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ABSTRACT

Introduction Despite available pharmacological and psychological treatments, remission rates for bipolar disorder remain relatively low. Current research implicates the experience of childhood trauma as a potential moderator of poor treatment outcomes among individuals with bipolar disorder. To date, the evidence reporting the influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder has not been systematically reviewed.

Method and analysis MEDLINE Complete, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials will be searched to identify randomised and nonrandomised studies of pharmacological and/or psychological interventions for bipolar disorder, which also assessed childhood trauma. To be eligible for inclusion, studies must have been conducted with adolescents or adults (≥10 years). Data will be screened and extracted by two independent reviewers. The methodological quality of the included studies will be assessed with the Cochrane Collaboration's Risk of Bias tool and the Newcastle-Ottawa Scale. If deemed viable, a meta-analysis will be conducted using a random effects model. Heterogeneity of evidence will be estimated with the I^2 statistics.

Ethics and dissemination This systematic review will use only previously published data. Therefore, ethical approval is not required. The results will be written in concordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines, published in peer-reviewed journals and presented at relevant conferences.

PROSPERO registration number CRD42020201891.

Strengths and limitations of this study

- This will be the first systematic review to involve the critical evaluation of the influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder.
- The screening and data extraction process will be completed by two independent reviewers and reported according to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.
- Standardised methodological appraisal tools will be used to assess risk of bias of the studies included in the review.
- Heterogeneity of evidence is likely as inclusive study design criteria were set for the review.
- The systematic review may be limited by the lack of available evidence, precluding a meta-analysis from being conducted.

INTRODUCTION

Bipolar disorder is a potentially debilitating illness that is characterised by manic and depressive episodes.[1–3] A manic episode is typically marked by an unusually elevated or irritable mood, whereas low mood or a significant loss of interest or pleasure occurs in a depressive episode.[4] Bipolar disorder may significantly impair social and occupational functioning[5 6] as well as the quality of life (QoL)[1 7–9] of the people affected. Despite available pharmacological and psychological treatments, the majority of individuals diagnosed with bipolar disorder fail to obtain complete remission and continue to report residual symptoms[10] with approximately 70% experiencing an affective relapse within 4 years.[11–14] These findings highlight the clinical importance of recognising environmental risk factors, such as childhood trauma, that contribute to the outcomes in bipolar disorder.[15 16]

Childhood trauma is commonly reported by individuals with a diagnosis of bipolar

disorder with prevalence rates as high as 50% being documented in various cross-sectional studies.[17–19] As an example, Sala *et al*[20] analysed data collected from a large community sample and reported that 54.3% of adults with bipolar disorder also had a history of childhood trauma. Specifically, 21.7% had experienced physical abuse, 26.0% sexual abuse, 38.4% emotional abuse, 13.6% physical neglect and 14.7% emotional neglect. This high prevalence is noteworthy as experiences of childhood trauma have been recognised to affect the clinical presentation of several major psychiatric disorders including bipolar disorder.[15 17 18 21]

In a comprehensive meta-analysis, Agnew-Blais and Danese[22] indicated an association between childhood trauma and more severe clinical characteristics of bipolar disorder. Broadly, the researchers reported that individuals with a history of childhood trauma were more likely to present with an earlier age at onset, rapid cycling, psychotic features, psychiatric comorbidities, suicide attempts and a greater number of affective episodes. Agnew-Blais and Danese[22] further highlighted that childhood trauma was related to the experience of more severe manic, depressive and psychotic symptoms among patients with bipolar disorder.

The reviewers' findings are largely echoed in recent longitudinal studies. Andreu Pascual *et al*,[23] for example, prospectively followed a large group of young people with bipolar disorder. The researchers demonstrated that the experience of at least one traumatic event in childhood was related to an earlier symptom onset, more severe affective symptoms, greater suicidal ideation, psychiatric comorbidities and greater functional impairment. Additionally, Andreu Pascual *et al*[23] noted that people who were exposed to a traumatic event after achieving symptomatic recovery were more likely to experience an affective relapse.

