OXFORD

International Journal of Neuropsychopharmacology (2023) 26(1): 61–69

https://doi.org/10.1093/ijnp/pyac057
Advance Access Publication: August 29, 2022
Review

REVIEW

The Impact of Posttraumatic Stress Disorder on Pharmacologic Intervention Outcomes for Adults With Bipolar Disorder: A Systematic Review

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Abstract

Background: The prevalence of posttraumatic stress disorder (PTSD) co-occurring in people with bipolar disorder (BD) is high. People with BD and PTSD may experience different outcomes and quality of life after pharmacologic treatment than those with BD alone. This review systematically explores the impact of PTSD on pharmacologic treatment outcomes for adults with BD.

Methods: We conducted a systematic search up to November 25, 2021, using MEDLINE Complete, Embase, American Psychological Association PsycInfo, and the Cochrane Central Register of Controlled Trials to identify randomized and nonrandomized studies of pharmacologic interventions for adults with BD that assessed for comorbid PTSD. We used the Newcastle-Ottawa Scale and Cochrane Risk of Bias tool to assess the risk of bias.

Results: The search identified 5093 articles, and we reviewed 62 full-text articles. Two articles met inclusion criteria (N = 438). One article was an observational study, and the other was a randomized comparative effectiveness trial. The observational study examined lithium response rates and found higher response rates in BD alone compared with BD plus PTSD over 4 years. The randomized trial reported more severe symptoms in the BD plus PTSD group than in those with BD alone following 6 months of quetiapine treatment. There was no significant difference in the lithium treatment group at follow-up.

Conclusions: Comorbid PTSD may affect quetiapine and lithium treatment response in those with BD. Because of the high risk of bias and low quality of evidence, however, these results are preliminary. Specific studies exploring comorbid BD and PTSD are required to inform pharmacotherapy selection and guidelines appropriately. (International Prospective Register of Systematic Reviews ID: CRD42020182540).

Received: June 14, 2022; **Revised:** August 5, 2022; **Accepted:** August 25, 2022

Introduction

Posttraumatic stress disorder (PTSD) frequently co-occurs with bipolar disorder (BD) and is more commonly reported by people with BD than in the general population (Otto et al., 2004; Assion et al., 2009; Hernandez et al., 2013; Cerimele et al., 2017; Reddy et al., 2017). This comorbidity can affect the prognosis of people with BD and PTSD, including an increased risk of experiencing rapid mood cycling and mood instability, lower quality of life (QOL), and a higher risk of suicide compared with those with either disorder alone (Assion et al., 2009; Quarantini et al., 2010; Carter et al., 2017; Katz et al., 2020). The individual presentation of BD and PTSD overlaps: Some symptoms—for example, mood swings, sleep disturbance, hopelessness, and suicidality—are seen in both disorders (American Psychiatric Association, 2013; Katz et al., 2020). Those with comorbid BD and PTSD may be under- or misdiagnosed, possibly because of the atypical presentation of each disorder (Goldberg and Fagin-Jones, 2004; Carter et al., 2017). Furthermore, PTSD may influence and exacerbate BD symptoms. For instance, the high level of distress associated with experiencing flashbacks to a traumatic event—a symptom of PTSD—may induce a BD mood episode (Otto et al., 2004; Aldinger and Schulze, 2017). The combination of these factors can make the assessment and treatment of comorbid BD and PTSD challenging.

