyperactivity disorder (ADHD). *Expert Opin Pharmacother.* (2019) 20:1457–70. doi: 10.1080/14656566.2019.1618270

52. Wender PH, Wolf LE, Wasserstein J. Adults with ADHD. An overview. *Ann N Y Acad Sci.* (2001) 931:1–16. doi: 10.1111/j.1749-6632.2001.tb05770.x

53. Larsson H, Rydén E, Boman M, Långström N, Lichtenstein P, Landén M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. *Br J Psychiatry.* (2013) 203:103–6. doi: 10.1192/bjp.bp.112.120808

54. Biederman J, Faraone SV, Petty C, Martelon MK, Woodworth KY, Wozniak J. Further evidence that pediatric-onset bipolar disorder comorbid with ADHD represents a distinct subtype: results from a large controlled family study. *J Psychiatr Res.* (2013) 47:15. doi: 10.1016/j.jpsychires.2012.08.002

55. van Hulzen KJE, Scholz CJ, Franke B, Ripke S, Klein M, McQuillin A, et al. Genetic overlap between attention-deficit/hyperactivity disorder and bipolar disorder: evidence from genome-wide association study meta-analysis. *Biol Psychiatry.* (2017) 82:634–41. doi: 10.1016/j.biopsych.2016.08.040

56. Masi G, Perugi G, Toni C, Millepiedi S, Mucci M, Bertini N, et al. Attention-deficit hyperactivity disorder – bipolar comorbidity in children and adolescents. *Bipolar Disord.* (2006) 8:373–81. doi: 10.1111/j.1399-5618.2006.00342.x

57. Kotov R, Waszczuk MA, Krueger RF, Forbes MK, Watson D, Clark LA, et al. The hierarchical taxonomy of psychopathology (HiTOP): a dimensional alternative to traditional nosologies. *J Abnorm Psychol.* (2017) 126:454–77. doi: 10.1037/abn0000258

58. Faraone SV. Attention-deficit hyperactivity disorder and the shifting sands of psychiatric nosology. *Br J Psychiatry.* (2013) 203:81–3. doi: 10.1192/bjp.bp.113.126524

59. Scheffer RF. Concurrent ADHD and bipolar disorder. *Curr Psychiatry Rep.* (2007) 9:415–9. doi: 10.1007/s11920-007-0054-2

60. Klassen LJ, Katzman MA, Chokka P. Adult ADHD and its comorbidities, with a focus on bipolar disorder. *J Affect Disord.* (2010) 124:1–8. doi: 10.1016/j.jad.2009.06.036

61. Perugi G, Vannucchi G. The use of stimulants and atomoxetine in adults with comorbid ADHD and bipolar disorder. *Expert Opin Pharmacother.* (2015) 16:2193–204. doi: 10.1517/14656566.2015.1079620

frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 06 September 2022
DOI 10.3389/fpsyt.2022.984829

OPEN ACCESS

EDITED BY
Domenico De Berardis,
Mental Health Center (CSM) and Psychiatric Service of Diagnosis and Treatment (SPDC), Italy

REVIEWED BY
Mei Hong Xiu,
Beijing Huilongguan Hospital, Peking University, China
Shen Li,
Tianjin Medical University, China

*CORRESPONDENCE
Shenglin She
shenglinshe@gzhmu.edu.cn
Yingjun Zheng
brainzheng@gzhmu.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

RECEIVED 02 July 2022
ACCEPTED 01 August 2022
PUBLISHED 06 September 2022

CITATION
Yi W, Wu H, Li R, Li H, Song Z, She S and Zheng Y (2022) Prevalence and associated factors of obesity and overweight in Chinese patients with bipolar disorder.
Front. Psychiatry 13:984829.
doi: 10.3389/fpsyt.2022.984829

Prevalence and associated factors of obesity and overweight in Chinese patients with bipolar disorder

Wenying Yi†, Haibo Wu†, Ruikeng Li, Haijing Li, Zhen Song, Shenglin She* and Yingjun Zheng*

The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China

Object: Despite abundant literature demonstrating a high prevalence of obesity and overweight in people with bipolar disorder (BD), little is known about this topic in China. Therefore, we assessed the prevalence and associated factors of obesity and overweight among inpatients with BD in our hospital, one of the largest public psychiatric hospitals in China.

Methods: In this retrospective, cross-sectional study, 1,169 inpatients ≥18 years with BD during 2019 were included. Obesity was defined as having a BMI ≥25 kg/m^2, and overweight was defined as having a BMI from 23 kg/m^2 to <25 kg/m^2. Binary logistic regression analysis was performed to identify factors associated with obesity and overweight.

Results: The prevalence of obesity and overweight was 21.0% and 32.2% in patients with BD, respectively. Compared to patients with overweight and normal weight, patients with obesity were older, had a longer duration of BD and a longer length of hospital stay, had a higher prevalence of diabetes and hypertension, and had a higher level of all metabolic indices, except for HDL cholesterol. Binary logistic regression analysis showed that duration of BD, uric acid, alanine aminotransferase (ALT), triglyceride, and LDL cholesterol were significantly associated with obesity, and male sex and uric acid level were significantly associated with overweight ($p < 0.05$).

Conclusions: Obesity and overweight were fairly prevalent in Chinese BD patients, and several factors were related to obesity and overweight. The results of the present study call for the need to implement early screening, prevention and interventions for obesity and overweight in patients with BD in China.

KEYWORDS

obesity, overweight, prevalence, risk factors, bipolar disorder

Introduction

Bipolar disorder (BD) is one of the most severe and function-impaired mental disorders with a high global burden. BD affected 4.53 million people in 2017 (1). The disability-adjusted life years (DALYs) of BD increased by 54.4%, from 6.02 million in 1990 to 9.29 million in 2017 (1).

In the United States, the estimated total annual national economic burden of BD/bipolar I disorder (BD-I) subtype was more than $195 billion, with ∼25% attributed to direct medical costs (2). People with BD/BD-I used health-care services more frequently and had higher direct medical costs than matched controls (2). A meta-analysis with 31 studies suggested that people with BD had a 7.42-fold increased risk of unnatural death and a 1.64-fold increased risk of natural death compared to the general population (3). A 1.73 times risk of deaths from circulatory illnesses, 2.92 times risk of deaths from respiratory illness, 2.25 times risk of deaths from respiratory illness, and 1.14 times risk of deaths from neoplasm caused these natural deaths in patients with BD (3). Data from a meta-analysis of 32 studies between 1984 and 2013 with 470,411 participants showed that the pooled prevalence of BD was generally lower in China than in Western countries (4). Recently, a study based on a multistage, stratified, cluster random sampling method with 20,884 participants also found that the prevalence of BD was lower in China than in other countries (5). However, Chinese patients with BD also had higher all-cause, natural-cause and unnatural-cause mortality rates than the general population (6). A study reported that Chinese men and women with BD had 6.78 years and 7.35 years of excess life-years lost, respectively (6). Respiratory diseases, cardiovascular diseases and cancers accounted for the majority of deaths among Chinese BD (6).

In recent years, the prevalence of obesity has increased globally, and obesity has become a major public health problem (7). In 2010, it was estimated that overweight and obesity cause 3.4 million deaths, 3.9% of years of life lost, and 3.8% of DALYs worldwide (7). Based on Chinese criteria, the estimated Chinese national prevalence rates of obesity and overweight were 16.4 and 34.3% between 2015 and 2019, respectively (8). Economic developments, sociocultural norms, substantial changes in dietary patterns, decreased physical activity levels, increased sedentary behaviors, genetic susceptibility, psychosocial factors, obesogens, and *in utero* and early-life exposures drive the growing burden of overweight and obesity in China (8). A Chinese study found that the total, direct, and indirect costs of the four obesity-related illnesses were up to $30,350.8 million, $28,642.5 million, and $1,708.3 million, respectively, with 12.7% attributable to general obesity and 28.7% attributable to central obesity (9). Even in 2003, the estimated total medical cost attributable to overweight and obesity reached ∼$2.74 billion, accounting for 25.5% of the total medical costs for the four obesity-related chronic diseases or 3.7% of the national total medical costs (10). If not eliminated, obesity is associated with an increased risk of diseases such as type 2 diabetes mellitus, fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnea and several cancers, leading to a decline in both quality of life and life expectancy (11). Moreover, previous evidence has shown that obesity is closely correlated with an increased risk of developing mental disorders, including mood disorders, anxiety disorders, personality disorders, attention deficit hyperactivity disorder (ADHD), binge eating disorders, trauma, BD, and schizophrenia (12). Maternal obesity has been found to be linked with neuropsychiatric disorders, including ADHD, autism spectrum disorders, anxiety, depression, schizophrenia, eating disorders, and impairments in cognition in offspring (13). Metabolic alterations, systemic inflammation, oxidative stress, neuroinflammation and impaired brain plasticity induced by a high-fat diet have been found to be tightly interconnected processes, implicating the role of obesity in the pathogenesis of neurological diseases (14).

People with BD have a high prevalence of obesity. A meta-analysis of 49 studies found that the pooled prevalence of general obesity (BMI $\geq$ 30 kg/m^2) was 29.0% among 322,494 adults with BD, which was significantly higher than their healthy counterparts (15). This meta-analysis also suggested that the pooled prevalence of abdominal obesity in 2,378 BD patients was up to 51.1%, and female BD patients and duration of BD were significantly associated with abdominal obesity (15). It has been reported that illness-related factors (mood-related factors, i.e., mania or depression), treatment-related factors (weight implications and other side effects of medications), and lifestyle factors (physical inactivity, poor diet, smoking, substance abuse) were associated with obesity among people with BD (16). Although current evidence remains controversial in most aspects of clinical outcomes, existing evidence suggests that obesity in BD places patients at considerable risk for poor outcomes, such as altering the course of BD, worsening global functioning, poor treatment response and a chronic course of illness, and enhancing rapid cycling (17). Furthermore, in young people with BD, obesity has been shown to be associated with physical abuse, suicide attempts, self-injurious behaviors, psychotropic medication, and psychiatric hospitalizations (18).

Despite the substantial number of studies assessing obesity and overweight in people with BD (15), little is known about obesity and overweight among Chinese patients with BD. To our knowledge, only two studies have assessed obesity in Chinese BD patients. One early prospective study of 148 Chinese adult patients with BD reported that the prevalence of obesity (BMI $\geq$25 kg/m^2) increased from 34.5% at baseline to 45.3% at the study endpoint (19). Another recently published study found that the prevalence of obesity and overweight were 17.74 and 34.68% in 124 patients with stable BD, respectively (20). Both of these studies suggested that obesity was prevalent in Chinese patients with BD, but they did not investigate the associated factors of obesity and overweight and only included a small sample.

Therefore, we conducted this study to investigate the prevalence and associated factors of obesity and overweight in a larger sample of inpatients with BD in China. This study will add to the body of knowledge on obesity and overweight among BD patients from a large public psychiatric hospital in China.

Methods

Subjects and study design

This retrospective observational study was conducted at the Affiliated Brain Hospital of Guangzhou Medical University, which is one of the largest public mental health centers with 1,920 beds for inpatient service in China. The ethics committee of the Affiliated Brain Hospital of Guangzhou Medical University approved this retrospective cross-sectional study. The diagnosis of mental disorders was established by two experienced psychiatrists according to the 10th revision of the International Classification of Diseases (ICD-10).

The inclusion criteria were as follows: (1) inpatients diagnosed with BD; (2) aged ≥18 years; (3) admitted to our hospital between January 1, 2019, and December 31, 2019; and (4) had a record of BMI at admission to the hospital. The exclusion criteria were as follows: (1) inpatients aged <18 years; (2) severe physical diseases, pregnancy, lactation, or missing BMI data. If the patients were readmitted during 2019, only the data of the first admission for the patients were collected and used for analysis.

Data collection and analysis

Data were extracted from the electronic databases of this hospital. The collected data were anonymized. The following data were collected for all of the included inpatients: sex, age, duration of BD, length of hospital stay, BMI at admission, and diagnoses at discharge. Laboratory results of the first blood tests were collected, including uric acid, alanine aminotransferase (ALT), triglyceride, total cholesterol, LDL cholesterol, and HDL cholesterol. The first blood tests are usually conducted on the second day after admission to our hospital.

Definitions of obesity and overweight

Based on the Asian-specific cutoff points (21), patients with a BMI < 23 kg/m^2 were defined as normal weight, patients with a BMI from 23 kg/m^2 to <25 kg/m^2 were defined as overweight, and patients with a BMI ≥ 25 kg/m^2 were defined as obese for both men and women.

Data analysis

Demographic and clinical variables of patients with obesity, overweight and normal weight were compared with the F test for continuous variables and the Chi-squared test for categorical variables. Continuous variables are presented as the mean and standard deviation, and categorical variables are presented as frequencies. A binary logistic regression was used to examine which factors were strongly associated with obesity and overweight (with normal weight as the reference group). All p-values were 2-tailed, and $p < 0.05$ was the threshold for statistical significance. All statistical analyses were performed with SPSS 21.0.

Results

Demographic and clinical characteristics of patients with BD

There were 10,046 inpatients in the Affiliated Brain Hospital of Guangzhou Medical University in 2019, among which 1,426 were BD patients aged ≥18 years. After excluding 257 (18.0%) patients without a recorded BMI, a total of 1169 patients (630 men and 539 women) were included in this study. There were no significant difference in age and gender between patients with BMI and patients without BMI.

The demographic and clinical characteristics of patients with obesity, patients who were overweight and patients with normal weight were compared and are presented in Table 1. The average age of all the included patients was 35.2 ± 13.8 years, ranging from 18 to 79 years. The average disease duration was 9.1 ± 9.3 years, and the average length of hospital stay was 37.5 ± 42.3 days. Among all of the patients, 70 (6.0%) patients had diabetes, and 81 (6.9%) patients had hypertension. Significant differences between the groups were found in the following variables: duration of BD, uric acid, ALT, triglyceride, TC, HDL cholesterol and LDL cholesterol ($p < 0.05$). There were significant differences in the prevalence of sex, diabetes and hypertension among the three groups ($p < 0.05$). Patients with obesity had much higher levels of all metabolic parameters than patients with overweight and normal weight, except for HDL ($p < 0.05$).

The prevalence of obesity and overweight

The overall prevalence of obesity and overweight in patients with BD was 21.0% (246/1169) and 32.2% (377/1169), respectively. A total of 22.2% (140/630) of men and 19.7% (106/539) of women were obese; 40.3% (254/630) of men and 22.8% (123/539) of women were

TABLE 1 Demographic and clinical characteristics of BD patients with obesity, patients with overweight and patients with normal weight.