Associations between the clinical presentation of bipolar disorder and specific types of childhood trauma have also been reported. For instance, Etain *et al*[24] implicated emotional and sexual abuse as independent moderators of an earlier age at of onset as well as individuals' history of suicide attempts. Maniglio[25] additionally summarised that sexual abuse experienced in childhood was related to comorbid substance use disorders and the incidence of psychotic symptoms. Due to the high prevalence of childhood trauma and its clear clinical relevance, research has recently begun to focus on childhood trauma as a potential moderator of treatment outcomes for both pharmacological and psychological interventions in bipolar disorder.[22 26]

Cakir *et al*[27] reported that experiences of emotional or physical abuse during childhood were significantly related to inadequate response to long-term treatment with anticonvulsants among outpatients with bipolar disorder. Etain *et al*[28] indicated a similar association between a history of childhood physical abuse and response to lithium treatment in euthymic patients with bipolar disorder. That is, greater exposure to physical abuse was inversely correlated with participants' levels of response to lithium. In addition to the correlation with physical abuse, the researchers demonstrated that participants who were exposed to multiple types of childhood trauma were more likely to inadequately respond to lithium than participants without a history of any childhood trauma.

Recent data collected from a randomised controlled trial (RCT) conducted to test the effectiveness of adjunctive infliximab for the treatment of adult outpatients with bipolar disorder contradicted prior research.[29] McIntyre *et al*[29] found that participants with a history of physical abuse showed a greater reduction in depression severity and, hence, a better treatment response than participants without a history of physical abuse. Potentially explaining McIntyre *et al*'s[29] findings, childhood trauma has repeatedly been linked to increased and persistent inflammation in bipolar disorder.[30 31] Therefore, an anti-inflammatory agent might target the underlying pathophysiological mechanisms, facilitating positive treatment effects.

While pharmacotherapy underpins the successful treatment of major psychiatric disorders, there is consensus that the optimal management of bipolar disorder relies on the integration of pharmacological and psychological interventions.[32 33] Conus *et al*[34] retrospectively audited the files of 118 patients with bipolar disorder who were provided a comprehensive treatment programme targeted at early intervention. The researchers reported that patients who experienced sexual and/or physical abuse in childhood and adolescence were more likely to disengage from treatment; notably, however, there was no association between a history of childhood trauma and either symptomatic or functional remission at end of treatment.

As such, evidence supporting the differential treatment outcomes among people with bipolar disorder who were exposed to significant traumatic experiences in childhood remains contentious. Several potentially relevant mediators of this association have been suggested including treatment nonadherence,[35–38] difficulties with forming a therapeutic alliance,[26 35 39] insecure attachment styles[26 40 41] and early maladaptive schemas[42–44], though these factors have not yet been extensively investigated among survivors of childhood trauma who have a diagnosis of bipolar disorder.

Additionally, a wide range of treatment outcomes have been considered in clinical research on bipolar disorder. Although researchers have traditionally focused on outcomes related to symptomatic and functional recovery, patients' personal recovery has increasingly received attention.[45] Personal recovery is frequently conceptualised as the process an individual undergoes to psychologically adapt to their disorder; a definition that expands patients' recovery beyond the reduction of psychiatric symptoms and impairments in functioning.[45 46] The evaluation of treatment outcomes that capture the experiences of the individual more broadly is encouraged as some patients continue to report significant impairments in functioning and QoL even though they only have

relatively mild symptoms.[45] Hence, symptom measures alone appear to be inadequate in assessing treatment effectiveness in bipolar disorder.

To date, there have been no systematic reviews focusing on the influence of childhood trauma on the treatment outcomes of pharmacological, psychological and combined interventions for adolescents and adults with bipolar disorder. This is despite current research demonstrating that experiences of childhood trauma may be highly relevant to the efficacy of treatments for bipolar disorder.[47–49] Research that aims to improve the prediction of treatment outcomes can greatly benefit patients with psychiatric disorders as this knowledge may reduce the burden associated with receiving inappropriate and/or suboptimal treatments and decrease patients' risk of experiencing a chronic illness course.[50]

Exploring the influence of exposure to childhood trauma on patients' treatment outcomes may, thus, assist the development of individualised interventions for people with bipolar disorder, promoting treatment success and ultimately facilitating recovery.[26 47] Clarification on the role that childhood trauma plays in the treatment of bipolar disorder has clear translational value with the potential to inform clinical guidelines and practice. A systematic exploration of the available evidence is particularly suitable for this endeavour because it allows for data to be collated from a variety of sources and illustrate areas of research that are underscored by a limited number of patients and/or conflicting evidence.