A review of prevalence, correlates, and treatment strategies for comorbid BD and PTSD (Otto et al., 2004) suggests that treatment could include antipsychotics, benzodiazepines, antidepressants, and mood stabilizers. Although antidepressants are the first-line treatment for PTSD, however, their use in BD is cautioned as antidepressant use may induce rapid cycling, mixed states, and a manic episode (Otto et al., 2004; Pacchiarotti et al., 2013). Furthermore, reviews on the prevalence, correlates, and treatment strategies for comorbid anxiety disorders (including PTSD) and BD suggest that the first-line treatment for people with comorbid BD and PTSD should be a mood stabilizer to address the BD symptoms, and then begin pharmacotherapy for PTSD when the maintenance phase of BD has been achieved (Freeman et al., 2002; Otto et al., 2004). Thus, tailored treatment options may be necessary. A rapid review by Cerimele et al. (2017), however, found no evidence-based strategies for pharmacologic treatments for those with comorbid BD and PTSD. In this systematic review, we aim to identify and explore the current pharmacologic treatment landscape for comorbid BD and PTSD. Specifically, the review compares pharmacologic treatment outcomes in individuals with comorbid BD and PTSD with those with BD alone.

Methods

The full protocol for the review is available (Russell et al., 2022) and was registered with the International Prospective Register of Systematic Reviews (ID: CRD42020182540). This systematic review was conducted in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page et al., 2021) (see supplementary Table S1). The search was conducted under the guidance and assistance of a medical research librarian from Deakin University.

Information Sources and Databases

Relevant articles were identified through electronic searchers of Medline Complete, American Psychological Association PsycInfo, EMBASE, and the Cochrane Central Register of Controlled Trials. Databases were searched by S.E.R. from their inception to March 31, 2021. The search strategy was re-run on November 25, 2021. In addition to the database search, reference lists were reviewed for any potential articles eligible for inclusion in the review.

Key Search Terms

We used the search framework Population, Intervention, Comparator, and Outcome to develop search terms related to BD, PTSD, and pharmacotherapy. A total of 29 key search terms were used in the search: 13 BD-specific terms, 2 PTSD-specific terms, and 12 terms for pharmacotherapy (eg, *bipolar disorder, mood disorder, manic episode, depression episode, post-traumatic stress disorder, stress disorders post traumatic, pharmacotherapy, drug therapy, treatment outcome*). A comprehensive list of search terms and database limiters can be found in supplementary Table S2 and the protocol (Russell et al., 2022).

Inclusion and Exclusion Criteria

We used the following inclusion criteria:

- The intervention is a pharmacologic treatment.
- The primary diagnosis was BDI, BDII, or another bipolar subtype, with a subgroup comorbid PTSD diagnosis within the primary BD sample. The diagnosis was confirmed by structured or semistructured diagnostic clinical interview (eg, Structured Clinical Interview for the DSM [SCID], Composite International Diagnostic Interview or Mini International Neuropsychiatric Interview [MINI]) or through psychiatrist diagnosis.
- The study was a randomized or non-randomized trial, crossover-trial, randomized controlled trial (RCT), cluster RCT, 1-arm trial, controlled nonrandomized trial, cohort study, case-control study, cross-sectional study, or open-label study.
- The study intervention could be of any length.
- Monotherapy or adjunctive therapies were used.
- Comparator of any intervention, waitlist controls, active comparators, nonexposed control group, treatment-as-usual or standard-care comparisons, or controls were used.
- BD outcomes were measured by any validated assessment tool (eg, Montgomery-Åsberg Depression Rating Scale, Young Mania Rating Scale, Bipolar Inventory of Symptom Scale [BISS], Bipolar Depression Rating Scale). Validated and nonvalidated self-reported symptom improvements and assessments of QOL were also included. Any other validated scales assessing BD were considered.
- The study used an adult population (≥18 years of age).
- Results were published in a peer-reviewed journal.
- Inpatients and outpatients were included in the study.
- The effects of the medication on reducing BD symptoms was tested.
- The article was in English.

We had 3 exclusion criteria:

- Case series, case reports, qualitative studies, reviews, and protocols
- Theses and poster presentations
- Children (<18 years of age)

We excluded studies of participants with a primary diagnosis of PTSD and a subsample of participants with comorbid BD because they did not fit the criteria of this review's main outcome.