	Obesity (*n*, %)	Overweight (*n*, %)	Normal weight (*n*, %)	X^2/F	*P*
Cases	246 (21.0)	377 (32.2)	546 (46.7)	-	-
Gender					
Male	140 (22.2)	254 (40.3)	236 (37.5)	53.489	0.001
Female	106 (19.7)	123 (22.8)	310 (57.5)		
Diabetes	25 (10.2)	20 (5.3)	25 (4.6)	9.854	0.007
Hypertension	29 (11.8)	25 (6.6)	27 (4.9)	12.393	0.002
Hyperlipidemia	85 (35.0)	70 (18.8)	61 (11.4%)	61.268	0.001
Age (years)	36.8 ± 12.9	35.4 ± 13.4	34.5 ± 14.5	2.319	0.099
The length of hospital stay (days)	42.7 ± 45.9	36.2 ± 43.7	36.2 ± 39.6	2.301	0.101
Duration (years)	11.9 ± 9.6	9.1 ± 9.3	7.9 ± 9.0	16.455	0.000
Uric acid (μmol/L) ($n = 1,166$)	448.9 ± 136.0	413.9 ± 110.4	361.3 ± 102.8	57.292	0.001
ALT (U/L) ($n = 1,168$)	31.4 ± 25.1	23.4 ± 18.1	20.5 ± 24.0	19.760	0.001
Total cholesterol (mmol/L) ($n = 1,152$)	4.8 ± 1.1	4.6 ± 1.0	4.3 ± 0.8	20.064	0.001
Triglyceride (mmol/L) ($n = 1,152$)	1.6 ± 0.8	1.3 ± 0.7	1.0 ± 0.6	51.237	0.001
HDL cholesterol (mmol/L) ($n = 1,152$)	1.2 ± 0.2	1.2 ± 0.3	1.3 ± 0.3	22.756	0.001
LDL cholesterol (mmol/L) ($n = 1,152$)	2.8 ± 0.9	2.6 ± 0.8	2.3 ± 0.6	37.872	0.001

TABLE 2 Associated factors for obesity in patients with BD.

	P	OR	95% CI
Age	0.053	0.982	0.965–1.000
Duration of BD	<0.001	1.058	1.033–1.084
Male	0.317	0.820	0.555–1.210
The length of hospital stay	0.195	1.003	0.999–1.007
Diabetes	0.867	0.937	0.438–2.002
Hypertension	0.192	0.604	0.283–1.288
Uric acid	<0.001	1.004	1.003–1.006
ALT	0.010	1.010	1.002–1.017
Total cholesterol	0.413	0.784	0.437–1.405
Triglyceride	<0.001	1.745	1.289–2.363
HDL cholesterol	0.189	0.553	0.229–1.337
LDL cholesterol	0.023	2.180	1.114–4.268

overweight, and this difference was significant ($X^2 = 53.489$, $p = 0.001$).

Factors associated with obesity and overweight in patients with BD

As shown in Table 2, after adjusting for relevant variables, the results of a stepwise forward binary logistic regression showed that the duration of BD, uric acid, ALT, triglyceride and LDL cholesterol were significantly associated with obesity ($p < 0.05$).

Factors associated with overweight in patients with BD

As shown in Table 3, a stepwise forward binary logistic regression suggested that male sex and uric acid were significantly associated with overweight ($p < 0.05$).

Discussion

Obesity is a major risk factor for non-communicable diseases in the general population and among people with mental

TABLE 3 Associated factors for overweight in patients with BD.

	P	OR	95% CI
Age	0.675	0.997	0.984–1.011
Duration of BD	0.112	1.015	0.997–1.034
Male	<0.001	2.060	1.509–2.812
The length of hospital stay	0.704	0.999	0.996–1.003
Diabetes	0.881	1.056	0.518–2.153
Hypertension	0.578	0.826	0.420–1.622
Uric acid	<0.001	1.003	1.001–1.004
ALT	0.637	0.998	0.992–1.005
Total cholesterol	0.533	1.200	0.676–2.131
Triglyceride	0.197	1.194	0.912–1.563
HDL cholesterol	0.251	0.628	0.284–1.389
LDL cholesterol	0.692	1.144	0.589–2.222

disorders. To the best of our knowledge, this is the first and largest sample-based study investigating the prevalence and associated factors of obesity and overweight in patients with BD in China. We found that the prevalence rates of obesity and overweight were 21.0% and 32.2% in 1,169 in patients with BD, respectively. Given the global trend of increased obesity in the general population and the high prevalence of obesity in people with mental disorders, it is not surprising that obesity and overweight were prevalent in our study. The prevalence of obesity was 31.9% in 2007 and 37.2% in 2017 among two large-sample nationally representative surveys in the Chinese general population, which was much higher than our findings (22). However, the total prevalence of overweight and obesity was 52.2% in 2007 and 58.0% in 2017 in that study, which is similar to the findings (53.2%) in our study. The mean age in that study was 44.8 years in 2007 and 43.8 years in 2017, both much higher than our study (35.2 years). Age is an independent risk factor for obesity (22). Another study in China with 441 thousand adults reported that people aged 45–54 years had the highest frequency of overweight and obesity (23). A meta-analysis with 101 studies including 698,905 participants identified that the prevalence of obesity increased with age, and people aged > 40 years had the highest percentage of obesity and overweight in Middle East countries (24). The lower mean age in our study may account for our lower prevalence of obesity. We found that overweight and obesity were prevalent, which is consistent with existing studies of people with BD (15). However, our 21.0% prevalence rate of obesity is lower than the 29.0% reported in a recent meta-analysis (15), similar to a previous study in China (20). That study with a smaller sample noted that the prevalence of obesity and overweight were 17.74 and 47.58% in 124 Chinese stable BD patients, respectively (20). The discrepancy between our study and other studies in the prevalence of overweight and obesity among BD patients may be due to differences in race, region, quality of health care, lifestyles, dietary habits, genetic factors, criteria for obesity, stage of BD, and psychotropic use.

We found that the duration of BD was significantly associated with obesity, which is consistent with the findings of a previous study among patients with BD at the initiation of the acute phase treatment (25). Some studies also found that the duration of BD was associated with a higher BMI (26), increased medical burden (27), worsening of both the clinical profile and brain structural alterations (28), metabolic syndrome (29), and diabetes (30). Recently, a positive correlation between the duration of BD and the number of mood episodes with both hypertension and the 10-year cardiovascular risk score has been found in patients with BD type I (31). A longer duration of BD may be linked with mood instability, chronicity, unhealthy lifestyles, and more complex psychopharmacological treatments involving antipsychotics, which may lead to insulin resistance, metabolic syndrome, and autonomic nervous system dysfunction, increasing the risk of developing obesity (31).

Conflicting results regarding gender differences in the prevalence of overweight and obesity have been reported in the general population and people with BD (15, 32). Between 1975 and 2014, the global age-standardized prevalence of obesity more than tripled in men (from 3.2 to 10.8%) and doubled in women (from 6.4% to 14.9%), and the global prevalence of morbid obesity and severe obesity was much higher in women than in men (32). However, according to a systematic analysis for the global burden of disease study in 2013, gender differences in the levels and trends of overweight and obesity were much smaller in both developed and developing countries (33). In addition, a meta-analysis showed that there were no sex differences in the prevalence of obesity in BD (15). Two studies suggested that male BD patients had a higher prevalence of obesity and overweight than female BD patients (25, 34), and we found that male BD patients had a higher prevalence of obesity and overweight and that male sex was significantly associated with overweight in our study. Interestingly, a study in the Chinese general population also found that men had higher rates of obesity and overweight than women in 2007 and 2017 (22). We speculate that different behavioral styles (excessive eating, drinking and smoking) may account for the higher prevalence of obesity and overweight in men with BD.

Uric acid is the end product of the purinergic system, and hyperuricemia has been recognized as a potentially treatable risk factor for cardiometabolic diseases; it could predict the development of hypertension, metabolic syndrome, type 2 diabetes, coronary artery disease, left ventricular hypertrophy, atrial fibrillation, myocardial infarction, stroke, heart failure and chronic kidney disease in the general population (35). In addition, hyperuricemia can accelerate hepatic and peripheral lipogenesis to cause obesity (36). People with BD have a high prevalence of hyperuricemia, with a figure ranging between 27.7 and 31.91% (37, 38). Increasing evidence from genetic and

clinical studies suggests that purinergic system dysfunction may play a role in the pathophysiology and therapeutics of BD (39), and increased uric acid levels are correlated with impulsivity, excitatory behavior, irritability, a hot temperament and severe manic symptoms in patients with BD. Moreover, hyperuricemia was associated with metabolic parameters in people with BD (37, 40). For example, a study in Italy reported that metabolic syndrome, abdominal circumference and triglyceride levels had a significant effect on uric acid in patients with BD (40). Hyperuricemia has also been found to be associated with metabolic syndrome and a larger waist circumference in Chinese patients with BD (37). A significant relationship between uric acid and a higher prevalence of obesity and overweight was found in the present study, which is consistent with previous studies (36). Our findings suggest that more studies investigating the potential association between uric acid and obesity should be conducted among patients with BD.

ALT is the liver enzyme most strongly correlated with liver fat accumulation and has been found to be closely related to obesity and metabolic syndrome (41). For example, a large sample-based study with 3,843 pediatric and adolescent subjects suggested that each unit increment in ALT elevated the odds of being metabolically unhealthy obese by 2% compared with metabolically healthy non-obese individuals (42). In a study with 5,411 adolescents aged 12–19 in the US, ALT levels were significantly correlated with BMI Z score and metabolic syndrome Z score ($p < 0.0001$) (43). A longitudinal study also indicated that weight gain was significantly associated with an increased risk of elevated ALT levels (44). Elevated ALT was also associated with natural death in BD (45). In line with these studies, we found that ALT was significantly associated with obesity in patients with BD.

We found that triglycerides and LDL cholesterol were associated with increased obesity in BD, consistent with previous studies showing an association between obesity and blood lipid-related parameters in the general population (46). Triglycerides were much higher in drug-naïve BD patients and BD patients taking medications than in healthy controls, and triglycerides were found to be associated with cognitive dysfunction and worse cognitive flexibility in BD (47). Triglycerides were the most accurate factor to identify individuals with greater cognitive impairment from among patients with severe mental disorders (48). In the general population, triglycerides are an independent risk factor for cardiovascular disease (49), and could serve as an independent marker for an increased risk of cardiovascular diseases in patients with type 2 diabetes mellitus (50). Furthermore, triglycerides are dose-dependently associated with increased risks of cardiovascular diseases and all-cause mortality in the general population (51). Notably, elevated triglycerides and other metabolic risk factors are highly prevalent yet under-treated in patients with BD (52).

There were several limitations in our study. First, a major limitation is its retrospective and naturalistic design, which cannot prove a direct causal association between any variables and obesity in patients with BD. Second, we only included inpatients with BD from a psychiatric hospital, and outpatients and patients in general hospitals and communities were not included. This population could not represent all patients with BD in China. Third, data on other important associated factors of obesity and overweight were not available, such as smoking, a family history of obesity, the type and duration of psychotropic medicine, physical activity, genetic factors and dietary habits. Not including these factors could limit our study, and these associated factors should be considered in future studies. Fourth, healthy controls matched for age and sex were not included in this study, so we could not compare obesity and overweight in patients with BD and the general population. Fifth, ∼20% of BD patients with missing BMI were excluded, which might cause potential selection bias. On the other hand, its large sample size is a strength of our study.

Conclusion

In summary, this is the first study to investigate the prevalence and associated factors of obesity and overweight in a relatively large sample of adult patients with BD in China. The present study provided detailed features of obesity and overweight in Chinese patients with BD. In this retrospective and cross-sectional study, obesity and overweight were prevalent among inpatients with BD. In a binary logistic regression analysis, duration of BD and the levels of uric acid, ALT, triglycerides, and LDL cholesterol were identified as predictors for the occurrence of obesity, whereas male sex and uric acid level were associated with a higher frequency of overweight. The results of the present study indicate a need to implement early screening, prevention and interventions for obesity and overweight in patients with BD in China.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

WY, HW, RL, HL, ZS, SS, and YZ designed the study and wrote the protocol. WY, HW, RL, HL, and ZS were collected data. WY and HW wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. He H, Hu C, Ren Z, Bai L, Gao F, Lyu J. Trends in the incidence and DALYs of bipolar disorder at global, regional, and national levels: results from the global burden of Disease Study 2017. *J Psychiatr Res.* (2020) 125:96–105. doi: 10.1016/j.jpsychires.2020.03.015

2. Bessonova L, Ogden K, Doane MJ, O'Sullivan AK, Tohen M. The economic burden of bipolar disorder in the United States: a systematic literature review. *Clinicoecon Outcomes Res.* (2020) 12:481–97. doi: 10.2147/CEOR.S259338

3. Hayes JF, Miles J, Walters K, King M, Osborn DP. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatr Scand.* (2015) 131:417–25. doi: 10.1111/acps.12408

4. Zhang L, Cao XL, Wang SB, Zheng W, Ungvari GS, Ng CH, et al. The prevalence of bipolar disorder in China: a meta-analysis. *J Affect Disord.* (2017) 207:413–21. doi: 10.1016/j.jad.2016.08.062

5. Zhang YS, Rao WW, Zeng LN, Lok G, Cui LJ Li JF, et al. Prevalence and correlates of bipolar disorder in the adult population of Hebei province, China. *J Affect Disord.* (2020) 263:129–33. doi: 10.1016/j.jad.2019.11.104

6. Chan J, Wong C, Yung N, Chen E, Chang WC. Excess mortality and life-years lost in people with bipolar disorder: an 11-year population-based cohort study. *Epidemiol Psychiatr Sci.* (2021) 30:e39. doi: 10.1017/S2045796021000305

7. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* (2012) 380:2224–60.

8. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. *Lancet Diabetes Endocrinol.* (2021) 9:373–92. doi: 10.1016/S2213-8587(21)00045-0

9. Li Q, Cai L, Cui W, Wang G, He J, Golden AR. Economic burden of obesity and four obesity-related chronic diseases in rural Yunnan Province, China. *Public Health.* (2018) 164:91–8. doi: 10.1016/j.puhe.2018.07.024

10. Zhao W, Zhai Y, Hu J, Wang J, Yang Z, Kong L, et al. Economic burden of obesity-related chronic diseases in Mainland China. *Obes Rev.* (2008) 9 Suppl 1:62–7. doi: 10.1111/j.1467-789X.2007.00440.x

11. Bluher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol.* (2019) 15:288–98. doi: 10.1038/s41574-019-0176-8

12. Perry C, Guillory TS, Dilks SS. Obesity and psychiatric disorders. *Nurs Clin North Am.* (2021) 56:553–63. doi: 10.1016/j.cnur.2021.07.010

13. Rivera HM, Christiansen KJ, Sullivan EL. The role of maternal obesity in the risk of neuropsychiatric disorders. *Front Neurosci.* (2015) 9:194. doi: 10.3389/fnins.2015.00194

14. Crispino M, Trinchese G, Penna E, Cimmino F, Catapano A, Villano I, et al. Interplay between peripheral and central inflammation in obesity-promoted disorders: the impact on synaptic mitochondrial functions. *Int J Mol Sci.* (2020) 21:5964. doi: 10.3390/ijms21175964

15. Liu YK, Ling S, Lui L, Ceban F, Vinberg M, Kessing LV, et al. Prevalence of type 2 diabetes mellitus, impaired fasting glucose, general obesity, and abdominal obesity in patients with bipolar disorder: a systematic review and meta-analysis. *J Affect Disord.* (2022) 300:449–61. doi: 10.1016/j.jad.2021.12.110

16. Tully A, Smyth S, Conway Y, Geddes J, Devane D, Kelly JP, et al. Interventions for the management of obesity in people with bipolar disorder. *Cochrane Database Syst Rev.* (2020) 7:CD013006. doi: 10.1002/14651858.CD013006.pub2

17. Gimenez-Palomo A, Gomes-da-Costa S, Dodd S, Pachiarotti I, Verdolini N, Vieta E, et al. Does metabolic syndrome or its component factors alter the course of bipolar disorder? A systematic review. *Neurosci Biobehav Rev.* (2022) 132:142–53. doi: 10.1016/j.neubiorev.2021.11.026

18. Girela-Serrano BM, Guerrero-Jimenez M, Spiers A, Gutierrez-Rojas L. Obesity and overweight among children and adolescents with bipolar disorder from the general population: a review of the scientific literature and a meta-analysis. *Early Interv Psychiatry.* (2022) 16:113–25. doi: 10.1111/eip.13137

19. Guan N, Liu H, Diao F, Zhang J, Zhang M, Wu T. Prevalence of metabolic syndrome in bipolar patients initiating acute-phase treatment: a 6-month follow up. *Psychiatry Clin Neurosci.* (2010) 64:625–33. doi: 10.1111/j.1440-1819.2010.02150.x

20. Li X, Shi X, Tan Y, Yu Y, Tang C, Xu G, et al. Metabolic indexes of obesity in patients with common mental disorders in stable stage. *BMC Psychiatry.* (2022) 22:91. doi: 10.1186/s12888-022-03752-2

21. Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pac J Clin Nutr.* (2008) 17:370–4.

22. Li Y, Teng D, Shi X, Teng X, Teng W, Shan Z, et al. Changes in the prevalence of obesity and hypertension and demographic risk factor profiles in China over 10 years: two national cross-sectional surveys. *Lancet Reg Health West Pac.* (2021) 15:100227. doi: 10.1016/j.lanwpc.2021.100227

23. Zhang L, Wang Z, Wang X, Chen Z, Shao L, Tian Y, et al. Prevalence of overweight and obesity in China: results from a cross-sectional study of 441 thousand adults, 2012-2015. *Obes Res Clin Pract.* (2020) 14:119–26. doi: 10.1016/j.orcp.2020.02.005

24. Okati-Aliabad H, Ansari-Moghaddam A, Kargar S, Jabbari N. Prevalence of obesity and overweight among adults in the middle east countries from 2000 to 2020: a systematic review and meta-analysis. *J Obes.* (2022) 2022:8074837. doi: 10.1155/2022/8074837

25. Kim B, Kim S, McIntyre RS, Park HJ, Kim SY, Joo YH. Correlates of metabolic abnormalities in bipolar I disorder at initiation of acute phase treatment. *Psychiatry Investig.* (2009) 6:78–84. doi: 10.4306/pi.2009.6.2.78

26. Calkin C, van de Velde C, Ruzickova M, Slaney C, Garnham J, Hajek T, et al. Can body mass index help predict outcome in patients with bipolar disorder? *Bipolar Disord.* (2009) 11:650–6. doi: 10.1111/j.1399-5618.2009.00730.x

27. Soreca I, Fagiolini A, Frank E, Houck PR, Thompson WK, Kupfer DJ. Relationship of general medical burden, duration of illness and age in patients with bipolar I disorder. *J Psychiatr Res.* (2008) 42:956–61. doi: 10.1016/j.jpsychires.2007.10.009

28. Melloni E, Poletti S, Vai B, Bollettini I, Colombo C, Benedetti F. Effects of illness duration on cognitive performances in bipolar depression are mediated by white matter microstructure. *J Affect Disord.* (2019) 249:175–82. doi: 10.1016/j.jad.2019.02.015

29. Grover S, Malhotra N, Chakrabarti S, Kulhara P. Metabolic syndrome in bipolar disorders. *Indian J Psychol Med.* (2012) 34:110–8. doi: 10.4103/0253-7176.101767

30. Kittel-Schneider S, Bury D, Leopold K, Haack S, Bauer M, Pfeiffer S, et al. Prevalence of prediabetes and diabetes mellitus type II in bipolar disorder. *Front Psychiatry.* (2020) 11:314. doi: 10.3389/fpsyt.2020.00314

31. Aguglia A, Salvi V, Amerio A, Gari M, Dragogna F, Mencacci C, et al. Number of episodes and duration of illness associated with hypertension and 10-year cardiovascular risk in patients with bipolar disorder type I. *Psychiatry Res.* (2022) 308:114344. doi: 10.1016/j.psychres.2021.114344

32. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet.* (2016) 387:1377–96. doi: 10.1016/S0140-6736(16)30054-X

33. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* (2014) 384:766–81.

34. McElroy SL, Frye MA, Suppes T, Dhavale D, Keck PJ, Leverich GS, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry.* (2002) 63:207–13. doi: 10.4088/JCP.v63n0306

35. Borghi C, Agabiti-Rosei E, Johnson RJ, Kielstein JT, Lurbe E, Mancia G, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. *Eur J Intern Med.* (2020) 80:1–11. doi: 10.1016/j.ejim.2020.07.006

36. Johnson RJ, Lanaspa MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. *Semin Nephrol.* (2011) 31:394–9. doi: 10.1016/j.semnephrol.2011.08.002

37. Chen J, Chen H, Feng J, Zhang L, Li J, Li R, et al. Association between hyperuricemia and metabolic syndrome in patients suffering from bipolar disorder. *BMC Psychiatry.* (2018) 18:390. doi: 10.1186/s12888-018-1952-z

38. Yang X, Tao H, Xiao L, Li C, Tang Y, Liu Y. Increased serum C3 and decreased UA in patients of bipolar disorder in Chinese Han population. *Front Psychiatry.* (2018) 9:381. doi: 10.3389/fpsyt.2018.00381

39. Ortiz R, Ulrich H, Zarate CJ, Machado-Vieira R. Purinergic system dysfunction in mood disorders: a key target for developing improved therapeutics. *Prog Neuropsychopharmacol Biol Psychiatry.* (2015) 57:117–31. doi: 10.1016/j.pnpbp.2014.10.016

40. Bartoli F, Crocamo C, Gennaro GM, Castagna G, Trotta G, Clerici M, et al. Exploring the association between bipolar disorder and uric acid: a mediation analysis. *J PSYCHOSOM RES.* (2016) 84:56–9. doi: 10.1016/j.jpsychores.2016.03.014

41. Kunutsor SK, Seddoh D. Alanine aminotransferase and risk of the metabolic syndrome: a linear dose-response relationship. *PLoS ONE.* (2014) 9:e96068. doi: 10.1371/journal.pone.0096068

42. Kelishadi R, Hemati Z, Qorbani M, Motlagh ME, Djalalinia S, Ahadi Z, et al. Association of alanine aminotransferase with different metabolic phenotypes of obesity in children and adolescents: the CASPIAN-V study. *Front Endocrinol (Lausanne).* (2020) 11:358. doi: 10.3389/fendo.2020.00358

43. Fermin CR, Lee AM, Filipp SL, Gurka MJ, DeBoer MD. Serum alanine aminotransferase trends and their relationship with obesity and metabolic syndrome in United States adolescents, 1999-2014. *Metab Syndr Relat Disord.* (2017) 15:276–82. doi: 10.1089/met.2017.0023

44. Flores YN, Auslander A, Crespi CM, Rodriguez M, Zhang ZF, Durazo F, et al. Longitudinal association of obesity, metabolic syndrome and diabetes with risk of elevated aminotransferase levels in a cohort of Mexican health workers. *J Dig Dis.* (2016) 17:304–12. doi: 10.1111/1751-2980.12341

45. Tsai SY, Lee CH, Kuo CJ, Chen CC, A. retrospective analysis of risk and protective factors for natural death in bipolar disorder. *J Clin Psychiatry.* (2005) 66:1586–91. doi: 10.4088/JCP.v66n1215

46. Su X, Peng D. The exchangeable apolipoproteins in lipid metabolism and obesity. *Clin Chim Acta.* (2020) 503:128–35. doi: 10.1016/j.cca.2020.01.015

47. Qiu Y, Li S, Teng Z, Tan Y, Xu X, Yang M, et al. Association between abnormal glycolipid level and cognitive dysfunction in drug-naive patients with bipolar disorder. *J Affect Disord.* (2022) 297:477–85. doi: 10.1016/j.jad.2021.10.100

48. Sanchez-Orti JV, Balanza-Martinez V, Correa-Ghisays P, Selva-Vera G, Vila-Frances J, Magdalena-Benedito R, et al. Specific metabolic syndrome components predict cognition and social functioning in people with type 2 diabetes mellitus and severe mental disorders. *Acta Psychiatr Scand.* (2022) 146:215–26. doi: 10.1111/acps.13433

49. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk.* (1996) 3:213–9. doi: 10.1097/00043798-199604000-00014

50. Ye X, Kong W, Zafar MI, Chen LL. Serum triglycerides as a risk factor for cardiovascular diseases in type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Cardiovasc Diabetol.* (2019) 18:48. doi: 10.1186/s12933-019-0851-z

51. Liu J, Zeng FF, Liu ZM, Zhang CX, Ling WH, Chen YM. Effects of blood triglycerides on cardiovascular and all-cause mortality: a systematic review and meta-analysis of 61 prospective studies. *Lipids Health Dis.* (2013) 12:159. doi: 10.1186/1476-511X-12-159

52. McElroy SL, Keck PJ. Metabolic syndrome in bipolar disorder: a review with a focus on bipolar depression. *J Clin Psychiatry.* (2014) 75:46–61. doi: 10.4088/JCP.13r08634

frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 20 October 2022
DOI 10.3389/fpsyt.2022.931374

OPEN ACCESS

EDITED BY
Claudia Carmassi,
University of Pisa, Italy

REVIEWED BY
Christoph Born,
Klinikum am Weissenhof, Germany
Outi Linnaranta,
National Institute for Health and Welfare, Finland
Rikinkumar S. Patel,
Duke University Medical Center, United States

*CORRESPONDENCE
Ana Moreno-Alcázar
amoreno.centreforum@gmail.com

†These authors share senior authorship

SPECIALTY SECTION
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

RECEIVED 28 April 2022
ACCEPTED 30 September 2022
PUBLISHED 20 October 2022

CITATION
Hogg B, Valiente-Gómez A, Redolar-Ripoll D, Gardoki-Souto I, Fontana-McNally M, Lupo W, Jiménez E, Madre M, Blanco-Presas L, Reinares M, Cortizo R, Massó-Rodriguez A, Castaño J, Argila I, Castro-Rodríguez JI, Comes M, Doñate M, Herrería E, Macias C, Mur E, Novo P, Rosa AR, Vieta E, Radua J, Padberg F, Pérez-Solà V, Moreno-Alcázar A and Amann BL (2022) High incidence of PTSD diagnosis and trauma-related symptoms in a trauma exposed bipolar I and II sample.
Front. Psychiatry 13:931374.
doi: 10.3389/fpsyt.2022.931374

High incidence of PTSD diagnosis and trauma-related symptoms in a trauma exposed bipolar I and II sample

Bridget Hogg[1,2,3,4], Alicia Valiente-Gómez[1,2,4], Diego Redolar-Ripoll[5,6], Itxaso Gardoki-Souto[1,3], Marta Fontana-McNally[1,2], Walter Lupo[1], Esther Jiménez[4,7], Mercè Madre[8,9,10], Laura Blanco-Presas[9,10,11], María Reinares[4,7], Romina Cortizo[12,13], Anna Massó-Rodriguez[14], Juan Castaño[13], Isabel Argila[9,10], José Ignacio Castro-Rodríguez[13], Mercè Comes[4,7], Marta Doñate[13,15], Elvira Herrería[9], Cristina Macias[1,16], Estanislao Mur[2,13], Patricia Novo[14,17], Adriane R. Rosa[18,19,20], Eduard Vieta[4,7], Joaquim Radua[4,7,21,22], Frank Padberg[23], Victor Pérez-Solà[2,4,13,24], Ana Moreno-Alcázar[1,2,4*†] and Benedikt L. Amann[1,2,4,23,24†]

[1]Centre Fòrum Research Unit, Institute of Neuropsychiatry and Addiction (INAD), Parc de Salut Mar, Barcelona, Spain, [2]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain, [3]PhD Programme, Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, [4]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto Carlos III, Madrid, Spain, [5]Neuromodulation Unit, Institut Brain, Barcelona, Spain, [6]Cognitive NeuroLab, Faculty of Psychology and Educational Sciences, Universitat Oberta de Catalunya (UOC), Barcelona, Spain, [7]Bipolar and Depressive Disorders Unit, Hospital Clinic, University of Barcelona, L'Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [8]Addictive Behaviours Unit, Psychiatry Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [9]Hospital Benito Menni-CASM, Sant Boi de Llobregat, Barcelona, Spain, [10]FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain, [11]Programa TEPT-AGRESX, Instituto de Neurociencias (ICN), Hospital Clinic, Barcelona, Spain, [12]Centro Salud Mental Adultos Ciutat Vella, Parc Sanitari Sant Joan de Déu, Barcelona, Spain, [13]Centro Salud Mental Adultos (CSMA), Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, Barcelona, Spain, [14]Centro de Salud Mental Infantil y Juvenil (CSMIJ), Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, Barcelona, Spain, [15]Parc Sanitari Sant Joan de Deu, Sant Boi de Llobegrat, Spain, [16]Centre Emili Mira, Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, Barcelona, Spain, [17]Day Hospital, Centro de Psicoterapia de Barcelona (CPB), Barcelona, Spain, [18]Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil, [19]Departamento de Farmacologia, Instituto de Ciências Básicas de Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [20]Postgraduate Program in Psychiatry and Behavioral Sciences, Federal University of Rio Grande doSul (UFRGS), Porto Alegre, Brazil, [21]Department of Clinical Neuroscience, Karolinska Institutet (KI), Solna, Sweden, [22]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [23]Clinic for Psychiatry and Psychotherapy, Klinikum der Universität München, Munich, Germany, [24]Departamento de Medicina y Ciencias de la Vida, Universitat Pompeu Fabra, Barcelona, Spain

Background: Post-traumatic stress disorder (PTSD) is an established comorbidity in Bipolar Disorder (BD), but little is known about the characteristics of psychological trauma beyond a PTSD diagnosis and differences in trauma symptoms between BD-I and BD-II.