OBJECTIVES

The aim of this systematic review is to investigate whether a history of childhood trauma affects the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder. Treatment outcomes detailing participants' symptomatic severity as well as functional and personal recovery will be explored. If sufficient data are available, it will be examined whether there are differential effects of (1) treatment type, (2) clinical features and (3) demographic factors in the context of childhood trauma.

METHODS AND ANALYSIS

Eligibility criteria

Relevant studies will be identified according to the following criteria:

Types of participants

Studies including adolescents and/or adults (≥10 years)[51] with a diagnosis of bipolar disorder will be eligible for the review. Diagnoses of bipolar I disorder, bipolar II disorder, cyclothymic disorder and bipolar disorder not elsewhere classified or not otherwise specified as set out by standardised diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) will be included. These inclusive eligibility criteria will permit a thorough assessment of the extant literature and support generalisability.

To be considered, studies must have confirmed participants' diagnosis of bipolar disorder either through a structured or semistructured diagnostic interview such as the Structured Clinical Interview for DSM,[52] the MINI International Neuropsychiatric Interview[53] and the Child and Adolescent Psychiatric Assessment[54] or through psychiatrist judgement, including in chart review. No restrictions will be placed on the setting of the studies; both in-patient and out-patient samples will be eligible.

Studies also including children (≤10 years) will only be eligible if the mean age of the sample is ≥10 years or the data for adolescent and adult participants are separately available. Additionally, studies that were conducted in heterogeneous clinical populations will only be included if more than 80% of the sample had bipolar disorder or the data for participants with bipolar disorder are separately available. However, studies that were conducted in populations exclusively consisting of individuals who were exposed to childhood trauma will be excluded.

Types of studies

To allow for a comprehensive evaluation of the available evidence,[55] broad design criteria will be implemented. Both randomised and nonrandomised studies of pharmacological and/or psychological interventions for bipolar disorder that included an assessment of childhood trauma will be eligible. RCTs, cluster RCTs, cross-over trials, controlled (nonrandomised) trials, one-arm trials, interrupted time series studies, controlled before–after studies, uncontrolled before–after studies, cohort studies, case–control and cross–sectional studies with quantitative data will be included. Case series, case reports and purely qualitative studies will be excluded.

Types of exposure measures

For the purpose of this review, childhood trauma is defined in the form of maltreatment and includes physical abuse, sexual abuse, emotional abuse, physical neglect and emotional neglect experienced during childhood and early adolescence (≤18 years). Participants' history of childhood trauma may be assessed with validated measures such as the Childhood Trauma Questionnaire[56] or indicated through clinician interviews. Studies that assessed childhood trauma via chart review will also be eligible. Additionally, studies that considered both childhood trauma and adulthood trauma will be included if the data for childhood trauma are separately available. Studies that exclusively assessed trauma experienced in adulthood (≥18 years) will be excluded from the review.

Types of interventions

Included in the review will be any pharmacological and/or psychological interventions administered for the management of bipolar disorder. Pharmacological interventions include, but are not limited to, mood stabilisers,

antidepressants, antipsychotics and antiepileptics. Psychological interventions refer, for instance, to psychoeducation, cognitive behavioural therapy, interpersonal and social rhythm therapy and family-focused therapy. Combined treatment approaches (eg, pharmacological and adjunctive psychological interventions) will also be considered. Studies that exclusively investigated lifestyle interventions, however, will be excluded from this review.

Types of outcome measures

Primary outcome—mean reduction in symptom severity

The primary outcome will be mean reduction in symptom severity as defined by change scores from baseline to end of treatment on: (a) the Young Mania Rating Scale (YMRS)[57] indicating mean reduction in mania severity and (b) the Montgomery-Åsberg Depression Rating Scale (MADRS)[58] indicating mean reduction in depression severity. Other validated scales assessing manic or depressive symptoms will also be considered.