Data Extraction

Two independent reviewers (S.E.R. and A.L.W.) screened articles for eligibility. The abstract and title screening, full-text screening, extraction of data, and assessment of bias were conducted by S.E.R. and A.L.W; M.M.A. acted as adjudicator at each stage to resolve any discrepancies. Studies were exported from the databases directly into Covidence systematic review software (Covidence, Melbourne, Victoria, Australia) Study details, including study characteristics, study sample, pharmacologic treatment assessments, and pharmacologic treatment outcomes, were extracted and recorded using Microsoft Excel software (Microsoft Corp, Redmond, WA, USA). Where necessary, raw data, including baseline, posttreatment mean scores, and SDs, were requested from authors of eligible studies.

There were minor changes from the protocol (Russell et al., 2022). Medication response rates have been included as an outcome measure; this information was not listed as an original review protocol. We decided to include these data as an outcome measure because they are commonly used to identify lithium response rates among participants with BD. Two clerical variations are also noted. The extraction and risk-of-bias assessment were completed using Excel software. Therefore, the custom REDCap extraction tool was not required because of the small sample of articles to extract. Similarly, we did not use Mendeley software because all articles were imported directly into Covidence for duplicate removal, screening, and full-text review.

Data Analysis

Data were narratively described and assessed. This work included systematic assessment for risk of bias and study descriptions, including differences and similarities in study design, population, interventions, and treatment outcomes. Each treatment outcome was reported in a summary of findings table. A meta-analysis could not be completed because of the small number of studies and different study designs.

Assessment of Risk of Bias and Quality Appraisal

Risk of bias in nonrandomized studies was assessed using the Newcastle-Ottawa Scale (Wells, et al., n.d.). The revised version of the Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011) was used to assess the risk of bias in randomized studies. Two independent reviewers (S.E.R. and A.L.W.) conducted all risk-of-bias assessments. Discrepancies between appraisals were resolved through discussion. S.E.R. evaluated the certainty of evidence for all treatment outcomes included in the review using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) for a narrative assessment (Guyatt et al., 2008; Murad et al., 2017). (For a summary of bias scores for each article, see Table 2 and Table 3 later in this article.)

Results

Initial Search Yield

A total of 6298 references were identified in the original search, of which Covidence removed 1205 duplicates, leaving 5093 to be screened by title and abstract. Of these, 62 were reviewed in full text. Subsequently, 58 articles were excluded (see Figure 1). Specifically, we excluded 34 studies for having a nonrelevant target population, 15 studies for nonrelevant publication type, 6 for having a primary PTSD cohort (Berlant, 2004; Holtzheimer et al., 2005; Mithoefer et al., 2011; Cameron et al., 2014; McCall et al., 2018; Stefanovics and Rosenheck, 2020), 1 for nonrelevant study design, 1 for having no comparison group, 1 for having nonrelevant treatment outcomes, and 2 for having no data available upon request.

Of the 4 eligible studies, 1 article had data available (Cakir et al., 2016). We contacted the authors of 3 articles to request raw data (Kemp et al., 2014; Caldieraro et al., 2018; Fortney et al., 2020). Of these, data were received for 1 article (Caldieraro et al., 2018), leading to the final inclusion of 2 articles in this review.

We reran the search on November 25, 2021, and no further articles were eligible for inclusion.

Description of Studies

An overview of the study characteristics included in this review is provided in Table 1. The Caldieraro et al. (2018) study included participants from the Bipolar Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (CHOICE) study, a multisite, randomized clinical trial of outpatients with BD, which compared the effectiveness of lithium and quetiapine with adjunctive personal treatments (Nierenberg et al., 2014). The Cakir et al. (2016) study was an observational study that included patients from a long-term follow-up program for BD. Participants were taking any available treatments for BD, including lithium, anticonvulsants, and antidepressants. Response rates were assessed (where possible) for each pharmacotherapy treatment.