Objective: (1) To present characteristics of a trauma-exposed BD sample; (2) to investigate prevalence and trauma symptom profile across BD-I and BD-II; (3) to assess the impact of a lifetime PTSD diagnosis vs. a history of trauma on BD course; and (4) to research the impacts of sexual and physical abuse.

Methods: This multi-center study comprised 79 adult participants with BD with a history of psychological trauma and reports baseline data from a trial registered in Clinical Trials (https://clinicaltrials.gov; ref: NCT02634372). Clinical variables were gathered through clinical interview, validated scales and a review of case notes.

Results: The majority (80.8%) of our sample had experienced a relevant stressful life event prior to onset of BD, over half of our sample 51.9% had a lifetime diagnosis of PTSD according to the Clinician Administered PTSD scale. The mean Impact of Event Scale-Revised scores indicated high levels of trauma-related distress across the sample, including clinical symptoms in the PTSD group and subsyndromal symptoms in the non-PTSD group. Levels of dissociation were not higher than normative values for BD. A PTSD diagnosis (vs. a history of trauma) was associated with psychotic symptoms [2(1) = 5.404, $p = 0.02$] but not with other indicators of BD clinical severity. There was no significant difference between BD-I and BD-II in terms of lifetime PTSD diagnosis or trauma symptom profile. Sexual abuse significantly predicted rapid cycling [2(1) = 4.15, $p = 0.042$], while physical abuse was not significantly associated with any clinical indicator of severity.

Conclusion: Trauma load in BD is marked with a lack of difference in trauma profile between BD-I and BD-II. Although PTSD and sexual abuse may have a negative impact on BD course, in many indicators of BD severity there is no significant difference between PTSD and subsyndromal trauma symptoms. Our results support further research to clarify the role of subsyndromic PTSD symptoms, and highlight the importance of screening for trauma in BD patients.

KEYWORDS

bipolar disorder, PTSD—post-traumatic stress disorder, psychological trauma, sexual abuse, physical abuse and neglect, dissociation

Introduction

Bipolar disorder (BD) is a severe mental illness which negatively impacts life expectancy (1) and is characterized by depressive and at least one manic or hypomanic episode in the case of BD Type I (BD-I), and by depressive and at least one hypomanic episode in the case of BD Type 2 (BD-II) (2). The aetiology of BD is understood to be complex, involving multiple genes (3) and *gene x environment* interactions (4), as well as environmental risk factors (5).

One factor which has received increasing attention in the aetiology and prognosis of BD is psychological trauma, which predicts increased comorbidity with other mental and somatic disorders (6), including, notably, post-traumatic stress disorder (PTSD) (7). The prevalence of PTSD in bipolar patients has been estimated between 4 and 40% according to reviews (8, 9), compared to an estimated lifetime prevalence of 6.2% in the general population (10). Research suggests there may be a higher prevalence of PTSD in patients with BD-I compared to BD-II (9, 11), but the symptom presentation appears to be similar across both subtypes (11).

Comorbidity of PTSD and BD leads to a higher symptom burden and lower quality of life (9), and psychological trauma during childhood has been associated with a more severe form of the disease: it has been implicated in an earlier onset of BD, increased suicidality, increased substance abuse, lower functioning, more hospitalizations, and faster cycling frequencies (6, 7, 12–14). It has also been associated with more psychosocial stressors occurring before the first and most recent affective episodes (6). Psychological trauma may partially mediate the relationship between a family history of mood disorder and its expression (15), and studies have shown that early life stress may interact with genes of several biological pathways to lead to a poorer prognosis in BD, including lower age at onset, or increased suicide risk (4, 12). Even at the subsyndromal level, post-traumatic stress symptoms are, like full PTSD, associated with significant social and work impairment and a greater number of suicide attempts in the general population (16), and were found to be associated with increased symptoms of anxiety in BD patients during the COVID-19 pandemic (17).

Evidence suggests that different forms of psychological trauma can increase the risk of psychiatric disorders in different ways (18). Physical, emotional, and sexual abuse in childhood are all independently associated with a greater risk of BD (15), and have all been shown to predict an increased number of suicide attempts and lower age of onset (6, 14, 19, 20), as well as cognitive impairment (21). However, childhood physical abuse and sexual abuse have also both been found to be associated with faster cycling frequencies, more substance abuse and comorbidity with other disorders, and more psychosocial stressors occurring before the first and most recent affective episode (6, 19, 20). Specifically, sexual abuse has been shown to be the strongest predictor of rapid cycling (20), and also to be associated with an increased number of mood episodes and with psychotic episodes (14). Meanwhile, physical abuse was associated with self-harm episodes, and both emotional abuse and physical abuse were associated with lower functioning (14), while more research is needed into the impact of emotional abuse in severe mental illness (22).

Despite strong evidence of the link between trauma and BD, and high comorbidity with PTSD, there has been little focus on how to treat this comorbidity (9). Additionally, more research is needed into dissociative disorders in patients with BD and other severe mental illnesses (22). To address these gaps in current research, a multi-center study (23) was implemented to evaluate the effectiveness of a trauma-focused psychotherapy called Eye Movement Desensitization and Reprocessing (EMDR) (24) in a trauma-exposed sample of adult BD I and BD II patients. During the baseline visit for this trial, we collected data covering the detailed retrospective trauma history, symptoms related to reported trauma and dissociation, and the clinical characteristics of a sample of 79 participants with BD and a history of psychological trauma.

In this paper, we present this data, the first to our knowledge to review the sociodemographic and clinical characteristics of a trauma-exposed bipolar disorder sample, with or without the presence of a diagnosis of PTSD. Based on the aforementioned research, we hypothesized that there would be significantly greater comorbidity between BD-I and PTSD and BD-II and PTSD, but that there would not be significant differences in the presentation of trauma symptoms according to BD subtype. Furthermore, we hypothesized that comorbidity with PTSD in a sample of traumatized BD patients would be associated with a worse disease course, and that reported sexual abuse and physical abuse would each be associated with a worse disease course. Therefore, our primary research objectives were the following:

1. To present the sociodemographic, trauma, and clinical characteristics of a sample of trauma-exposed BD patients.
2. To investigate if there is significantly greater comorbidity between BD-I and PTSD than between BD-II and PTSD.
3. To investigate if the presentation of trauma symptoms, in terms of re-experiencing, avoidance, arousal, or dissociative symptoms, is the same across BD-I and BD-II.

Our secondary research objectives were:

1. To investigate if a lifetime PTSD diagnosis as compared to never having received a PTSD diagnosis is associated with a history of psychotic symptoms, suicidal ideation and suicide attempts, current rapid cycling, an earlier onset of disease, a lower level of functioning, and a greater degree of cognitive impairment.
2. To investigate if reporting having experienced sexual abuse, compared to not reporting having experienced sexual, is associated with a history of psychotic symptoms, suicidal ideation and suicide attempts, current rapid cycling, an earlier onset of disease, and a greater number of hospital admissions.
3. To investigate if reporting having experienced physical abuse, compared to not reporting having experienced physical abuse, is associated with a history of psychotic symptoms, suicidal ideation and suicide attempts, current rapid cycling, an earlier onset of disease, and a greater number of hospital admissions.

Materials and methods

Data

The data in this paper is the baseline data from a study evaluating the effectiveness of a trauma-focused therapy in traumatized bipolar patients (23). This was a multicenter project comprising three hospitals from the Barcelona area of Spain (Hospital Benito Menni, Hospital Clínic of Barcelona and Hospital Parc de Salut Mar). The trial was registered prior to starting enrolment at Clinical Trials (https://clinicaltrials.gov) under reference NCT02634372.

Participants

Participants who met criteria for BD-I or BD-II according to DSM-IV criteria, based on clinical interview and a review of case notes, were referred to the study by their referent psychiatrist. The inclusion criteria for participants was: (1) to be aged between 18 and 65; (2) to have experienced two to six affective episodes over the previous 12 months; (3) current clinical status of euthymia or subsyndromal symptoms at the moment of the assessment, defined by a score representing the past week on the Bipolar Depression Rating Scale (BDRS) of <14 and a score representing the previous 2 days on the Young Mania Rating Scale (YMRS) of <12; (4) Presence of a traumatic

event according to the Clinician Administered PTSD CAPS-DX scale 0; (5) Current trauma symptoms as indicated by a score >0 on the Impact of Events Scale-Revised (IES-R). The inclusion criteria were designed to enable the testing of the primary hypothesis of the clinical trial comparing EMDR therapy with Supportive Psychotherapy. The EMDR therapy protocol was designed for use with all patients excluding those with active acute symptoms in the present moment, and therefore we screened for active acute symptoms. To be able to test the impact on number of affective episodes, it was necessary to include patients with multiple previous episodes, and the 12-month criteria ensures recent instability as well as permitting classification into rapid cycling (≥4 episodes in the previous year) or not. Exclusion criteria were: (1) current substance abuse/dependency, i.e., not meeting criteria for early remission (three to 12 months without meeting criteria) or sustained remission (over 12 months without meeting criteria) (25), with the exception of nicotine; (2) neurological disease or brain trauma history; (3) current suicidal ideation; (4) having received a trauma-focused therapy within the previous 2 years.

Variables of study

Patient data was collected by trained evaluators who were all qualified psychologists or psychiatrists working within the participating centers. Each patient was assigned a code, and this was used throughout the data collection to ensure anonymity. A Case Report Form (CRF) was designed to capture baseline data such as sociodemographic variables and clinical variables related to the onset and course of BD. The following data was collected through clinical interview contrasted with a review of medical case notes:

1. Age of onset, defined as the first manic, hypomanic, mixed or depressive episode as per DSM-IV criteria. This data was based on patient recall during the clinical interview, contrasted with notes from medical records.
2. History of psychotic symptoms, defined as having ever experienced psychotic symptoms in line with DSM-IV criteria, based on clinical interview and a review of medical records.
3. Number of relapses over the last year, with a relapse defined as a manic, hypomanic, mixed, or depressive affective episode as per DSM-IV criteria, with data gathered through clinical interview and a review of medical records.
4. Current rapid cycling, defined as four or more affective episodes over the previous 12 month period, with data gathered through clinical interview and a review of medical records.
5. History of suicide attempts, based on patient recall and review of medical records.
6. Current pharmacological treatment, based on their current prescription, and current psychological treatment, based on patient report and medical records.
7. Family history of psychiatric disorder, based on patient recall and review of medical records.
8. Use of substances, collected through patient self-report.

Clinical features, trauma history and symptomatology, functioning and cognitive impairment were all assessed by means of validated scales. Where available, we used scales specifically designed for use in a BD population, and where this was not possible we used the gold standard or most widely used scale. Clinical severity was measured using the following scales:

1. The Bipolar Depression Rating Scale (BDRS) (26), Spanish validation (BDRS-S) (27). This clinician-administered scale is used to assess depressive and mixed symptoms in BD-I and BD-II patients. The BDRS includes 20 items, which sum to a total score between zero and 50. Scores of <8 indicate euthymia and ≥8 and <14 the presence of subsyndromal symptoms. A score of ≥14 indicates the presence of an acute depressive episode. The Spanish validation was carried out with a relatively small sample size but shows robust psychometric properties and captures depressive and mixed symptoms in Spanish bipolar patients.
2. The Young Mania Rating Scale (YMRS) (28), Spanish validation (29), is a clinician-administered scale composed of 11 items aimed at quantifying the severity of manic and hypomanic features. Of the 11 items, four items (irritability, speech, thought content and disruptive/aggressive behavior) are graded on a scale of 0 to 8, while the remaining seven items are graded on a 0 to 4 scale. Total scores range between 0 and 60: scores of <6 indicate euthymia, between ≥7 and <12 indicate the presence of subsyndromal symptoms, while scores of ≥12 indicate the presence of moderate to severe manic symptomatology. The Spanish validation shows this is a reliable tool for the assessment of manic symptoms in patient with manic or hypomanic symptoms in Spain.

Reported trauma history and symptomatology were evaluated using the below scales:

1. The Clinician-Administered PTSD Scale (CAPS-DX) (30), Spanish validation (31). The CAPS is the gold standard for determining a diagnosis of PTSD according to DSM-IV criteria. It provides a diagnosis of both current and lifetime PTSD. The Spanish validation showed good reliability, internal consistency and rest-retest values, similar to the original version.
2. The Impact of Event Scale-Revised (IES-R) (32), Spanish validation (33). The IES-R is a 22-item self-report scale.

It measures the presence of subjective distress related to a specific traumatic event, yielding an overall score and one for each of its three subscales, intrusion, avoidance, and hyperarousal, which correspond to the DSM-IV diagnostic criteria for PTSD. Higher scores indicate greater distress and a score of >32 has been suggested as the cut off for the presence of PTSD symptoms (34). The Spanish validation in a large sample showed adequate internal consistency and convergent validity with other scales of psychopathology, but some difficulties with the test-retest validity.

3. The Holmes-Rahe Life Stress Inventory (35), Spanish validation (36). This scale measures the number of stressful events that have occurred over the previous 12 months. Each potential stressful event is accorded a weighted score depending on how stressful it is estimated to be, and these are summed to provide a total score. A score of under 150 reflects low levels of stress and a low risk of stress-related illness, scores from 150–299 reflect a moderate level of stress which can imply a 50% risk of developing a stress-related illness, and scores of 300 and over reflect a high level of stress which can imply an 80% risk of developing a stress-related illness. The Spanish validation includes a cultural adaptation of the items.
4. Dissociative Experiences Scale (DES) (37), Spanish validation (38). This scale assesses the presence of dissociation, by asking participants the percentage of time they experience a range of dissociative symptoms. The results yield an average total score and an average score for each of the three subscales: amnesia, absorption, and depersonalization. Total scores of 30 or higher indicate a potential Dissociative Identity Disorder. The DES is the scale most often employed to measure dissociative symptoms in bipolar patients (39). The Spanish validation was carried out in healthy adults and in inpatients with schizophrenia. The scale was shown to be valid in both populations, with improved validity in a psychiatric population when the scale was administered by a clinician.

The level of functioning and cognitive impairment was evaluated using the following scales:

1. Functioning Assessment Short Test (FAST) (40). This scale evaluates level of functioning through 24 items assessing six domains: autonomy, work, cognitive functioning, finances, interpersonal relationships, and leisure. Each item is scored from 0–3, and overall scores range from 0-72. Higher scores indicate a lower level of functioning. This scale was originally developed in Spanish for a Spanish population.
2. Screen for Cognitive Impairment in Psychiatry (SCIP) (41), Spanish validation (42). The SCIP is a clinician-administered scale which assesses cognitive impairment in psychiatric patients. This scale briefly assesses five different cognitive domains: immediate verbal learning, delayed verbal learning, working memory, verbal language, and processing speed. The scale provides a score for each subdomain and then a global score obtained by summing all scores. Lower scores indicate a greater level of cognitive impairment. The Spanish validation was carried out in a psychiatric population of patients with schizophrenia, and showed good validity and reliability.