Secondary outcomes—related to symptomatic recovery

1. Treatment response as defined by either:
   - a reduction of 50% (or greater) on the YMRS, the MADRS or any other validated scale assessing manic or depressive symptoms or
   - a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression—Improvement[59 60] scale or
   - other criteria specifying treatment response as defined by the study authors.
2. Symptomatic remission as defined by either:
   - a score of ≤12 on the YMRS[61–63] or
   - a score of ≤10 on the MADRS[64 65] or
   - a score of 1 (normal, not at all ill) or 2 (borderline mentally ill) on the Clinical Global Impression—Severity[59 60] scale or
   - other criteria specifying remission as defined by the study authors.
3. Relapse/recurrence defined as a new affective episode according to the DSM or ICD criteria and/or by[66–70]:
   - a score of ≥12 on the YMRS indicating a hypomanic recurrence;
   - a score of ≥20 on the YMRS indicating a manic recurrence;
   - a score of ≥22 on the MADRS indicating a depressive recurrence;
   - a score of ≥20 on the YMRS and a score of ≥22 on the MADRS indicating a mixed recurrence or
   - other criteria specifying relapse/recurrence as defined by the study authors.

Secondary outcomes—related to functional and personal recovery

1. Improvement in global functioning as defined by change scores from baseline to end of treatment on the Global Assessment of Functioning[71] scale or any other validated scale assessing functioning.
2. Improvement in QoL as defined by change scores from baseline to end of treatment on the Quality of Life in Bipolar Disorder—Brief[72] scale or any other validated scale assessing QoL.

Types of publications

This review will be restricted to studies reported in English and published in peer-reviewed journals.

Information sources and search strategy

MEDLINE Complete via Ebsco, Embase via embase.com, PsycINFO via Ebsco and the Cochrane Central Register of Controlled Trials via cochranelibrary.com will be searched from database inception to December 2020 to identify relevant studies. The specific search strategies were developed using standardised subject terms (eg, medical subject headings (MeSH) terms, Emtree terms) and keywords related to bipolar disorder, childhood trauma and pharmacological or psychological interventions. The Population, Intervention, Comparison, Outcome framework was used to develop the search terms. The standardised subject terms were tailored to each individual database and truncation and wildcards were applied as appropriate. Drafts of the search strategies for each database are reported in online supplemental file 1.

The studies identified in the database searches will be checked against the eligibility criteria outlined above. First, the titles and abstracts will be independently screened by two reviewers. Subsequently, two reviewers will retrieve and assess the full texts of studies that appear eligible for the review. Reasons for the exclusion of studies will be recorded. Discrepancies between the reviewers will be discussed and assessed by a third author, if necessary. The original study authors will be contacted for additional information if outcomes of interest are not reported. Finally, the database searches will be supplemented by reviewing the reference lists of all included publications for additional studies. Prior to the final data analysis, the searches will be rerun to allow for the inclusion of newly published studies.

Data management and extraction

The online reference management database Covidence[73] will be used to manage the records during the review process. Covidence allows for publication screening, handling of duplicate records, evaluation of risk of bias and extraction of study characteristics and outcomes according to the eligibility criteria. The following data will be independently extracted by two reviewers:

1. Study characteristics (eg, study author, year of publication).
2. Study design (eg, randomised, nonrandomised).
3. Sample characteristics (eg, N, country/ies, setting).
4. Participant characteristics (eg, mean age, % women, diagnoses).
5. Diagnostic assessment (eg, assessment tool).
6. Clinical features (eg, age at onset, % rapid cycling, number of episodes, number of suicide attempts).
7. Childhood trauma assessment (eg, definition, assessment tool).

8. Exposure details (eg, n exposed, trauma types, time of exposure).
9. Treatment characteristics (eg, type, dose, duration, number of sessions).
10. Outcome assessment (eg, definition, assessment tool).
11. Results (eg, reported inferential statistics, confidence intervals (CIs), effect sizes).

Assessment of methodological quality

For randomised trials, the Cochrane Collaboration's Risk of Bias tool[74 75] will be used. Specifically, the included studies will be evaluated according to the following sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Based on the available information, studies will be rated as low risk or high risk. If insufficient information is provided to evaluate risk of bias of a study, it will be rated as unclear and the study author will be contacted for further details.

For nonrandomised studies of interventions, the Newcastle-Ottawa Scale (NOS)[76] will be used. When using the NOS, studies are rated depending on sample selection, comparability of groups and assessment of exposure or outcome. Where needed, the quality assessment with the NOS will be supplemented by using the critical appraisal tools developed by the Joanna Briggs Institute.[77] The quality assessments (both for randomised and nonrandomised studies) will be completed by two independent reviewers.

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE)[78] approach will be used to assess the quality of evidence for each of the outcomes. In the GRADE approach, the quality of evidence is rated across all identified studies resulting in one of four grades: high, moderate, low and very low (table 1). As a rule of thumb, evidence from randomised trials is of high quality whereas evidence from nonrandomised studies of interventions is of low quality.[78] However, the quality of evidence can be rated down due to risk of bias, inconsistency of results, indirectness of evidence, imprecision or publication bias.[78] The quality of evidence can be rated up if studies report a large magnitude of effect or a clear dose–response gradient or in situations where all residual confoundings would decrease the indicated effect.[78]

Data synthesis and statistical analysis

For each of the outcomes included in the review, the results will be synthesised using tabulation and visual displays via forest plots, as appropriate. Randomised trials and nonrandomised studies of interventions will be separately presented and grouped according to treatment type (pharmacological, psychological, combination). A narrative evaluation of these results will additionally be provided. The following will be calculated if sufficient data are available:

For categorical outcome variables, risk ratios or odds ratios with 95% CIs will be calculated. For continuous outcome variables, mean differences or standardised mean differences with 95% CIs will be calculated. Mean differences will be used when the studies included in the review measured treatment outcomes with the same scale. Standardised mean differences will be used when the studies included in the review measured treatment outcomes with different scales.

Heterogeneity of evidence will be determined with Higgins I^2 statistics calculations. If substantial heterogeneity between the studies is indicated ($I^2 \geq 50\%$),[74 79] possible reasons for the variability will be considered by analysing the characteristics of the studies included. If meta-analyses are deemed sensible based on the heterogeneity analysis, a random effects model will be used. All statistical analyses will be conducted with the software Comprehensive Meta-Analysis.[80]

As per guidelines from the Cochrane Handbook for Systematic Reviews of Interventions V.6.0,[74] randomised trials and nonrandomised studies of interventions will not be combined in one meta-analysis. Instead, randomised trials and nonrandomised studies will be separately analysed. Additionally, nonrandomised studies of interventions that were judged to have a high risk of bias will be excluded from the meta-analysis.[74] For any meta-analysis with ≥10 studies, funnel plot asymmetry will be evaluated and possible explanations for

Table 1 Quality of evidence grades as stipulated in the GRADE handbook[78]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE, Grading of Recommendation, Assessment, Development and Evaluation.

the asymmetry will be considered (eg, publication bias), if applicable.[74]

Subgroup analyses

Where substantial heterogeneity is indicated ($I^2 \geq 50\%$) and sufficient data are available, subgroup and meta-regression analyses will be performed to explore potential effect modifiers. Individual subgroup analyses will be conducted for the following categorical variables: trauma type (physical, sexual, emotional); treatment type (pharmacological, psychological, combination) and demographic features (age group (adolescent, adult sample)). Meta-regression analyses will be conducted for continuous variables describing participants' clinical (age at onset (mean years), rapid cycling (% rapid cycling), number of episodes, number of suicide attempts) and demographic features (age (mean years), gender (% women)). Other subgroups may be identified where necessary. Sensitivity analyses will be completed to determine the robustness of the meta-analyses.

Presentation and reporting of results

This systematic review will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[81] In accordance with the PRISMA guidelines, the study selection process will be detailed in a flowchart, including number of studies excluded at each stage of the review and reasons for exclusion. The PRISMA-Protocols checklist is reported in online supplemental file 2.

ETHICS AND DISSEMINATION

Only previously published data will be used in this systematic review; hence, ethical approval is not required. This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 31 August 2020. The findings will be published in peer-reviewed journals and presented at relevant conferences. Multiple publications may be derived from this protocol.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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