Sample sizes, outcome measures, and duration of treatment were inconsistent among studies. The mean (SD) age across both studies was 40.20 (0.40) years, and sex in both studies was 60% female. The primary aim of the Caldieraro et al. (2018) study was to compare treatment outcomes of individuals with BD depression with and without psychosis; the secondary aim was to compare the effect of lithium and quetiapine in the psychotic subgroup. The primary objective of the study by Cakir et al. (2016) was to investigate the potential influence of childhood trauma on psychiatric comorbidity, clinical presentation, and long-term treatment outcomes in BD.

Caldieraro et al. (2018) used an electronic version of the MINI tool (Lecrubier et al., 1997) for the diagnosis of both current and lifetime diagnoses of BD and PTSD. Cakir et al. (2016) used the SCID-IV Axis I Disorders to confirm the diagnoses of BD and PTSD. The study by Caldieraro et al. (2018) included adult outpatients with BDI and BDII in a depressive episode. The Cakir et al. (2016) study included adult outpatients with BDI who reported being euthymic for 3 months upon enrolment.

Assessment of Symptom Reduction and Pharmacologic Response Rates

Upon request, Caldieraro et al (2018) provided the BISS mean scores at baseline and at the end of 24-week treatment follow-up as well as baseline change scores for BD alone and comorbid BD and PTSD. The BISS is a validated, 44-item structured interview that assesses BD mood symptoms across 5 domains: depression, irritability, anxiety, mania, and psychosis. It is rated on a scale from 0 to 4, with higher scores displaying increased symptom severity (Gonzalez et al., 2008).

Cakir et al. (2016) reported pharmacologic treatment response rates. Two psychiatrists assessed treatment responses that were categorized as poor or good. The study team discussed contradictory cases. A poor response (or a nonresponse) was