Data analysis

Since the data in this paper come from a study where the sample size was determined to understand the effectiveness of EMDR therapy compared to Supportive Therapy, in which the sample size calculation was based on a survival analysis using the statistical package "powerSurvEpi" for R (http://www.r-project.org/) (40), we performed a second sample size calculation to ensure the sample size is sufficient to meet the objectives of the current paper. In this case, the sample size was based on a correlation test, given the difficulty of exact data regarding the prevalence of BD patients with a history of psychological trauma in the population. A sample of 79 patients, with a statistical power of 80% and a type I error rate of 0.05, is sufficient to detect low correlations ($R = 0.31$) (43, 44).

All statistical analyses were carried out using STATA Statistics/Data analysis, version 16.1 (StataCorp LLC, Texas, USA). Fitness to parametric assumptions was checked for all variables, and the Shapiro–Wilk test was used to assess the normality of data distribution. With regards to the descriptive analysis of the sociodemographic and clinical data, the arithmetic mean was used for quantitative variables and the proportion for categorical variables. In the case of the impossibility of reconciling patient recall data with medical history, or failure to log a valid response to an item, listwise deletion was applied and analyses are based on the total number of valid responses for each question. The standard area and the confidence interval, set at 95%, were calculated for both quantitative and categorical variables. Pearson Chi squared test was used to analyze the relationship between two binomial categorical variables, and a two-sample *t*-test was used for analysing the relationship with the quantitative dependent variables.

Firstly, the relationship between BD-I or BD-II and a lifetime diagnosis of PTSD was analyzed. The lifetime PTSD group comprised both those with a current and lifetime diagnosis of PTSD; while those who had never met criteria for PTSD comprised the non-PTSD group. The current and lifetime PTSD diagnoses were included together as most of the variables against which it was planned to be analyzed were not current (e.g., lifetime number of hospital admissions, lifetime number of suicide attempts, ever having experienced psychotic symptoms, ever having experienced suicidal ideation). Secondly, analyses were carried out for the relationship between BD-I and BD-II

and the impact of the traumatic event (IES-R) and dissociative symptoms (DES). Thirdly, the relationship between a lifetime diagnosis of PTSD and a range of clinical symptoms: having experienced suicidal ideation, attempted suicide, experienced psychotic symptoms, rapid cycling, number of suicide attempts, age of BD onset, number of hospital admissions, stressful events over the previous 12 months (Holmes & Rahe scale), level of functioning (FAST), and level of cognitive impairment (S-SCIP) was analyzed. Fourthly, analyses were carried out to determine the relationship between sexual abuse and four categorical variables (whether the participant had experienced suicidal ideation, had a history of suicide attempts, had experienced psychotic symptoms, and rapid cycling), and two quantitative variables (age of onset of BD, and number of hospital admissions). Finally, this analysis was repeated with physical abuse instead of sexual abuse as the independent variable. In all analyses, *p*-value significance was set at <0.05.

We also present adjusted *p*-values based on applying the Holm-Bonferroni correction for multiple comparisons (45). Although only two independent groups are compared in the study, several dependent variables are evaluated. Performing multiple comparisons of the two independent groups for the independent variables may increase the type I error (alpha α1 type error), increasing the risk of falsely rejecting the null hypothesis, being true in the population. To account for this possible effect, we performed the Holm-Bonferroni procedure. However, applying the adjustment for multiple comparisons increases the risk of a type II error, of falsely accepting the null hypothesis, and this risk is arguably greater where the analyses are pre-planned and based on prior evidence (46–49). Therefore, we present both adjusted and unadjusted *p*-values.

Ethical approval

The study received ethical approval from the Ethics Committee of the Germanes Hospitalàries del Sagrat Cor de Jesús (reference number: PR-2014-15), the Hospital Clínic of Barcelona (reference number: HCB/2015/1005) and the Hospital Parc de Salut Mar (reference number: 2015/6502/l). All participants signed informed consent prior to enrolment.

Results

Sociodemographic and clinical variables

In total, 82 subjects agreed to participate in the study, but three did not complete the baseline assessment, leaving a total sample of 79. Most of our sample were females (77.2%, $n = 61$) and Caucasian (94.6%, $n = 70$). The mean age was 46.56 [SD (standard deviation) ± 8.408] and participants had spent an average of 13.74 (SD ± 3.834) years in education. Of the sample, 40.5% ($n = 32$) were single, 38.0% ($n = 30$) married or in a civil partnership, 1.3% ($n = 1$) widowed and 20.3% ($n = 16$) separated. The majority (61.8%, $n = 47$) were on temporary or permanent sick leave, while 22.3% ($n = 17$) were employed and working either full- or part-time. These results can be seen in full in Table 1.

The average age of onset of BD in our sample was 29.53 (SD ± 10.840) years old. Age of onset was significantly higher in BD-II patients than BD-I (33.10 years compared to 28.39 years, $p = 0.044$), and in women compared to men (30.89 years compared to 24.65 years, $p = 0.017$).

Patients had experienced on average 3.27 hospital admission during their lifetime, and 2.48 affective episodes in the previous 12 months. In our sample, 73.4% ($n = 58$) had a diagnosis of BD-I compared to 26.6% ($n = 21$) with a diagnosis of BD-II, 13.9% ($n = 11$) experienced rapid cycling, and 46.2% ($n = 36$) had experienced psychotic symptoms. Regarding suicidality, 79.7% ($n = 63$) had experienced suicidal ideation and 39.7% ($n = 31$) had attempted suicide. Data regarding severity was available for 29 patients, and in over half of those cases (51.7%; $n = 15$) the attempt had resulted in severe injury. The most common medications taken by our sample were mood stabilizers (94.6%; $n = 70$) and anti-psychotics (75.7%; $n = 56$).

Comparison of the sociodemographic and clinical variables in the current study, as compared to large BD samples from four other studies which are not specifically in a traumatized population (45–48), as well as sociodemographic data for the Barcelona area can be seen in Supplementary Table S1. Our sample had a higher proportion of females and higher age of onset than other studies. The proportion of BD-II patients was, while a minority, greater than in the majority of other studies. Educational level was lower than in other studies and reflected the norms for the Barcelona area. Suicidality was similar to other studies, while a history of psychotic symptoms and current rapid cycling were lower than in most other studies.

Reported trauma symptoms and profile

The majority (79.7%; $n = 59$) had experienced a relevant stressful life event prior to onset of BD. Over half of our sample (51.9%; $n = 40$) had a lifetime diagnosis of PTSD according to the CAPS. In more than half of these cases, the lifetime diagnosis of PTSD was current, meaning 27.3% of the total sample ($n = 21$) had a current PTSD diagnosis. To carry out the clinical interview for PTSD, using the CAPS scale, participants are asked for the reported traumatic event which most affects them. In nearly half of cases (45.3%; $n = 34$), this was not related to a specific reported traumatic event category. Following this, physical abuse, sexual abuse, and the sudden death of a loved one were all chosen by 12.0% of participants ($n = 9$), followed by violent death (9.3%; $n = 7$), followed by a life-threatening illness (5.3%; $n = 4$) and transport accident (4.0%; $n = 3$). The average

TABLE 1 Sociodemographic characteristics of the sample.

Variable		Obs/Freq	Mean /Percentage*	Std. Err.	[95% Conf. Interval]	
Age		79	46.56	1	45	48
Education (years of studies)		57	13.74	1	13	15
Sex	Male	18	22.8%	0.050	0.142	0.34
	Female	61	77.2%	0.050	0.661	0.858
Race	Caucasian	70	94.6%	0.027	0.857	0.979
	Latin American	3	4.1%	0.024	0.013	0.125
	Asian	1	1.4%	0.014	0.002	0.096
Relationship status	Single	32	40.5%	0.058	0.299	0.528
	Married/civil partnership	30	38.0%	0.057	0.261	0.486
	Widowed	1	1.3%	0.014	0.002	0.096
	Separated/divorced	16	20.3%	0.048	0.130	0.324
Employment status	Student	4	5.3%	0.027	0.021	0.143
	Homemaker	1	1.3%	0.014	0.002	0.096
	Employed full-time	14	18.4%	0.047	0.119	0.308
	Employed part-time	3	3.9%	0.020	0.007	0.108
	Temporary sick leave	32	42.1%	0.059	0.325	0.555
	Permanent disability payments due to mental illness	14	18.4%	0.044	0.098	0.277
	Permanent disability payments for other reasons	1	1.3%	0.014	0.002	0.096
	Unemployed	5	6.8%	0.030	0.029	0.160
	Other	2	2.6%	0.014	0.002	0.096

Data are presented as mean or number (%).
Obs/Freq: Number of cases observed/Frequency; Std. Error: Standard Error; Conf.: Confidence.
*Age and education data are presented as means. The rest of the variables are presented as percentages.

age of the participant at the time of the event was 24.18 (SD ± 16.327). However, approximately half of our sample (50.0%; $n = 38$) reported having experienced sexual abuse, while a lower percentage reported having experienced physical abuse (42.1%, $n = 32$). In our sample, over the previous 12 months, participants reported on the Holmes and Rahe scale having experienced an average of 6.72 stressful events each, with an average total score of 214, indicating a moderate level of stress. These results can be seen in Table 2.

Across our sample, the mean score on the IES-R was 38.95, indicating PTSD symptoms. In this scale, participants with a lifetime diagnosis of PTSD had a significantly higher average score of 47.19 compared to 29.72 in the non PTSD group [$t(72) = -2.783$, $p = 0.007$]. Regarding dissociative symptoms, the average score on the DES was 13.24, and was significantly higher in the PTSD group (an average score of 15.53 compared to 10.75), [$t(70) = -2.224$, $p = 0.029$].

BD subtype and presence of lifetime diagnosis of PTSD

The Chi squared analysis found no significant between-group differences between Bipolar Type (BD-I or BD-II) and the presence or not of a lifetime diagnosis of PTSD [$\chi^2(1) = 0.702$, $p = 0.402$].

Trauma symptom profile per BD subtype

Our results showed no significant differences in the expression of trauma symptoms between BD subtypes in terms of intrusion, avoidance, hyperarousal, or dissociative symptoms. These results can be seen in Supplementary Table S2.

Impact of PTSD on disease course and cognition

A lifetime PTSD diagnosis was significantly associated with having experienced psychotic symptoms [$\chi^2(1) = 5.404$, $p = 0.02$]. Our results showed that PTSD did not have a significant impact on disease course in terms of suicidal ideation or behavior, or rapid cycling (please see Table 3). No significant difference was found between lifetime PTSD diagnosis and age of onset, number of hospital admissions, level of functioning according to the FAST, or cognition according to the SCIP, when compared to the sample without a PTSD diagnosis. These results

TABLE 2 Clinical characteristics of the sample.

Variable		Obs/Freq	Mean/Percentage*	Std. Err.	(95% Conf. Interval)	
Age of onset of bipolar disorder		78	29.53	1	28	33
Number of hospital admissions		77	3.27	1	2	5
Number of affective episodes in the last year		79	2.48	0	2	3
Number of suicide attempts		78	0.85	0	0	1
BDRS (total score)		79	9.29	1	8	11
YMRS (total score)		79	2.23	0	2	3
Holmes and Rahe Scale (number of events)		74	6.72	1	6	8
Holmes and Rahe Scale (total score)		74	214	18	177	251
Age of CAPS event		57	24.18	2	20	29
IES-R (total score)		75	38.95	2.973	33.1	44.8
DES (total score)		74	13.24	1.105	11.1	15.4
BD subtype	BD-I	58	73.4%	0.093	0.447	0.815
	BD-II	21	26.6%	0.093	0.185	0.553
Presence of rapid cycling	No	68	86.1%	0.071	0.6424	0.944
	Yes	11	13.9%	0.071	0.056	0.358
Ever experienced psychotic symptoms	No	42	53.8%	0.093	0.447	0.815
	Yes	36	46.2%	0.093	0.185	0.553
Stressful event at time on onset	No	15	20.3%	0.077	0.079	0.399
	Yes	59	79.7%	0.077	0.601	0.921
Ever experienced suicidal ideation	No	16	20.3%	0.052	0.018	0.275
	Yes	63	79.7%	0.052	0.725	0.982
Suicide attempt	No	47	60.3%	0.056	0.494	0.712
	Yes	31	39.7%	0.056	0.288	0.506
Severity of Suicide attempt	No	14	48.3%	0.098	0.276	0.658
	Yes	15	51.7%	0.098	0.342	0.724
Adherence to treatment	Good	73	94.8%	0.063	0.684	0.964
	Partial	4	5.2%	0.063	0.036	0.316
Mood stabilizers	No	4	5.4%	0.052	0.018	0.275
	Yes	70	94.6%	0.052	0.725	0.982
Antipsychotic	No	18	24.3%	0.071	0.056	0.358
	Yes	56	75.7%	0.071	0.642	0.944
Anxiolytic	No	41	55.4%	0.095	0.214	0.589
	Yes	33	44.6%	0.095	0.411	0.786
Antidepressant	No	42	57.5%	0.097	0.376	0.755
	Yes	31	42.5%	0.095	0.214	0.589
Other Meds	No	59	79.7%	0.077	0.601	0.921
	Yes	15	20.3%	0.077	0.079	0.399
CAPS selected event	Accident (transport)	3	4.0%	0.052	0.018	0.275
	Physical abuse	9	12.0%	0.071	0.056	0.358
	Sexual abuse	9	12.0%	0.063	0.036	0.316
	Life-threatening illness	4	5.3%	0.038	0.005	0.246
	Violent death	7	9.3%	0.052	0.018	0.275
	Sudden death	9	12.0%	0.071	0.056	0.358
	Other	34	45.3%	0.095	0.214	0.589

Data are presented as mean or number (%).
Obs/Freq: Number of cases observed/Frequency; Std. Error: Standard Error; Conf.: Confidence; BDRS: Bipolar Depression Rating Scale; YMRS: Young Mania Rating Scale; IES-R: Impact of Event Scale-Revised; DES: Dissociative Experiences Scale.
*Variables up to and including "DES Score" are presented as means. The rest of the variables are presented as percentages.

can be seen in Table 4. The *p*-values were no longer significant following application of the Holm-Bonferroni to adjust for multiple comparisons.

We conducted sensitivity analyses to understand whether there was a significantly different impact from a current PTSD diagnosis as compared to a historical (but not current) PTSD diagnosis. We found no significant differences between the current and historical PTSD group, or the current and never PTSD groups, on any of the variables tested (total FAST score, total SCIP score, rapid cycling, history of psychotic symptoms, age of onset, history of suicide attempts or suicidal ideation). The only significant difference on these variables when comparing the lifetime PTSD group with the never PTSD group was in the history of psychotic symptoms [$\chi^2(1) = 6.175$, $p = 0.013$; please see Supplementary Table S3], in line with the findings from our main analysis.

Impact of sexual and physical abuse on disease course

Sexual abuse was shown to be significantly associated with rapid cycling [$\chi^2(1) = 4.15$, $p = 0.042$]; results were not significant following application of the Holm-Bonferroni to adjust for multiple comparisons. There was no significant association between sexual abuse and suicidal ideation, psychotic symptoms, or history of ever having attempted suicide, or physical abuse and any of the aforementioned variables (see Table 3). Similarly, there was no significant association between sexual or physical abuse and number of suicide attempts, age of onset of BD, or number of hospital admissions. These results can be seen in full in Supplementary Table S4.

Discussion

Our study is one of the first to analyze a range of clinical and trauma variables in a sample of BD patients exclusively with a history of psychological trauma. Our sample was mostly Caucasian and 77.2% were female, which was higher than the proportion of females in previous studies with large bipolar samples (see Supplementary Table S1) and despite evidence showing BD is estimated to affect both genders almost equally (49). The large proportion of females in our specific sample of BD patients with a history of trauma may reflect evidence showing women are more likely to experience high-impact trauma, experience trauma at an earlier age, and are approximately two to three times more likely to suffer from PTSD (50). In BD patients, PTSD is a more common comorbidity in female BD patients than in male (49, 51). Just over half of our sample (54.1%) had a lifetime diagnosis of PTSD, with this being current in 30.4% of the total sample, and the average age at which the most important traumatic event occurred was 24.18.

The level of education of our participants was representative for the Barcelona area (see Supplementary Table S2), and lower than in other studies, where the samples were found to be more highly educated than the general population (45, 46, 48). Most patients in our sample were unable to work either temporarily or permanently due to BD. Most of our sample of traumatized BD patients (79.7%) had suffered from suicidal ideation at some point in their lives, and 39.7% had carried out a suicide attempt, comparable to data from other BD samples (see Supplementary Table S2). Of note, current suicidal ideation was a criterion for exclusion in our study. In our sample, 13.9% currently experienced rapid cycling, lower than in other samples but participants were excluded from our study if they had experienced >6 mood episodes in the previous 12 months. A history of psychotic symptoms was present in 46.2% of our overall sample, lower than in some other samples but this may partially be due to the higher proportion of BD-II patients, where psychotic symptoms are not a feature of the disease course.

The average age of participants in our sample was 46.56 years and the average age of BD onset was 29.53 years. The age of onset in our study is much higher than the late teens and early twenties reported in other studies (see Supplementary Table S1). This may partially be explained by the fact that, as compared to other studies, the mean age of our sample was higher, there was a higher percentage of females, and BD-II patients formed a larger proportion of the total sample than in other studies: females were shown in our study to have a significantly later age of onset than males, and the same pattern was found for BD-II patients as compared to BD-I, both patterns reflected in other research (52). However, a surprising finding was that there was no significant association between age of onset and physical abuse, sexual abuse, or a lifetime PTSD diagnosis, although our data showed a non-significant trend towards a higher age of onset than participants who had never had a PTSD diagnosis. This tendency was against expectations, given the prior research showing that childhood trauma is associated with a significantly lower age of onset (12). In our study, in the majority of cases (79.7%), BD onset happened in the context of a stressful life event, which supports previous findings that adverse life events can precede mood symptoms (53, 54), and that traumatic stress disorders can significantly increase the probability of subsequent onset of BD (55). However, our data points to a bidirectional relationship between BD and trauma. Firstly, our results showed that the sample had on average experienced levels of stressful life events in the 12 months prior to evaluation which put them at a 50% risk of developing a stress-related illness, which supports previous findings that BD patients suffer more adverse life events in general than healthy controls (56). Furthermore, the average age for the most traumatic event experienced by our sample was 24.18 (although this figure is subject to bias as this variable was the only one

TABLE 3 The impact of a lifetime PTSD diagnosis, sexual and physical abuse on categorical variables of disease course.

		No	Yes	Mean	Std. Err.	95% CI		$\chi^2(1)$	*P*-value
Lifetime PTSD diagnosis									
History of psychotic symptoms	**No**	24	16	0.333	0.079	0.179	0.487	**5.404**	**0.020**
	Yes	12	24	0.6	0.077	0.448	0.752		
History of suicidal ideation	**No**	8	7	0.784	0.068	0.651	0.916	0.208	0.648
	Yes	29	33	0.825	0.060	0.707	0.943		
History of suicide attempts	**No**	24	22	0.333	0.079	0.179	0.487	1.079	0.299
	Yes	12	18	0.45	0.079	0.296	0.604		
Rapid Cycling	**No**	34	32	0.081	0.045	−0.007	0.169	2.220	0.136
	Yes	3	8	0.2	0.063	0.076	0.324		
Sexual abuse									
History of psychotic symptoms	**No**	24	17	0.351	0.078	0.198	0.505	3.065	0.080
	Yes	13	21	0.553	0.081	0.395	0.711		
History of suicidal ideation	**No**	10	6	0.737	0.071	0.597	0.877	1.267	0.260
	Yes	28	32	0.842	0.059	0.726	0.958		
History of suicide attempts	**No**	22	24	0.405	0.081	0.247	0.564	0.108	0.742
	Yes	15	14	0.368	0.078	0.215	0.522		
Rapid Cycling	**No**	36	30	0.053	0.036	−0.018	0.124	**4.146**	**0.042**
	Yes	2	8	0.211	0.066	0.081	0.340		
Physical abuse									
History of psychotic symptoms	**No**	25	16	0.432	0.075	0.285	0.578	0.199	0.656
	Yes	19	15	0.484	0.090	0.308	0.660		
History of suicidal ideation	**No**	10	6	0.773	0.063	0.649	0.897	0.176	0.675
	Yes	34	26	0.813	0.069	0.677	0.948		
History of suicide attempts	**No**	30	16	0.318	0.070	0.181	0.456	2.105	0.147
	Yes	14	15	0.484	0.090	0.308	0.660		
Rapid Cycling	**No**	36	30	0.182	0.058	0.068	0.296	2.308	0.129
	Yes	8	2	0.063	0.043	−0.021	0.146		

Std. Error: Standard Error; CI: Confidence Interval.

with a substantial amount of missing data [$n = 57$], due to not being systematically collected in the CAPS). In nearly a third of the sample where age of trauma event was available (32.14%, $n = 18$), the traumatic event selected for the CAPS occurred after the onset of bipolar disorder, and in 14.29% ($n = 8$) of cases, the traumatic event stemmed from a BD affective episode, While there is a body of research showing that the experience of psychosis can cause PTSD (57), there has been no similar research to the authors' knowledge into PTSD related to BD mood episodes, despite these clearly having the potential to be traumatic based on our data. Our data points to the importance of research focusing not just on childhood trauma but also on adult traumatic experiences, including experiences related to severe mood episodes and hospitalization experiences, to further elucidate the complex relationship between trauma and clinical disease course. Additionally, clinicians may need to include ongoing assessment of the occurrence and impact of adult trauma experiences, experienced in the context of the BD disease course, in addition to screening for childhood trauma.

The data from our study showed participants experienced on average high levels of current trauma symptoms. The impact caused by the traumatic event, measured by the IES-R, was on average well above the cut off for clinical post-traumatic stress symptoms in the group with lifetime PTSD diagnosis, with an average score of 47.19 compared to a cut off score of >32 (34), indicating high levels of distress caused by the traumatic event. Yet it is of note that the group with no lifetime diagnosis of PTSD also had on average symptoms nearing this cut off point (29.72), suggesting a high level of subsyndromal post-traumatic stress symptoms even in those in our sample without a lifetime PTSD diagnosis. In terms of dissociation, there was a significantly higher level of dissociative symptoms in the lifetime PTSD group than in the non-lifetime PTSD group. However, the scores in both groups were well below the >25 score correlated with PTSD, and in line with the

TABLE 4 Impact of lifetime diagnosis of PTSD on quantitative variables of disease course.

	Obs	Mean	Std. Err.	Std. Dev.	95% Conf. Interval		*t*	Deg. Freedom	*P*-value
Age of onset									
No lifetime PTSD Dx	37	27.892	1.809	11.002	23.851	36.788	0.748	74	0.162
Lifetime PTSD Dx	39	31.410	1.716	10.718	27.400	40.275			
Number of hospital admissions									
No lifetime PTSD Dx	36	2.778	1.105	6.629	0.535	5.021	−0.747	73	0.458
Lifetime PTSD Dx	39	3.744	0.710	4.435	2.306	5.181			
FAST total									
No lifetime PTSD Dx	37	30.703	2.187	13.304	26.267	35.138	0.748	75	0.457
Lifetime PTSD Dx	40	28.275	2.379	15.045	23.463	33.087			
SCIP total									
No lifetime PTSD Dx	36	65.667	2.833	16.996	59.916	71.417	−0.237	73	0.813
Lifetime PTSD Dx	39	66.641	2.955	18.455	60.658	72.624			

Obs: Number of cases observed; Std. Error: Standard Error; Conf.: Confidence; Deg.: Degrees of; Dx: Diagnosis; FAST: Functioning Assessment Short Test for Bipolar Disorder; SCIP: The Screen for Cognitive Impairment in Psychiatr.

mean score of 14.8 on this scale for BD patients, according to a recent meta-analysis which found bipolar disorder patients to be the psychiatric group with lowest levels of dissociation (58). Our results also support dissociative symptoms not being at a clinical level, even in a sample of traumatized BD patients, and our results indicate that the sample was not characterized by complex PTSD, where it has been argued that dissociation is a major feature (59). Our data is useful given the previous lack of information focusing on dissociative symptoms in severe mental illness (22), but contrasts with some prior studies which have found higher levels of dissociation in BD patients (39, 60). One possible explanation for this is that these studies appear to have applied the DES as a self-administered scale, whereas to improve validity and avoid inflated scores in psychiatric patients, we applied the DES as a clinician-administered scale (38). Additionally, in our study, no participants were in an acute affective phase, and further research can clarify the effect of an acute mood episode on dissociative symptoms.

Of note, in our study, we use retrospective reports of trauma. Retrospective and prospective reports show a poor level of agreement (61), and while retrospective reports of adverse childhood experiences can predict negative life outcomes and psychopathology (62, 63), retrospective reports of childhood maltreatment are more strongly associated with early adult life psychopathology than prospective reports, suggesting that the recollection of having been maltreated is more closely associated with psychopathology than prospective measures (64), although other studies have found both retrospective and prospective reports of childhood trauma predict psychopathology (65, 66). There is a dearth of studies analyzing the association between BD and prospective measures of trauma, and our data should be interpreted in the context of the relationship between patient recall of trauma and clinical BD course.

Regarding our first hypothesis, an association was found between BD comorbidity with PTSD and psychotic symptoms. This no longer reached statistical significance once adjustments for multiple comparisons, to decrease possibility of a type I error (i.e., a false positive) were applied. However, adjustments for multiple comparisons increase the risk of a type II error (i.e., a false negative), and arguably are not indicated in situations where hypotheses are planned a priori based on prior evidence, rather than testing for multiple random associations (67–70). Therefore, we present both adjusted and unadjusted *p*-values and note that the interpretation of results must be made with caution.

The tendency in our results to a link with psychosis is unsurprising given the large body of literature which supports a link between trauma and psychosis generally (71). Psychological trauma may increase risk of psychotic symptoms in people vulnerable to psychosis (72), and previous research has shown a link between comorbid PTSD in BD and psychotic symptoms (73). Within our sample, 46.2% had experienced psychotic symptoms, lower than in some studies which have estimated that over half of BD patients experience psychotic symptoms (74, 75), although our study included BD-II patients. It has been argued that psychotic symptoms do not necessarily reflect a worse disease course as they do not have a significant impact on functioning (75) yet psychotic symptoms can be traumatizing for those experiencing them (76). The association between psychotic symptoms in BD and PTSD and its implications for treatment warrant further research.

No significant association was found between PTSD and an earlier onset of BD or suicidality, which was somewhat unexpected given previous research (6, 7, 51). There was also no

significant difference found in level of functioning or cognitive impairment. Our results are striking compared to the wide body of literature showing that a PTSD diagnosis in non-BD patients is associated with increased suicidality (77) and can negatively affect functioning and cognition (78, 79). Furthermore, previous research in BD patients has shown that comorbid PTSD has a significant further negative impact (20) over and above the negative impact that BD itself has on functioning and cognition (80, 81). Our sample only included BD patients with a history of trauma, which is not representative of all BD patients. In fact, a trauma history may be present in as few as 50% of BD patients (82), although other studies suggest higher estimates (73). One possible explanation for our results is the high level of subsyndromal psychological trauma symptoms even in the non-PTSD diagnosis group. Indeed, subsyndromal PTSD has been shown in other populations to be associated with significant psychosocial impairment (83, 84) and with increased suicidality (85). One study which compared three groups of BD patients (patients with comorbid PTSD, patients with trauma but no PTSD diagnosis, and patients with no trauma history), found that BD patients with PTSD were significantly more likely than BD patients with no trauma to have a worse disease course, in terms of significantly more rapid cycling and manic symptoms, but there was no significant difference when comparing the comorbid PTSD group with the trauma group, or the trauma group with the no trauma group (86). The impact of comorbidity between BD and psychological trauma, without a diagnosis of PTSD, warrants further investigation. If psychological trauma without a PTSD diagnosis has a similar impact on disease course, this would have important ramifications for screening for and treating psychological trauma in BD patients.

Our second hypothesis, that there would be significantly more cases of PTSD in BD-I patients than BD-II, was not proven, which contrasted with prior evidence from Hernandez et al. (11). In the study by Hernandez and colleagues, the lifetime PTSD diagnosis was 21.3% in BD-I and 15.6% in BD-II. Unsurprisingly, in our sample of BD patients with a history of trauma, the proportion was higher: 49.1% of BD-I and 57.1% of BD-II patients had a lifetime PTSD diagnosis. It is possible that BD-I patients may suffer more rates of psychological trauma but, within BD subtypes with a trauma history, there is not a significantly greater chance of developing PTSD. Indeed, our third hypothesis, that there would be no difference in trauma symptom profile between BD-I and BD-II was shown to be correct: there was no significant difference in levels of post-traumatic stress symptoms or levels of dissociation. This adds to previous evidence (9, 11) which suggests that the different BD subtypes do not influence the expression of trauma symptoms. This data suggests also that addressing PTSD as a comorbidity in BD does not need to differentiate by BD subtype, which could be a useful insight for planning therapeutic approaches for addressing the presentation of trauma symptoms in BD.

Our fourth hypothesis, that the presence of reported sexual abuse would be correlated with a worse disease course, was proven only in the case of rapid cycling, when *p*-values were unadjusted. This is in line with previous studies that found childhood trauma is related to rapid cycling (12) and sexual abuse is the strongest predictor of it (20). Rapid cycling can indicate poor prognosis and be associated with a greater number of suicide attempts (87). The impact of sexual abuse can be treated with psychological treatments such as Trauma Focused Cognitive Behavioral Therapy (TF-CBT) and EMDR (88), and these therapeutic approaches can be adapted specifically for PTSD within the context of bipolar disorder (89, 90). Further research can investigate whether including trauma-focused treatment for BD patients with a history of sexual abuse can improve symptoms of rapid cycling.