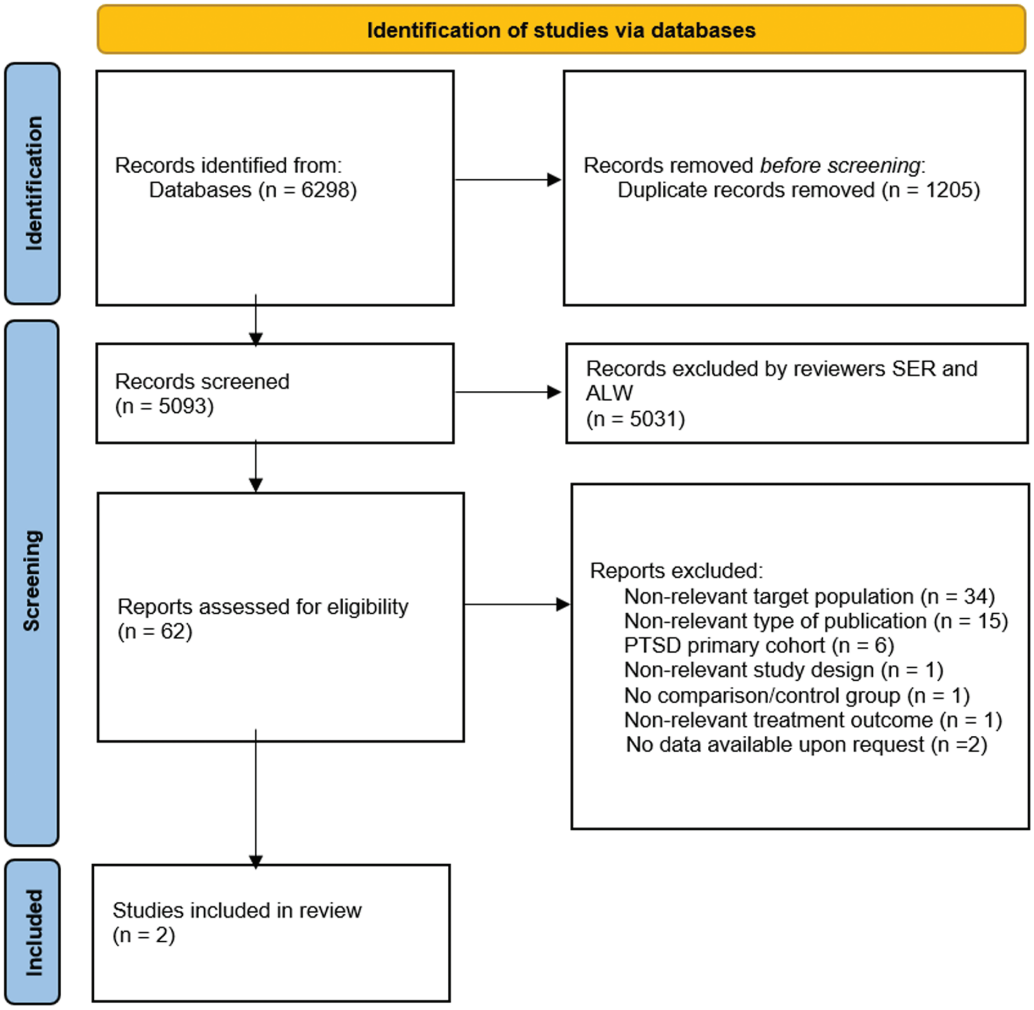

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses flowchart. PTSD, posttraumatic stress disorder.

defined as a lack of reduction in episodes' duration, frequency, or severity during treatment. A good response was defined by a lack of minor or major episodes, with minimal mood changes that did not require additional medication during treatment (except for short-duration benzodiazepine treatments). Only lithium response rates were reported for the comorbid BD and PTSD comparison in the study by Cakir et al. (2016). There were insufficient data to report on anticonvulsant response rates.

Lithium Treatment

Both studies examined lithium treatment in comorbid BD and PTSD compared with BD alone. Caldieraro et al. (2018) assessed BISS mean scores at baseline and at the end of 24-week treatment follow-up as well as the change scores for BD alone and comorbid BD and PTSD. At baseline, there was a statistically significant difference in symptom severity in those undergoing lithium treatment, with the comorbid BD and PTSD group (mean [SD]= 63.8 [12.6]) having more severe symptoms than those with BD alone (mean [SD] =55.5 [16.6]; $P=.04$). No significant differences were evident at follow-up (comorbid BD and PTSD: mean [SD] =32.2 [17.6]; BD alone: mean [SD] =27.8 [17.9]; $P=.34$) or in baseline to follow-up changes score ($P=.50$) (see Table 1).

Cakir et al. (2016) reported lithium response rates between BD alone and comorbid BD and PTSD and found higher rates of good responses in the BD alone group (49/76 [64.5%]) compared with those with comorbid BD and PTSD (6/16 [37.5%]; Fisher exact test $P=.05$).

Quetiapine Treatment

Caldieraro et al. (2018) reported BISS mean scores for quetiapine treatment for those with BD alone compared with those with comorbid BD and PTSD at baseline and 24-week follow-up as well as baseline change scores. Results indicated statistically significant differences at baseline ($P=.01$), with more severe symptoms reported in the comorbid BD and PTSD group (mean [SD] =70.2 [11.2]) compared with the BD alone group (mean [SD]=55.5 [16.6]). There was also a significant difference at the week 24 follow-up ($P=.03$), where more severe symptoms were reported in the comorbid BD and PTSD group (mean [SD]=35.7 [21.0]) compared with the BD alone group (mean [SD]=25.1 [18.4]). No significant differences were reported at baseline to follow-up change scores ($P=.32$).

Risk-of-Bias Assessment

Using the Cochrane Risk of Bias tool (Higgins et al., 2011), the study by Caldieraro et al. (2018) was judged to have a low risk of bias in all domains, except D3 ("missing outcome data") and D5

Table 1. Summary of Findings

Author *Study Design*	Intervention	Dose	Diagnosis	% Female	Country	Total No. Sample size	BD Arm, No.	BD+PTSD Arm, No.	Age, Overall Mean (SD), y	Primary Outcome Measure	Findings
Caldieraro, et al. (2018) *RCT*	Lithium	Not reported	BDI, BDII and depressive episode	60.1% (total)	USA	303	128	18	Pooled mean age: 39.8	BISS	Significant difference in BISS scores between groups at baseline, and no difference at 24-wk follow-up
	Quetiapine	Not reported	BDI, BDII and depressive episode	60.1% (total)	USA	303	139	18	Pooled mean age: 39.8	BISS	Significant difference in BISS scores between groups at baseline and 24-wk follow-up
Cakir et al. (2016) *Observational*	Lithium	Not reported	BDI and euthymic	60.7%	Turkey	135	76	16	40.6 (12.8)	Lithium response rate	Significant difference in lithium response rate

Abbreviations: BD, bipolar disorder; BISS: Bipolar Inventory of Symptoms Scale; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial.

Table 2. Cochrane Risk of Bias Tool for Randomized Studies

Caldieraro et al. (2018)	Risk of Bias
Domain 1. Randomization process	+
Domain 2. Deviations from intended interventions	+
Domain 3. Missing outcome data	-
Domain 4. Measurement of the outcome	+
Domain 5. Selection of the reported result	-
Overall	High risk of bias

Table 3. Newcastle-Ottawa Scale Risk of Bias Tool for Nonrandomized Studies

Author	Selection				Comparability	Outcome			Overall
Cakir et al. (2016)	1	2	3	4	5	6	7	8	******
	–	*	*	*	–	*	*	*	/9

("selection of the reported result") (Table 2). The data analyzed from the Caldieraro et al. (2018) study was not publicly available in the article, but we did request them. Therefore, there is a possibility of bias because of selective reporting and missingness of data. The study was scored as having a high risk of bias (Table 2).

Using the Newcastle-Ottawa Scale, the Cakir et al. (2016) study was judged to have low risk of bias in all domains, except "Selection, representativeness of exposed cohort" and "Comparability of cohorts based on the design or analysis" (Table 3). In this report, (1) the participants were limited to BDI outpatients in a euthymic mood state and (2) a nonstandardized psychiatrist assessment reporting pharmacologic response rates was used. Taken together, these aspects limit the representativeness and comparability of the study. There is a possibility of bias because of comparability and selection procedures. The Cakir et al. (2016) study scored 6 out of 9 on the Newcastle-Ottawa Scale, which suggested a high risk of bias because of the lack of score in the comparability domain.

Certainty Assessment

Table 4 displays the certainty of assessment and is presented according to the GRADE guidelines for a narrative assessment (Guyatt et al., 2008; Murad et al., 2017). The Cakir et al. (2016) and Caldieraro et al. (2018) studies displayed similar certainty of assessment, including a high risk of bias.

DISCUSSION

Much of the literature documents the increased rates of comorbid BD and PTSD in the BD population as well as the negative impact of each disorder on the functioning, symptomology, and QOL of individuals (Otto et al., 2004; Cerimele et al., 2017). This review pools the currently available evidence to determine whether PTSD affects BD pharmacological treatment outcomes. Two studies consisting of 438 participants met inclusion criteria for this review. In summary, the evidence for the randomized study by Caldieraro et al. (2018) reports significantly higher symptom severity at baseline in those with comorbid BD and PTSD compared with BD alone (for both lithium and quetiapine treatment). This difference was seen after 24 weeks of quetiapine treatment, but the significant baseline difference was not

Table 4. Grading of Recommendation, Assessment, Development and Evaluation Assessment as Reported for a Narrative Assessment

Author	Outcome	Participants, No.	Effect	Quality of Evidence (GRADE)
Caldieraro et al. (2018)	Reduction in BD symptom severity using the BISS	303	Study showed small reduction in severity (lithium treatment) or no effect (quetiapine treatment)	Low certainty ++00 because of risk of bias, indirectness, and imprecision
Cakir et al. (2016)	Treatment response	135	Study showed no or small effect	Very low certainty ++00 because of risk of bias and imprecision

Abbreviations: BD, bipolar disorder; BISS: Bipolar Inventory of Symptoms Scale; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

retained after 24 weeks of lithium treatment. The comorbid BD and PTSD group showed reduced symptom severity scores to a level similar to those with BD alone, suggesting that both groups respond to lithium treatment. Furthermore, the baseline to 24-week follow-up for both the lithium and the quetiapine treatment groups showed no significant difference, but both treatment groups did show a reduction (although not significant) in symptom severity scores over time. Cakir et al. (2016) reported that the BD group had significantly better lithium response rates compared with the comorbid BD and PTSD group. Across both studies, the results display contradictory evidence regarding lithium treatment and negative results regarding quetiapine treatment for comorbid BD and PTSD compared with BD alone.

The findings by Cakir et al. (2016) are supported by a pharmacogenetics study (Bremer et al., 2007) that identifies candidate genes and clinical characteristics for participants with BD on lithium treatment. Bremer et al. (2007) reported using lithium response rates as the primary outcome measure. Bremer et al. (2007) found that those with comorbid BD and PTSD had lower lithium response rates than those with BD alone, but the definition of a "good" vs "bad" or "nonresponse" to lithium in the Bremer et al. (2007) study was inconsistent with the Cakir et al. (2016) study. Additionally, no other studies were identified that used BISS scores to assess comorbid BD and PTSD. These findings reflect the lack of available evidence that is also highlighted in the rapid review by Cerimele et al. (2017), which found no studies comparing pharmacologic treatment strategies in comorbid BD and PTSD.

Case reports have examined other pharmacologic treatments in those with comorbid BD and PTSD. Malek-Ahmadi and Hanretta (2004) found that oxcarbazepine may reduce PTSD symptoms in a patient with comorbid BD and PTSD at 4 weeks of treatment that persisted over 16 months. Topiramate treatment has also been examined in comorbid BD and PTSD. A retrospective case series examining topiramate in those with BD and comorbid conditions suggested improvement in symptoms in comorbid BD and PTSD (Guille and Sachs, 2002).

Quality, Completeness, and Generalizability of Evidence

This systematic review attempted to clarify pharmacologic treatment-selection response in comorbid BD and PTSD. In addition to the large gaps in the literature, the low-quality GRADE ratings lead to a low certainty of the evidence for a narrative assessment. First, few studies are available, with only 1 eligible randomized trial—despite the importance of understanding appropriate pharmacologic treatments for those with comorbid BD and PTSD being highlighted in a recent rapid review by Cerimele et al. (2017). Previous research on clinical correlates and prevalence also addressed the need for trials in this area (Otto et al., 2004; Bauer et al., 2005; Simon et al., 2007; Neria et al., 2008; Assion et al., 2009; Quarantini et al., 2010; Hernandez et al., 2013; Carter et al., 2017; Katz et al., 2020).

Both studies in this review used just 1 outcome measure for the assessment of pharmacologic treatments: BISS in the Caldieraro et al. (2018) study and psychiatrist assessment in the Cakir et al. (2016) study. A more comprehensive evaluation of BD, including functioning and QOL measures, is needed to accurately assess treatment effectiveness. Additionally, many pharmacologic treatments are available for both BD and PTSD (Phoenix Australia - Centre for Posttraumatic Mental Health, n.d.; Malhi et al., 2015, 2021; National Institute for Health and Care Excellence, 2020). This review was able to assess only 2 agents—lithium and quetiapine—limiting the generalizability of these results within the treatment landscape.

The small sample sizes in both studies, particularly the comorbid BD and PTSD group (n = 16 in Cakir et al. [2016] and n = 33 in Caldieraro et al. [2018]) may lead to low statistical power in comparative analysis. Additionally, the eligibility criteria for the studies were largely restrictive (eg, people with BDI who were euthymic for at least 3 months upon enrolment, on constant maintenance treatment for 3 years, or people with BD depression). Taken together, these factors affect the generalizability of the results from this review.

Limitations

This review included only English-language articles. As such, important articles may have been omitted. Another possible limitation is that this review investigated only BD pharmacologic treatment studies for the comorbid BD and PTSD population, excluding PTSD pharmacologic treatment studies. The systematic search identified 6 studies of PTSD pharmacologic treatments that had a comorbid BD and PTSD subgroup (see Figure 1). These studies were not eligible for assessment, however, and would require a separate systematic review process. Because of the inclusion and exclusion criteria, only BD treatments could be evaluated for the current systematic review. For this systematic review, all available and eligible evidence was included, but excluding the PTSD pharmacotherapy studies limits the scope of reporting on appropriate treatments for the comorbid BD and PTSD population accurately.

Clinical Implications

The findings of this systematic review, although preliminary, suggest that lithium treatment may potentially be useful in the treatment of comorbid BD and PTSD. Additionally, quetiapine treatment may be less effective in comorbid BD and PTSD than

in those with BD alone. This review also highlights the need for assessment of PTSD in BD cohort studies and patients, given its increased prevalence and effect on symptoms, functioning, and QOL. Given that this systematic review was able to assess just 2 studies, however, both with a high risk of bias, these results must be interpreted with caution.

Conclusions

Although PTSD may affect treatment response to quetiapine and lithium in those with BD, the lack of studies limits the conclusions that can be drawn. Future directions include exploring the pharmacotherapeutic treatments of comorbid BD and PTSD in studies of a PTSD cohort to capture all the available evidence for how this comorbidity affects pharmacologic treatments and outcomes. Furthermore, this review highlights that more research (including randomized and nonrandomized intervention studies) into comorbid BD and PTSD is required to assess and evaluate appropriate pharmacologic treatments for this comorbidity.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Acknowledgments

Funding: None
The authors would like to acknowledge and thank Medical Research Librarian Blair Kelly, Deakin University, for assisting with the search strategy design and development.

Conflict of Interest

Author S.E.R. has received grant/research support from Deakin University. Author A.L.W. has received grant/research support from Deakin University. Author O.M.D. is an R.D. Wright Biomedical NHMRC Career Development Fellow (APP1145634) and has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical Research Institute, Deakin University, Lilly, NHMRC and ASBDD/Servier. O.M.D has also received in kind support from BioMedica Nutracuticals, NutritionCare, and Bioceuticals. Author B.E.K. has received research support from Deakin University, Australian Rotary Health, the Australian Government Research Training Program, and the International Society for the Study of Personality Disorders. Author D.R.S. is supported by an NHMRC Medical Research Future Fund (1200214). Author M.M.A. has received grant/research support from Deakin University, Australasian Society for Bipolar Depressive Disorders, Lundbeck, Australian Rotary Health, Ian Parker Bipolar Research Fund & Cooperative Research Centre for Mental Health, and PDG Geoff and Betty Betts Award from Rotary Club of Geelong. Author M.B is supported by an NHMRC Senior Principal Research Fellowship (1059660) and has received grant/research support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer and Servier. Author M.B. is a co-inventor of 2 provisional patents regarding the use of NAC and related compounds for psychiatric indications, which, while assigned to the Mental Health Research Institute, could lead to personal remuneration upon a commercialization event. Author A.T. has received travel or grant support from NHMRC, AMP Foundation, Stroke Foundation, Hunter Medical Research Institute, Helen Macpherson Smith Trust, Schizophrenia Fellowship NSW, SMHR, ISAD, the University of Newcastle, and Deakin University.

Author Contributions

S.E.R., A.T., M.M.A., A.L.W., and O.M.D. conceptualized and designed the research question and developed the search strategy. S.E.R. and A.L.W. screened, reviewed, and assessed the included articles. S.E.R., A.L.W., D.R.S., M.M.A., B.E.K., O.M.D., M.B., and A.T. edited, revised, and approved the final version of the manuscript.

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