Our fifth hypothesis, that reported physical abuse would be correlated with a worse disease course as compared to not reporting having experienced physical abuse, was not proven with any variables. Our findings for sexual and physical abuse do not support previous findings regarding their negative impact on disease course (6, 14, 20). Our results are the first, to the authors' knowledge, to review the impact of physical and sexual abuse only in a sample of BD patients with a psychological trauma history. Therefore, while sexual and physical abuse have been shown in previous research to have a significant impact on disease course, this effect seems to be muted when compared against people who have suffered trauma but not specifically sexual or physical abuse. Another explanation is that our study did not specify physical and sexual abuse in childhood, and there is a strong body of evidence showing that the impact of trauma is greater in childhood (18). Further research can clarify the specific effects of sexual, physical, and emotional abuse at different life stages within a traumatized sample, and whether these warrant specific treatment approaches.

Regarding the clinical implications of our research, the high rates of PTSD within our traumatized sample reflect an important comorbidity which not only can impact prognosis (13) and treatment outcomes (91) but also warrants treatment as a clinical disorder with its own impact on functioning and suffering. Our research supports not only general screening for comorbid psychological trauma and comorbid PTSD in BD patients, which is already implemented in some countries and settings but is not universal, but also ongoing evaluating of whether there has been a traumatic impact due to a BD mood episode or hospitalization.

Clinicians can use information about comorbid trauma symptoms to tailor the BD treatment plan, paying particular attention to possible indicators of worse prognosis such as rapid cycling or psychotic symptoms. Additionally, the inclusion of pharmacological and psychological treatment for clinical trauma symptoms can help clinicians in alleviating the overall symptomatology in patients, and future research should elucidate if this can improve the prognosis of BD course itself.

Strengths of this multicentric study include the exhaustive trauma evaluation, including dissociative symptoms which have received little attention to date (22), and which were assessed through a clinician-administered scale to reduce bias (38), and the PTSD diagnosis which was determined through clinical interview using the gold-standard CAPS. A further strength is that we included "real world" bipolar patients within a pragmatic randomized controlled trial (RCT) with few exclusion criteria. However, some limitations have to be considered as well. We did not evaluate further psychiatric comorbidities using a (semi) structured diagnostic interview, although comorbidities were checked through a review of case notes. Our patients clinically had further psychiatric and somatic comorbidities and it would have been interesting including this variable in our analysis, as prior results indicate negative effects on the course of the illness (92). Furthermore, our study did not include a control group of BD patients without psychological trauma, as the data was taken from a RCT comparing EMDR vs. ST in trauma-exposed bipolar patients. The lack of a non-traumatized control group makes interpretation of the impact of subsyndromic trauma symptoms more challenging. In our study, we collected data regarding the total lifetime number of BD episodes for each participant but many subjects struggled to identify hypomanic episodes or quantify episodes, so this data was not reliable enough to be used. Additionally, emotional abuse was not evaluated, and the timepoint for reported sexual abuse and physical abuse was not assessed. Due to the cross-sectional design of this study, conclusions about causality cannot be drawn. Trauma history was based on subjective recall, which can result in recall bias (93). However, it has been shown that psychopathology is associated more with subjective than objective recall of traumatic events (94). Additionally, trauma history was gathered through use of the gold standard CAPS interview, and we have clarified throughout the paper that this is reported trauma history.

In summary, our paper provides further evidence of the lack of difference in how trauma symptoms are presented across BD subtypes, and provides important data regarding the high levels of trauma symptoms in BD subjects, even when criteria for a PTSD diagnosis are not met. The evidence shows there are few differences in clinical BD severity between the PTSD and subsyndromic PTSD group, although we also found a possible tendency for there to be a correlation between PTSD and psychotic symptoms, as well as between sexual abuse and rapid cycling, which can be clinically helpful in the identification and treatment of both. It prompts further investigation to understand the impact of comorbidity with a history of psychological trauma in BD patients, including subsyndromal PTSD symptoms, and highlights the importance of screening for psychological trauma in the BD population.

Data availability statement

The data that support the findings of this study are openly available in Figshare at https://figshare.com/articles/dataset/Bipolar_Disorder_and_psychological_trauma/19601359.

Ethics statement

The study received Ethical Approval from the Ethics Committee of the Germanes Hospitalàries del Sagrat Cor de Jesús (Reference Number: PR-2014-15), the Hospital Clínic of Barcelona (Reference Number: HCB/2015/1005) and the Hospital Parc de Salut Mar (Reference Number: 2015/6502/l). The patients/participants provided their written informed consent to participate in this study.

Author contributions

BA conceived the idea for the study and led the study. AM-A coordinated the study. BH, AV-G, IG-S, WL, EJ, MM, LB-P, MR, RC, AM-R, and JC were involved in the recruitment and evaluation of patients and data collection. BH, IG-S, MF-M, and AM-A prepared the data for analysis. DR carried out the statistical analysis. BH worked on the first draft of the paper with BA, AM-A, DR-R, and AV-G. All authors contributed to the interpretation of results and the final draft and approved the final draft.

Funding

This work was supported by a grant for BA from the Plan Nacional de I + D + i and co-funded by the Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación, Plan Nacional 2008-2011 with the following Research Project (PI/15/02242). Furthermore, BA has been supported by a NARSARD Independent Investigator Grant from the Brain and Behavior Research Foundation (Number: 24397).

Acknowledgments

BA is very grateful to the Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación, Plan Nacional 2008-2011 and 2013-2016 for a specific Grant (PI/15/02242) for this project, and to the Brain & Behavior Research Foundation, NARSAD for an Independent Investigator Grant (24397) related to this project. AM-A wants to thank also to the Secretaria d'Universitats i Recerca del

Departament d'Economia i Coneixement (2017 SGR 46 to Unitat de Recerca del Centre Fòrum), Generalitat de Catalunya (Government of Catalonia) for the recognition as an Emerging Research Group. BH thanks the support and funding of the Instituto de Salud Carlos III with a PFIS Grant (FI10/00017). We acknowledge also the continuous support by the CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental, Instituto Carlos III).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.931374/full#supplementary-material

References

1. Kessing LV, Vradi E, Andersen PK. Life expectancy in bipolar disorder. *Bipolar Disord.* (2015) 17:543–8. doi: 10.1111/bdi.12296

2. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet.* (2013) 381:1663. doi: 10.1016/S0140-6736(13)60989-7

3. Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, et al. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol Psychiatry.* (2008) 13:197–207. doi: 10.1038/sj.mp.4002012

4. Misiak B, Stramecki F, Gaweda Ł, Prochwicz K, Sasiadek MM, Moustafa AA, et al. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. *Mol Neurobiol.* (2018) 55:5075–100. doi: 10.1007/s12035-017-0708-y

5. Bortolato B, Köhler CA, Evangelou E, León-Caballero J, Solmi M, Stubbs B, et al. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. *Bipolar Disord.* (2017) 19:84–96. doi: 10.1111/bdi.12490

6. Leverich GS, McElroy SL, Suppes T, Keck PE, Denicoff KD, Nolen WA, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry.* (2002) 51:288–97. doi: 10.1016/S0006-3223(01)01239-2

7. Maniglio R. The impact of child sexual abuse on the course of bipolar disorder: a systematic review. *Bipolar Disord.* (2013) 15:341–58. doi: 10.1111/bdi.12050

8. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of bipolar disorder. *Psychiatry Clin Neurosci.* (2017) 71:6–17. doi: 10.1111/pcn.12433

9. Cerimele JM, Bauer AM, Fortney JC, Bauer MS. Patients with co-occurring bipolar disorder and posttraumatic stress disorder: a rapid review of the literature. *J Clin Psychiatry.* (2017) 78:e506–14. doi: 10.4088/JCP.16r10897

10. *National Comorbidity Survey*. Available online at: https://www.hcp.med.harvard.edu/ncs/index.php (accessed April 8, 2022).

11. Hernandez JM, Cordova MJ, Ruzek J, Reiser R, Gwizdowski IS, Suppes T, et al. Presentation and prevalence of PTSD in a bipolar disorder population: a STEP-BD examination. *J Affect Disord.* (2013) 150:450–5. doi: 10.1016/j.jad.2013.04.038

12. Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B. The role of childhood trauma in bipolar disorders. *Int J Bipolar Disord.* (2016) 4:2. doi: 10.1186/s40345-015-0042-0

13. Daruy-Filho L, Brietzke E, Lafer B, Grassi-Oliveira R. Childhood maltreatment and clinical outcomes of bipolar disorder. *Acta Psychiatr Scand.* (2011) 124:427–34. doi: 10.1111/j.1600-0447.2011.01756.x

14. Larsson S, Aas M, Klungsøyr O, Agartz I, Mork E, Steen NE, et al. Patterns of childhood adverse events are associated with clinical characteristics of bipolar disorder. *BMC Psychiatry.* (2013) 13:1–9. doi: 10.1186/1471-244X-13-97

15. Jansen K, Cardoso TA, Fries GR, Branco JC, Silva RA, Kauer-Sant'Anna M, et al. Childhood trauma, family history, and their association with mood disorders in early adulthood. *Acta Psychiatr Scand.* (2016) 134:281–6. doi: 10.1111/acps.12551

16. Zlotnick C, Franklin CL, Zimmerman M. Does "subthreshold" posttraumatic stress disorder have any clinical relevance? *Compr Psychiatry.* (2002) 43:413–9. doi: 10.1053/comp.2002.35900

17. Carmassi C, Bertelloni CA, Dell'Oste V, Barberi FM, Maglio A, Buccianelli B, et al. Tele-psychiatry assessment of post-traumatic stress symptoms in 100 patients with bipolar disorder during the COVID-19 pandemic social-distancing measures in Italy. *Front Psychiatry.* (2020) 11:580736. doi: 10.3389/fpsyt.2020.580736

18. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. *Nat Rev Neurosci.* (2016) 17:652–666. doi: 10.1038/nrn.2016.111

19. Álvarez MJ, Roura P, Osés A, Foguet Q, Solà J, Arrufat FX. Prevalence and clinical impact of childhood trauma in patients with severe mental disorders. *J Nerv Ment Dis.* (2011) 199:156–61. doi: 10.1097/NMD.0b013e31820c751c

20. Etain B, Aas M, Andreassen OA, Lorentzen S, Dieset I, Gard S, et al. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. *J Clin Psychiatry.* (2013) 74:991–8. doi: 10.4088/JCP.13m08353

21. Jiménez E, Solé B, Arias B, Mitjans M, Varo C, Reinares M, et al. Impact of childhood trauma on cognitive profile in bipolar disorder. *Bipolar Disord.* (2017) 19:363–74. doi: 10.1111/bdi.12514

22. Mauritz MW, Goossens PJJ, Draijer N, van Achterberg T. Prevalence of interpersonal trauma exposure and trauma-related disorders in severe mental illness. *Eur J Psychotraumatol.* (2013) 4:19985. doi: 10.3402/ejpt.v4i0.19985

23. Moreno-Alcázar A, Radua J, Landín-Romero R, Blanco L, Madre M, Reinares M, et al. Eye movement desensitization and reprocessing therapy versus supportive therapy in affective relapse prevention in bipolar patients with a history of trauma: study protocol for a randomized controlled trial. *Trials.* (2017) 18:160. doi: 10.1186/s13063-017-1910-y

24. Shapiro F. Eye movement desensitization: a new treatment for post-traumatic stress disorder. *J Behav Ther Exp Psychiatry.* (1989) 20:211–7. doi: 10.1016/0005-7916(89)90025-6

25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association (2013).

26. Berk M, Malhi GS, Cahill C, Carman AC, Hadzi-Pavlovic D, Hawkins MT, et al. The bipolar depression rating scale (BDRS): its development, validation and utility. *Bipolar Disord.* (2007) 9:571–9. doi: 10.1111/j.1399-5618.2007.00536.x

27. Sarró S, Madre M, Fernández-Corcuera P, Valentí M, Goikolea JM, Pomarol-Clotet E, et al. Transcultural adaption and validation of the Spanish version of the Bipolar Depression Rating Scale (BDRS-S). *J Affect Disord.* (2015) 172:110–5. doi: 10.1016/j.jad.2014.10.009

28. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* (1978) 133:429–35. doi: 10.1192/bjp.133.5.429

29. Colom F, Vieta E, Martínez-Arán A, Garcia-Garcia M, Reinares M, Torrent C, et al. Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale. *Med Clin.* (2002) 119:366–71. doi: 10.1016/S0025-7753(02)73419-2

30. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a clinician-administered PTSD scale. *J Trauma Stress.* (1995) 8:75–90. doi: 10.1002/jts.2490080106

31. Bobes J, Calcedo-Barbaa García M, Francois M, Rico-Villademoros F, Gonzalez MP, Bascarán MT, et al. Evaluación de las propiedades psicométricas de la versión española de cinco cuestionarios para la evaluación del trastorno de estrés postraumático. *Actas Esp Psiquiatr.* (2000) 28:207–18.

32. Weiss DS. The impact of event scale: Revised. In: Wilson JP, Tang CSK, editors. *Cross-Cultural Assessment of Psychological Trauma and PTSD*. Boston, MA: Springer (2007). p. 219–38. doi: 10.1007/978-0-387-70990-1_10

33. Baguena Puigcerver MJ, Villarroya E, Beleña A, Díaz A, Roldán C, Reig R. Psychometric properties of the Spanish version of the impact of event scale revised (EIE-R). *Análisis y Modificación de Conducta.* (2001) 27:581–604.

34. Creamer M, Bell R, Failla S. Psychometric properties of the impact of event scale - revised. *Behav Res Ther.* (2003) 41:1489–96. doi: 10.1016/j.brat.2003.07.010

35. Holmes TH, Rahe RH. The social readjustment rating scale. *J Psychosom Res.* (1967) 11:213–8. doi: 10.1016/0022-3999(67)90010-4

36. González De Rivera Y, Revuelta JL, Fumero AM. La valoración de sucesos vitales: Adaptación española de la escala de Holmes y Rahe. *Psiquis.* (1983) 4:7–11.

37. Bernstein EM, Putnam FW. Psychometric properties of the dissociative experiences scale. *J Nerv Ment Dis.* (1995) 183:231–5. doi: 10.1097/00005053-199504000-00008

38. Icaran E, Colom R, Orengo Garcia F. Dissociative experiences: a measurement scale. *Anuario de Psicología.* (1996) 70:69–84.

39. Rajkumar RP. Dissociative symptoms and disorders in patients with bipolar disorders: a scoping review. *Front Psychiatry.* (2022) 13:925983. doi: 10.3389/fpsyt.2022.925983

40. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clin Pract Epidemiol Ment Health.* (2007) 3:5. doi: 10.1186/1745-0179-3-5

41. Purdon SE. *The Screen for Cognitive Impairment in Psychiatry (SCIP): Instructions and Three Alternative Forms*. Edmonton: PNL Inc. (2005).

42. Pino O, Guilera G, Rojo JE, Gómez-Benito J, Bernardo M, Crespo-Facorro B, et al. Spanish version of the Screen for Cognitive Impairment in Psychiatry (SCIP-S): Psychometric properties of a brief scale for cognitive evaluation in schizophrenia. *Schizophr Res.* (2008) 99:139–48. doi: 10.1016/j.schres.2007.09.012

43. Hulley SB, Cumming SR, Browner WS, Grady D, Newman TB. *Designing Clinical Research: An Epidemiologic Approach*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins (2013). Appendix 6C, p. 79.

44. Cohen J. *Statistical Power for the Behavioural Sciences*. 2nd ed. New York, NY: Routledge (1988). p. 567.

45. Suppes T, Leverich GS, Keck PE, Nolen WA, Denicoff KD, Altshuler LL, et al. The Stanley Foundation Bipolar Treatment Outcome Network - II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord.* (2001) 67:45–59. doi: 10.1016/S0165-0327(01)00432-3

46. Mitchell PB, Johnston AK, Corry J, Ball JR, Malhi GS. Characteristics of bipolar disorder in an Australian specialist outpatient clinic: comparison across large datasets. *Aust N Z J Psychiatry.* (2009) 43:109–17. doi: 10.1080/00048670802607220

47. Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). *Bipolar Disord.* (2004) 6:395–405. doi: 10.1111/j.1399-5618.2004.00140.x

48. Kogan JN, Otto MW, Bauer MS, Dennehy EB, Miklowitz DJ, Zhang HW, et al. Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Bipolar Disord.* (2004) 6:460–469. doi: 10.1111/j.1399-5618.2004.00158.x

49. Diflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. *Int Rev Psychiatry.* (2010) 22:437–52. doi: 10.3109/09540261.2010.514601

50. Olff M. Sex and gender differences in post-traumatic stress disorder: an update. *Eur J Psychotraumatol.* (2017) 8:1351204. doi: 10.1080/20008198.2017.1351204

51. Reddy MK, Meyer TD, Wittlin NM, Miller IW, Weinstock LM. Bipolar I disorder with comorbid PTSD: Demographic and clinical correlates in a sample of hospitalized patients. *Compr Psychiatry.* (2017) 72:13–7. doi: 10.1016/j.comppsych.2016.08.007

52. Baldessarini RJ, Bolzani L, Cruz N, Jones PB, Lai M, Lepri B, et al. Onset-age of bipolar disorders at six international sites. *J Affect Disord.* (2010) 121:143–6. doi: 10.1016/j.jad.2009.05.030

53. Johnson SL, Cuellar AK, Gershon A. The influence of trauma, life events, and social relationships on bipolar depression. *Psychiatr Clin North Am.* (2016) 39:87. doi: 10.1016/j.psc.2015.09.003

54. Koenders MA, Giltay EJ, Spijker AT, Hoencamp E, Spinhoven P, Elzinga BM. Stressful life events in bipolar I and II disorder: cause or consequence of mood symptoms? *J Affect Disord.* (2014) 161:55–64. doi: 10.1016/j.jad.2014.02.036

55. Okkels N, Trabjerg B, Arendt M, Pedersen CB. Traumatic stress disorders and risk of subsequent schizophrenia spectrum disorder or bipolar disorder: a nationwide cohort study. *Schizophr Bull.* (2017) 43:180–6. doi: 10.1093/schbul/sbw082

56. Hosang GM, Korszun A, Jones L, Jones I, Gray JM, Gunasinghe CM, et al. Adverse life event reporting and worst illness episodes in unipolar and bipolar affective disorders: measuring environmental risk for genetic research. *Psychol Med.* (2010) 40:1829–37. doi: 10.1017/S003329170999225X

57. Buswell G, Haime Z, Lloyd-Evans B, Billings J. A systematic review of PTSD to the experience of psychosis: prevalence and associated factors. *BMC Psychiatry.* (2021) 21:1–13. doi: 10.1186/s12888-020-02999-x

58. Lyssenko L, Schmahl C, Bockhacker L, Vonderlin R, Bohus M, Kleindienst N. Dissociation in psychiatric disorders: a meta-analysis of studies using the dissociative experiences scale. *Am J Psychiatry.* (2018) 175:37–46. doi: 10.1176/appi.ajp.2017.17010025

59. van der Hart O, Nijenhuis ERS, Steele K. Dissociation: An insufficiently recognized major feature of complex posttraumatic stress disorder. *J Trauma Stress.* (2005) 18:413–23. doi: 10.1002/jts.20049

60. Steardo L, Carbone EA, Ventura E, de Filippis R, Luciano M, Segura-Garcia C, et al. Dissociative symptoms in bipolar disorder: impact on clinical course and treatment response. *Front Psychiatry.* (2021) 12:1848. doi: 10.3389/fpsyt.2021.732843

61. Baldwin JR, Reuben A, Newbury JB, Danese A. Agreement between prospective and retrospective measures of childhood maltreatment: a systematic review and meta-analysis. *JAMA Psychiatry.* (2019) 76:584–93. doi: 10.1001/jamapsychiatry.2019.0097

62. Reuben A, Moffitt TE, Caspi A, Belsky DW, Harrington H, Schroeder F, et al. Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *J Child Psychol Psychiatry.* (2016) 57:1103–12. doi: 10.1111/jcpp.12621

63. Naicker SN, Norris SA, Richter LM. Secondary analysis of retrospective and prospective reports of adverse childhood experiences and mental health in young adulthood: filtered through recent stressors. *EClinicalMedicine.* (2021) 40:101094. doi: 10.1016/j.eclinm.2021.101094

64. Newbury JB, Arseneault L, Moffitt TE, Caspi A, Danese A, Baldwin JR, et al. Measuring childhood maltreatment to predict early-adult psychopathology: Comparison of prospective informant-reports and retrospective self-reports. *J Psychiatr Res.* (2018) 96:57–64. doi: 10.1016/j.jpsychires.2017.09.020

65. Scott KM, Smith DR, Ellis PM. Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. *Arch Gen Psychiatry.* (2010) 67:712–9. doi: 10.1001/archgenpsychiatry.2010.71

66. Scott KM, McLaughlin KA, Smith DAR, Ellis PM. Childhood maltreatment and DSM-IV adult mental disorders: comparison of prospective and retrospective findings. *Br J Psychiatry.* (2012) 200:469–75. doi: 10.1192/bjp.bp.111.103267

67. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiol.* (1990) 1:43–6. doi: 10.1097/00001648-199001000-00010

68. Althouse AD. Adjust for multiple comparisons? It's not that simple. *Ann Thorac Surg.* (2016) 101:1644–5. doi: 10.1016/j.athoracsur.2015.11.024

69. Perneger TV. What's wrong with Bonferroni adjustments. *Br Med J.* (1998) 316:1236–8. doi: 10.1136/bmj.316.7139.1236

70. Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC Med Res Methodol.* (2002) 2:1–4. doi: 10.1186/1471-2288-2-8

71. Hardy KV, Mueser KT. Editorial: trauma, psychosis and posttraumatic stress disorder *Front Psychiatry.* (2017) 8:220. doi: 10.3389/fpsyt.2017.00220

72. Spauwen J, Krabbendam L, Lieb R, Wittchen HU, van Os J. Impact of psychological trauma on the development of psychotic symptoms: relationship with psychosis proneness. *Br J Psychiatry.* (2006) 188:527–33. doi: 10.1192/bjp.bp.105.011346

73. Carmassi C, Bertelloni CA. Dell'Oste V, Foghi C, Diadema E, Cordone A, et al. Post-traumatic stress burden in a sample of hospitalized patients with Bipolar Disorder: Which impact on clinical correlates and suicidal risk? *J Affect Disord.* (2020) 262:267–72. doi: 10.1016/j.jad.2019.10.044

74. Dunayevich E, Keck PE. Prevalence and description of psychotic features in bipolar mania. *Curr Psychiatry Rep.* (2000) 2:286–90. doi: 10.1007/s11920-000-0069-4

75. Burton CZ, Ryan KA, Kamali M, Marshall DF, Harrington G, McInnis MG, et al. Psychosis in bipolar disorder: does it represent a more "severe" illness? *Bipolar Disord.* (2018) 20:18–26. doi: 10.1111/bdi.12527

76. Rodrigues R, Anderson KK. The traumatic experience of first-episode psychosis: a systematic review and meta-analysis. *Schizophr Res.* (2017) 189:27–36. doi: 10.1016/j.schres.2017.01.045

77. Panagioti M, Gooding PA, Tarrier N. A meta-analysis of the association between posttraumatic stress disorder and suicidality: the role of comorbid depression. *Compr Psychiatry.* (2012) 53:915–30. doi: 10.1016/j.comppsych.2012.02.009

78. Sumner JA, Hagan K, Grodstein F, Roberts AL, Harel B, Koenen KC. Posttraumatic stress disorder symptoms and cognitive function in a large cohort of middle-aged women. *Depress Anxiety.* (2017) 34:356. doi: 10.1002/da.22600

79. Hayes JP, VanElzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. *Front Integr Neurosci.* (2012) 6:89. doi: 10.3389/fnint.2012.00089

80. Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry.* (2004) 161:262–70. doi: 10.1176/appi.ajp.161.2.262

81. Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord.* (2007) 9:103–13. doi: 10.1111/j.1399-5618.2007.00327.x

82. Assion HJ, Brune N, Schmidt N, Aubel T, Edel MA, Basilowski M, et al. Trauma exposure and post-traumatic stress disorder in bipolar disorder. *Soc Psychiatry Psychiatr Epidemiol.* (2009) 44:1041–9. doi: 10.1007/s00127-009-0029-1

83. Cukor J, Wyka K, Jayasinghe N, Difede JA. The nature and course of subthreshold PTSD. *J Anxiety Disord.* (2010) 24:918–23. doi: 10.1016/j.janxdis.2010.06.017

84. Kornfield SL, Klaus J, McKay C, Helstrom A, Oslin D. Subsyndromal posttraumatic stress disorder symptomatology in primary care military veterans: treatment implications. *Psychol Serv.* (2012) 9:383–9. doi: 10.1037/a0028082

85. Marshall RD, Olfson M, Hellman F, Blanco C, Guardino M, Struening EL. Comorbidity, impairment, and suicidality in subthreshold PTSD. *Am J Psychiatry.* (2001) 158:1467–73. doi: 10.1176/appi.ajp.158.9.1467

86. Quarantini LC, Miranda-Scippa Â, Nery-Fernandes F, Andrade-Nascimento M. Galvão-de-Almeida A, Guimarães JL, et al. The impact of comorbid posttraumatic stress disorder on bipolar disorder patients. *J Affect Disord.* (2010) 123:71–6. doi: 10.1016/j.jad.2009.08.005

87. Garcia-Amador M, Colom F, Valenti M, Horga G, Vieta E. Suicide risk in rapid cycling bipolar patients. *J Affect Disord.* (2009) 117:74–8. doi: 10.1016/j.jad.2008.12.005

88. Cowan A, Ashai A, Gentile JP. Psychotherapy with survivors of sexual abuse and assault. *Innov Clin Neurosci.* (2020) 17:22–26.

89. Otto MW, Perlman CA, Wernicke R, Reese HE, Bauer MS, Pollack MH. Posttraumatic stress disorder in patients with bipolar disorder: a review of prevalence, correlates, and treatment strategies. *Bipolar Disord.* (2004) 6:470–9. doi: 10.1111/j.1399-5618.2004.00151.x

90. Novo P, Landin-Romero R, Radua J, Vicens V, Fernandez I, Garcia F, et al. Eye movement desensitization and reprocessing therapy in subsyndromal bipolar patients with a history of traumatic events: a randomized, controlled pilot-study. *Psychiatry Res.* (2014) 219:122–8. doi: 10.1016/j.psychres.2014.05.012

91. Cakir S, Tasdelen Durak R, Ozyildirim I, Ince E, Sar V. Childhood trauma and treatment outcome in bipolar disorder. *J Trauma Dissociation.* (2016) 17:397–409. doi: 10.1080/15299732.2015.1132489

92. Amann BL, Radua J, Wunsch C, König B, Simhandl C. Psychiatric and physical comorbidities and their impact on the course of bipolar disorder: a prospective, naturalistic 4-year follow-up study. *Bipolar Disord.* (2017) 19:225–34. doi: 10.1111/bdi.12495

93. Frissa S, Hatch SL, Fear NT, Dorrington S, Goodwin L, Hotopf M. Challenges in the retrospective assessment of trauma: Comparing a checklist approach to a single item trauma experience screening question. *BMC Psychiatry.* (2016) 16:20. doi: 10.1186/s12888-016-0720-1

94. Danese A, Widom CS. Objective and subjective experiences of child maltreatment and their relationships with psychopathology. *Nat Hum Behav.* (2020) 4:811–8. doi: 10.1038/s41562-020-0880-3

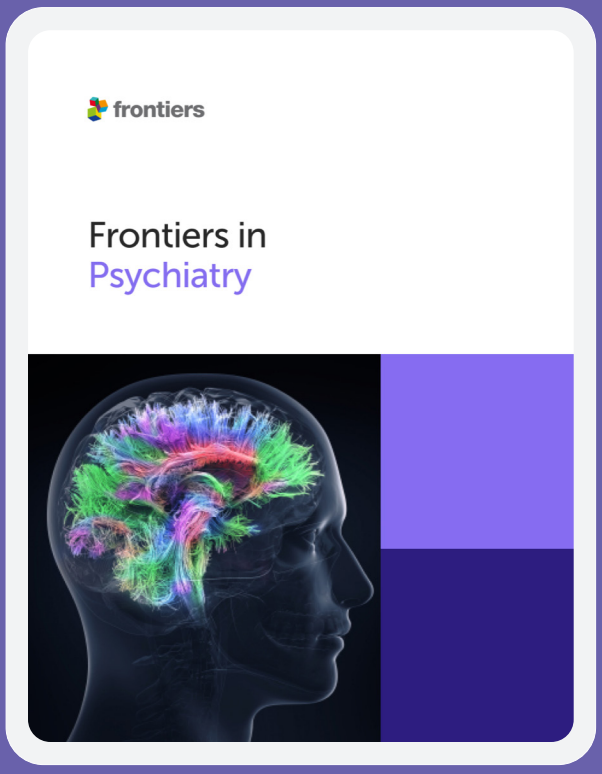
Frontiers in Psychiatry

Explores and communicates innovation in the field of psychiatry to improve patient outcomes

The third most-cited journal in its field, using translational approaches to improve therapeutic options for mental illness, communicate progress to clinicians and researchers, and consequently to improve patient treatment outcomes.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact