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The influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder: protocol for a systematic review and meta-analysis

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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 amongst 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 (CENTRAL) will be searched to identify randomised and non-randomised 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 (PRISMA) guidelines, published in peer-reviewed journals, and presented at relevant conferences.

PROSPERO registration number: CRD42020201891

Keywords: bipolar disorder, childhood trauma, treatment outcomes, pharmacotherapy, psychotherapy, systematic review, meta-analysis

ARTICLE SUMMARY

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 PRISMA 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 liberal 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 2] Bipolar disorder may significantly impair social and occupational functioning[3 4] as well as the quality of life (QoL)[1 5-7] 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[8] with approximately 70% experiencing an affective relapse within four years.[9-12] These findings highlight the clinical importance of recognising environmental risk factors that contribute to the outcomes in bipolar disorder.[13 14]

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.[15-17] As an example, Sala et al.[18] 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.[13 15 16 19]

In a recent meta-analysis, Agnew-Blais and Danese[20] 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[20] further highlighted that childhood trauma was related to the experience of more severe manic, depressive, and psychotic symptoms among patients with bipolar disorder.

Associations between the clinical presentation of bipolar disorder and specific types of childhood trauma have also been reported. For instance, Etain et al.[21] implicated emotional and sexual abuse as independent moderators of an earlier age at of onset as well as individuals' history of suicide attempts. Maniglio[22] additionally summarised that sexual abuse experienced in childhood was related to comorbid substance use disorders and the incidence of psychotic symptoms. Despite the high prevalence of childhood trauma and its clear clinical relevance, research has only recently begun to focus on childhood trauma as a potential moderator of treatment outcomes for both pharmacological and psychological interventions in bipolar disorder.[20 23]

Cakir et al.[24] 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.[25] indicated a similar association between a history of childhood physical abuse and response to lithium treatment in euthymic bipolar disorder patients. 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 conducted to test the effectiveness of adjunctive infliximab for the treatment of adult outpatients with bipolar disorder, contradicted prior research.[26] McIntyre et al.[26] 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[26] findings, childhood trauma has repeatedly been linked to increased and persistent inflammation in bipolar disorder.[27 28] 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.[29 30] Conus et al.[31] retrospectively audited the files of 118 patients with bipolar disorder who were provided a comprehensive treatment program 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 non-adherence,[32-35] difficulties with forming a therapeutic alliance,[23 32 36] insecure attachment styles,[23 37 38] and early maladaptive schemas (EMS);[39-41] 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 recovery, patients' functional and personal recovery has increasingly received attention.[42] 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.[42] Hence, symptom measures alone appear to be inadequate in assessing treatment effectiveness in bipolar disorder.

To date, there has 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 highlighting that experiences of childhood trauma may be highly relevant to the efficacy of treatments for bipolar disorder.[43-45] Therefore, exploring exposure to childhood trauma as a moderator of treatment outcomes may assist the development of individualised and targeted interventions for people with bipolar disorder, ultimately facilitating treatment success.[23 43]

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. If sufficient data are available, it will be explored whether there are differential effects of (1) treatment type (pharmacological, psychological, combination), (2) disorder-related features (age at onset, number of episodes), and (3) demographic factors (age, gender) 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)[46] 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.

To be considered, studies must have confirmed participants' diagnosis of bipolar disorder either through a structured or semi-structured diagnostic interview such as the Structured Clinical Interview for DSM (SCID),[47] the MINI International Neuropsychiatric Interview (M.I.N.I.),[48] and the Child and Adolescent Psychiatric Assessment (CAPA)[49] 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,[50] liberal design criteria will be implemented. Both randomised and non-randomised studies of pharmacological and/or psychological interventions for bipolar disorder which included an assessment of childhood trauma will be eligible. Randomised controlled trials (RCTs), cluster RCTs, cross-over trials, controlled (non-randomised) trials, one-arm trials, interrupted time series (ITS) studies, controlled before-after (CBA) 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 early life (≤ 18 years). Participants' history of childhood trauma

may be assessed with validated measures such as the Childhood Trauma Questionnaire (CTQ)[51] or indicated through clinician interviews. Studies that assessed childhood trauma via in 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 (CBT), interpersonal and social rhythm therapy (IPSRT), and family-focused therapy (FFT). Combined treatment approaches (e.g., pharmacological and adjunctive psychological interventions) will also be considered.

Types of outcome measures

Primary outcome – mean reduction in symptom severity in both phases of the disorder

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)[52] indicating mean reduction in mania severity; and (b) the Montgomery-Åsberg Depression Rating Scale (MADRS)[53] 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. a reduction of 50% (or greater) on the YMRS, the MADRS, or any other validated scale assessing manic or depressive symptoms; or

b. a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression – Improvement (CGI-I)[54 55] scale; or

c. other criteria specifying treatment response as defined by the study authors.

2. Symptomatic remission as defined by either:

a. a score of ≤ 12 on the YMRS;[56-58] or

b. a score of ≤ 10 on the MADRS;[59 60] or

c. a score of 1 (normal, not at all ill) or 2 (borderline mentally ill) on the Clinical Global Impression – Severity (CGI-S)[54 55] scale; or

d. 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:[61-65]

a. a score of ≥ 12 on the YMRS indicating a hypomanic recurrence;

b. a score of ≥ 20 on the YMRS indicating a manic recurrence;

c. a score of ≥ 22 on the MADRS indicating a depressive recurrence;

d. a score of ≥ 20 on the YMRS and a score of ≥ 22 on the MADRS indicating a mixed recurrence; or

e. 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 (GAF)[66] 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 (QoL.BD-Brief)[67] 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 (CENTRAL) 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 (e.g., medical subject headings [MeSH] terms, Emtree terms) and keywords related to bipolar disorder, childhood trauma, and pharmacological or psychological interventions. The PICO (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 supplementary 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 re-run to allow for the inclusion of newly published studies.

Data management and extraction

The online reference management database Covidence[68] 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 (e.g., study author, year of publication)
2. Study design (e.g., randomised, non-randomised)
3. Sample characteristics (e.g., N, country/ies, setting)
4. Participant characteristics (e.g., age range, % gender, diagnoses)
5. Disorder-related features (e.g., age at onset, number of episodes)
6. Treatment characteristics (e.g., type, dose, duration, number of sessions)
7. Diagnostic assessment (e.g., assessment tool)
8. Childhood trauma assessment (e.g., definition, assessment tool)
9. Outcome assessment (e.g., definition, assessment tool)
10. Results (e.g., reported inferential statistics, confidence intervals, effect sizes)

Assessment of methodological quality

For randomised trials, the Cochrane Collaboration's Risk of Bias tool[69 70] 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 non-randomised studies of interventions, the Newcastle-Ottawa Scale (NOS)[71] will be used. When using the NOS, studies can be awarded a maximum of nine stars 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 (JBI).[72] The quality assessments

(both for randomised and non-randomised studies) will be completed by two independent reviewers.

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE)[73] 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, very low (table 1). As a rule of thumb, evidence from randomised trials is of high quality whereas evidence from non-randomised studies of interventions is of low quality. However, the quality of evidence can be rated down due to risk of bias, inconsistency of results, indirectness of evidence, imprecision, or publication bias. 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 confounding would decrease the indicated effect.

Table 1 Quality of Evidence Grades as stipulated in the GRADE handbook[73]

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.

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 non-randomised studies of interventions will be separately presented and grouped according to

treatment type (pharmacological, psychological, combination). The following will be calculated if sufficient data are available:

For categorical outcomes, risk ratios (RR) or odds ratios (OR) with 95% confidence intervals will be calculated. For continuous outcomes, mean differences or standardised mean differences with 95% confidence intervals will be calculated. Mean differences will be utilised when the studies included in the review measured treatment outcomes with the same scale. Standardised mean differences will be utilised 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 ($I^2 \geq 50\%$),[69 74] 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, conducted with the software Comprehensive Meta-Analysis (CMA).[75]

As per guidelines from the Cochrane Handbook for Systematic Reviews of Interventions 6.0,[69] randomised trials and non-randomised studies of interventions will not be combined in one meta-analysis. Instead, randomised trials and non-randomised studies will be separately analysed. Additionally, non-randomised studies of interventions that were judged to have a high risk of bias will be excluded from the meta-analysis.[69] For any meta-analyses with ≥ 10 studies, funnel plot asymmetry will be evaluated and possible explanations for the asymmetry considered (e.g., publication bias), if applicable.[69]

Subgroup analysis

Where substantial heterogeneity is indicated ($I^2 \geq 50\%$) and sufficient data are available, subgroup analyses will be performed by treatment type (pharmacological, psychological, combination), disorder-related features (age at onset, number of episodes), and demographic

factors (age, gender). Sensitivity analyses will be conducted 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.[76] 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 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist can be found in online supplementary 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 the 31st of August 2020 (CRD42020201891). 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.

CONCLUSION

This will be the first review to involve a systematic exploration of the available evidence reporting the influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder. The

findings will clarify the role that childhood trauma plays in the treatment of bipolar disorder and will consequently have the potential to inform clinical guidelines and practice.

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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. **AT** has received travel/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.

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Supplementary Table 1 The search strategy for MEDLINE Complete

Number	Search Terms
S44	S12 AND S26 AND S42 (only English publications)
S43	S12 AND S26 AND S42
S42	S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41
S41	TI psychoeducation or AB psychoeducation
S40	TI antipsychotic* or AB antipsychotic*
S39	TI antidepressant* or AB antidepressant*
S38	TI "mood stabilizers" or AB "mood stabilizers"
S37	TI "mood stabilisers" or AB "mood stabilisers"
S36	TI intervention* or AB intervention*
S35	TI therap* or AB therap*
S34	TI treatment* or AB treatment*
S33	(MH "treatment outcome")
S32	(MH "lithium")
S31	(MH "tranquilizing agents+")
S30	(MH "antidepressive agents+")
S29	(MH "drug therapy")
S28	(MH "cognitive behavioral therapy+")
S27	(MH "psychotherapy+")
S26	S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S25	TI psychological trauma or AB psychological trauma
S24	TI (early AND trauma*) or AB (early AND trauma*)
S23	TI (adverse AND child* AND experience*) or AB (adverse AND child* AND experience*)
S22	TI (child* AND neglect) or AB (child* AND neglect)
S21	TI (child* AND abuse) or AB (child* AND abuse)
S20	TI (child* AND maltreatment) or AB (child* AND maltreatment)
S19	TI (child* AND trauma) or AB (child* AND trauma)
S18	(MH "domestic violence")
S17	(MH "psychological trauma+")
S16	(MH "battered child syndrome")
S15	(MH "child abuse+")
S14	(MH "adverse childhood experiences")
S13	(MH "adult survivors of child adverse events+")
S12	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S11	TI BPAD OR AB BPAD
S10	TI BPD OR AB BPD
S9	TI BD OR AB BD
S8	TI hypomanic OR AB hypomanic
S7	TI hypomania OR AB hypomania
S6	TI manic OR AB manic
S5	TI mania OR AB mania
S4	TI cyclothymi* OR AB cyclothymi*
S3	TI bipolar OR AB bipolar

S2	(MH "cyclothymic disorder")
S1	(MH "bipolar and related disorders+")

Supplementary Table 2 The search strategy for Embase

Number	Search Terms
S47	#46 AND 'article'/it AND [english]/lim
S46	#12 AND #28 AND #45
S45	#29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44
S44	psychoeducation:ti,ab
S43	antipsychotic*:ti,ab
S42	antidepressant*:ti,ab
S41	'mood stabilizers':ti,ab
S40	'mood stabilisers':ti,ab
S39	intervention*:ti,ab
S38	therap*:ti,ab
S37	treatment*:ti,ab
S36	'treatment outcome'/de
S35	'lithium'/de
S34	'neuroleptic agent'/exp
S33	'antidepressant agent'/exp
S32	'drug therapy'/de
S31	'cognitive behavioral therapy'/exp
S30	'psychotherapy'/exp
S29	'intervention study'/de
S28	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
S27	psychological NEAR/5 trauma:ti,ab
S26	(early AND trauma*):ti,ab
S25	(adverse AND child* AND experience*):ti,ab
S24	(child* AND neglect):ti,ab
S23	(child* AND abuse):ti,ab
S22	(child* AND maltreatment):ti,ab
S21	(child* AND trauma):ti,ab
S20	'domestic violence'/de
S19	'psychotrauma'/exp
S18	'battered child syndrome'/de
S17	'child abuse survivor'/exp
S16	'child abuse'/exp
S15	'childhood trauma survivor'/de
S14	'childhood trauma'/de
S13	'childhood adversity'/de
S12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
S11	BPAD:ti,ab
S10	BPD:ti,ab
S9	BD:ti,ab
S8	hypomanic:ti,ab
S7	hypomania:ti,ab
S6	manic:ti,ab
S5	mania:ti,ab

S4	cyclothymi*:ti,ab
S3	bipolar:ti,ab
S2	'mania'/exp
S1	'bipolar disorder'/exp

Supplementary Table 3 The search strategy for PsycINFO

Number	Search Terms
S232	S15 AND S33 AND S230 (only English publications; academic journals)
S231	S15 AND S33 AND S230
S230	S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89 or S90 or S91 or S92 or S93 or S94 or S95 or S96 or S97 or S98 or S99 or S100 or S101 or S102 or S103 or S104 or S105 or S106 or S107 or S108 or S109 or S110 or S111 or S112 or S113 or S114 or S115 or S116 or S117 or S118 or S119 or S120 or S121 or S122 or S123 or S124 or S125 or S126 or S127 or S128 or S129 or S130 or S131 or S132 or S133 or S134 or S135 or S136 or S137 or S138 or S139 or S140 or S141 or S142 or S143 or S144 or S145 or S146 or S147 or S148 or S149 or S150 or S151 or S152 or S153 or S154 or S155 or S156 or S157 or S158 or S159 or S160 or S161 or S162 or S163 or S164 or S165 or S166 or S167 or S168 or S169 or S170 or S171 or S172 or S173 or S174 or S175 or S176 or S177 or S178 or S179 or S180 or S181 or S182 or S183 or S184 or S185 or S186 or S187 or S188 or S189 or S190 or S191 or S192 or S193 or S194 or S195 or S196 or S197 or S198 or S199 or S200 or S201 or S202 or S203 or S204 or S205 or S206 or S207 or S208 or S209 or S210 or S211 or S212 or S213 or S14 or S215 or S216 or S217 or S218 or S219 or S220 or S221 or S222 or S223 or S224 or S225 or S226 or S227 or S228 or S229
S229	TI psychoeducation or AB psychoeducation
S228	TI antipsychotic* or AB antipsychotic*
S227	TI antidepressant* or AB antidepressant*
S226	TI "mood stabilizers" or AB "mood stabilizers"
S225	TI "mood stabilisers" or AB "mood stabilisers"
S224	TI intervention* or AB intervention*
S223	TI therap* or AB therap*
S222	TI treatment* or AB treatment*
S221	DE "Lithium"
S220	DE "Tetrabenazine"
S219	DE "Sulpiride"
S218	DE "Spiroperidol"
S217	DE "Risperidone"
S216	DE "Reserpine"
S215	DE "Quetiapine"
S214	DE "Olanzapine"
S213	DE "Nialamide"
S212	DE "Molindone"
S211	DE "Clozapine"
S210	DE "Aripiprazole"
S209	DE "Thiothixene"
S208	DE "Pimozide"
S207	DE "Phenothiazine Derivatives"

S206	DE "Neuroleptic Drugs"
S205	DE "Minor Tranquilizers"
S204	DE "Meprobamate"
S203	DE "Haloperidol"
S202	DE "Doxepin"
S201	DE "Benactyzine"
S200	DE "Amitriptyline"
S199	DE "Tranquilizing Drugs"
S198	DE "Zimeldine"
S197	DE "Venlafaxine"
S196	DE "Tricyclic Antidepressant Drugs"
S195	DE "Trazodone"
S194	DE "Tranylcypromine"
S193	DE "Sulpiride"
S192	DE "Sertraline"
S191	DE "Serotonin Norepinephrine Reuptake Inhibitors"
S190	DE "Pipradrol"
S189	DE "Pheniprazine"
S188	DE "Phenelzine"
S187	DE "Paroxetine"
S186	DE "Nomifensine"
S185	DE "Nialamide"
S184	DE "Nefazodone"
S183	DE "Molindone"
S182	DE "Moclobemide"
S181	DE "Mianserin"
S180	DE "Methylphenidate"
S179	DE "Lithium Carbonate"
S178	DE "Isocarboxazid"
S177	DE "Iproniazid"
S176	DE "Fluvoxamine"
S175	DE "Fluoxetine"
S174	DE "Citalopram"
S173	DE "Bupropion"
S172	DE "Antidepressant Drugs"
S171	DE "Drug Therapy"
S170	DE "Virtual Reality Exposure Therapy"
S169	DE "Prolonged Exposure Therapy"
S168	DE "In Vivo Exposure"
S167	DE "Implosive Therapy"
S166	DE "Imaginal Exposure"
S165	DE "Systematic Desensitization Therapy"
S164	DE "Response Cost"
S163	DE "Reciprocal Inhibition Therapy"
S162	DE "Implosive Therapy"
S161	DE "Exposure Therapy"
S160	DE "Dialectical Behavior Therapy"

S159	DE "Conversion Therapy"
S158	DE "Aversion Therapy"
S157	DE "Behavior Therapy"
S156	DE "Prolonged Exposure Therapy"
S155	DE "Cognitive Processing Therapy"
S154	DE "Acceptance and Commitment Therapy"
S153	DE "Workplace Intervention"
S152	DE "School Based Intervention"
S151	DE "Group Intervention"
S150	DE "Family Intervention"
S149	DE "Early Intervention"
S148	DE "Crisis Intervention"
S147	DE "Intervention"
S146	DE "Video-Based Interventions"
S145	DE "Treatment Planning"
S144	DE "Treatment Outcomes"
S143	DE "Treatment Guidelines"
S142	DE "Trauma Treatment"
S141	DE "Trauma-Informed Care"
S140	DE "Therapeutic Processes"
S139	DE "Symptoms Based Treatment"
S138	DE "Spiritual Care"
S137	DE "Speech Therapy"
S136	DE "Sociotherapy"
S135	DE "Social Casework"
S134	DE "Sex Therapy"
S133	DE "Self-Help Techniques"
S132	DE "Respite Care"
S131	DE "Pain Management"
S130	DE "Relaxation Therapy"
S129	DE "Rehabilitation"
S128	DE "Psychoeducation"
S127	DE "Private Practice"
S126	DE "Physical Treatment Methods"
S125	DE "Personal Therapy"
S124	DE "Partial Hospitalization"
S123	DE "Outpatient Treatment"
S122	DE "Multisystemic Therapy"
S121	DE "Multimodal Treatment Approach"
S120	DE "Movement Therapy"
S119	DE "Mindfulness-Based Interventions"
S118	DE "Mind Body Therapy"
S117	DE "Milieu Therapy"
S116	DE "Mental Health Programs"
S115	DE "Medical Treatment (General)"
S114	DE "Maintenance Therapy"
S113	DE "Life Sustaining Treatment"

S112	DE "Language Therapy"
S111	DE "Involuntary Treatment"
S110	DE "Intervention"
S109	DE "Interdisciplinary Treatment Approach"
S108	DE "Integrated Services"
S107	DE "Institutionalization"
S106	DE "Hydrotherapy"
S105	DE "Human Services"
S104	DE "Human Potential Movement"
S103	DE "Hospice"
S102	DE "Horticulture Therapy"
S101	DE "Health Care Services"
S100	DE "Habilitation"
S99	DE "Disease Management"
S98	DE "Cross Cultural Treatment"
S97	DE "Creative Arts Therapy"
S96	DE "Counseling"
S95	DE "Computer Assisted Therapy"
S94	DE "Cognitive Techniques"
S93	DE "Cognitive Stimulation Therapy"
S92	DE "Cognitive Behavior Therapy"
S91	DE "Client Treatment Matching"
S90	DE "Client Transfer"
S89	DE "Caregiving"
S88	DE "Bibliotherapy"
S87	DE "Behavior Modification"
S86	DE "Anxiety Management"
S85	DE "Alternative Medicine"
S84	DE "Aftercare"
S83	DE "Adventure Therapy"
S82	DE "Adjunctive Treatment"
S81	DE "Addiction Treatment"
S80	DE "Treatment"
S79	DE "Transactional Analysis"
S78	DE "Supportive Psychotherapy"
S77	DE "Strategic Therapy"
S76	DE "Solution Focused Therapy"
S75	DE "Relationship Therapy"
S74	DE "Reality Therapy"
S73	DE "Rational Emotive Behavior Therapy"
S72	DE "Psychotherapeutic Techniques"
S71	DE "Psychotherapeutic Counseling"
S70	DE "Psychodynamic Psychotherapy"
S69	DE "Psychodrama"
S68	DE "Psychoanalysis"
S67	DE "Primal Therapy"
S66	DE "Persuasion Therapy"

S65	DE "Network Therapy"
S64	DE "Narrative Therapy"
S63	DE "Logotherapy"
S62	DE "Interpersonal Psychotherapy"
S61	DE "Integrative Psychotherapy"
S60	DE "Insight Therapy"
S59	DE "Individual Psychotherapy"
S58	DE "Hypnotherapy"
S57	DE "Humanistic Psychotherapy"
S56	DE "Guided Imagery"
S55	DE "Group Psychotherapy"
S54	DE "Gestalt Therapy"
S53	DE "Geriatric Psychotherapy"
S52	DE "Feminist Therapy"
S51	DE "Eye Movement Desensitization Therapy"
S50	DE "Expressive Psychotherapy"
S49	DE "Experiential Psychotherapy"
S48	DE "Existential Therapy"
S47	DE "Emotion Focused Therapy"
S46	DE "Eclectic Psychotherapy"
S45	DE "Couples Therapy"
S44	DE "Conversion Therapy"
S43	DE "Client Centered Therapy"
S42	DE "Child Psychotherapy"
S41	DE "Brief Relational Therapy"
S40	DE "Brief Psychotherapy"
S39	DE "Autogenic Training"
S38	DE "Analytical Psychotherapy"
S37	DE "Affirmative Therapy"
S36	DE "Adolescent Psychotherapy"
S35	DE "Adlerian Psychotherapy"
S34	DE "Psychotherapy"
S33	S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32
S32	TI psychological trauma or AB psychological trauma
S31	TI (early AND trauma*) or AB (early AND trauma*)
S30	TI (adverse AND child* AND experience*) or AB (adverse AND child* AND experience*)
S29	TI (child* AND neglect) or AB (child* AND neglect)
S28	TI (child* AND abuse) or AB (child* AND abuse)
S27	TI (child* AND maltreatment) or AB (child* AND maltreatment)
S26	TI (child* AND trauma) or AB (child* AND trauma)
S25	DE "Domestic Violence"
S24	DE "Emotional Trauma"
S23	DE "Battered Child Syndrome"
S22	DE "Verbal Abuse"
S21	DE "Sexual Abuse"

S20	DE "Physical Abuse"
S19	DE "Emotional Abuse"
S18	DE "Child Neglect"
S17	DE "Child Abuse"
S16	DE "Childhood Adversity"
S15	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14	TI BPAD OR AB BPAD
S13	TI BPD OR AB BPD
S12	TI BD OR AB BD
S11	TI hypomanic OR AB hypomanic
S10	TI hypomania OR AB hypomania
S9	TI manic OR AB manic
S8	TI mania OR AB mania
S7	TI cyclothymi* OR AB cyclothymi*
S6	TI bipolar OR AB bipolar
S5	DE "Mania"
S4	DE "Cyclothymic Disorder"
S3	DE "Bipolar II Disorder"
S2	DE "Bipolar I Disorder"
S1	DE "Bipolar Disorder"

Supplementary Table 4 The search strategy for CENTRAL

Number	Search Terms
S44	#12 AND #26 AND #42 (in Trials)
S43	#12 AND #26 AND #42
S42	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
S41	(psychoeducation):ti,ab
S40	(antipsychotic*):ti,ab
S39	(antidepressant*):ti,ab
S38	("mood stabilizers"):ti,ab
S37	("mood stabilisers"):ti,ab
S36	(intervention*):ti,ab
S35	(therap*):ti,ab
S34	(treatment*):ti,ab
S33	MeSH descriptor: [Treatment Outcome] this term only
S32	MeSH descriptor: [Lithium] this term only
S31	MeSH descriptor: [Tranquilizing Agents] explode all trees
S30	MeSH descriptor: [Antidepressive Agents] explode all trees
S29	MeSH descriptor: [Drug Therapy] this term only
S28	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees
S27	MeSH descriptor: [Psychotherapy] explode all trees
S26	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
S25	(psychological NEAR/5 trauma):ti,ab
S24	((early AND trauma*)):ti,ab
S23	((adverse AND child* AND experience*)):ti,ab
S22	((child* AND neglect)):ti,ab
S21	((child* AND abuse)):ti,ab
S20	((child* AND maltreatment)):ti,ab
S19	((child* AND trauma)):ti,ab
S18	MeSH descriptor: [Domestic Violence] this term only
S17	MeSH descriptor: [Psychological Trauma] explode all trees
S16	MeSH descriptor: [Battered Child Syndrome] this term only
S15	MeSH descriptor: [Child Abuse] explode all trees
S14	MeSH descriptor: [Adverse Childhood Experiences] this term only
S13	MeSH descriptor: [Adult Survivors of Child Adverse Events] explode all trees
S12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
S11	(BPAD):ti,ab
S10	(BPD):ti,ab
S9	(BD):ti,ab
S8	(hypomanic):ti,ab
S7	(hypomania):ti,ab
S6	(manic):ti,ab
S5	(mania):ti,ab
S4	(cyclothymi*):ti,ab
S3	(bipolar):ti,ab
S2	MeSH descriptor: [Cyclothymic Disorder] this term only

S1	MeSH descriptor: [Bipolar and Related Disorders] explode all trees

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 15
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp File 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13-14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	13-14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13-14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13-14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12-13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder: protocol for a systematic review and meta-analysis

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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 amongst 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 (CENTRAL) will be searched to identify randomised and non-randomised 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 (PRISMA) guidelines, published in peer-reviewed journals, and presented at relevant conferences.

PROSPERO registration number: CRD42020201891

Keywords: bipolar disorder, childhood trauma, treatment outcomes, pharmacotherapy, psychotherapy, systematic review, meta-analysis

ARTICLE SUMMARY

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 PRISMA 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 four 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 bipolar disorder patients. 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 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 program 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 non-adherence,[35-38] difficulties with forming a therapeutic alliance,[26 35 39] insecure attachment styles,[26 40 41] and early maladaptive schemas (EMS);[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 has 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 semi-structured diagnostic interview such as the Structured Clinical Interview for DSM (SCID),[52] the MINI International Neuropsychiatric Interview (M.I.N.I.),[53] and the Child and Adolescent Psychiatric Assessment (CAPA)[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 non-randomised studies of pharmacological and/or psychological interventions for bipolar disorder which included an assessment of childhood trauma will be eligible. Randomised controlled trials (RCTs), cluster RCTs, cross-over trials, controlled (non-randomised) trials, one-arm trials, interrupted time series (ITS) studies, controlled before-after (CBA) 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 (CTQ)[56] or indicated through clinician interviews. Studies that assessed childhood trauma via in 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 (CBT), interpersonal and social rhythm therapy (IPSRT), and family-focused therapy (FFT). Combined treatment approaches (e.g., 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. a reduction of 50% (or greater) on the YMRS, the MADRS, or any other validated scale assessing manic or depressive symptoms; or
   b. a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression – Improvement (CGI-I)[59 60] scale; or
   c. other criteria specifying treatment response as defined by the study authors.

2. Symptomatic remission as defined by either:
    a. a score of ≤ 12 on the YMRS;[61-63] or
    b. a score of ≤ 10 on the MADRS;[64 65] or
    c. a score of 1 (normal, not at all ill) or 2 (borderline mentally ill) on the Clinical Global Impression – Severity (CGI-S)[59 60] scale; or
    d. 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. a score of ≥ 12 on the YMRS indicating a hypomanic recurrence;
    b. a score of ≥ 20 on the YMRS indicating a manic recurrence;
    c. a score of ≥ 22 on the MADRS indicating a depressive recurrence;
    d. a score of ≥ 20 on the YMRS and a score of ≥ 22 on the MADRS indicating a mixed recurrence; or
    e. 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 (GAF)[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 (QoL.BD-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 (CENTRAL) 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 (e.g., medical subject headings [MeSH] terms, Emtree terms) and keywords related to bipolar disorder, childhood trauma, and pharmacological or psychological interventions. The PICO (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 supplementary 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 re-run 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 (e.g., study author, year of publication)

2. Study design (e.g., randomised, non-randomised)
3. Sample characteristics (e.g., N, country/ies, setting)
4. Participant characteristics (e.g., mean age, %female, diagnoses)
5. Diagnostic assessment (e.g., assessment tool)
6. Clinical features (e.g., age at onset, %rapid cycling, number of episodes, number of suicide attempts)
7. Childhood trauma assessment (e.g., definition, assessment tool)
8. Exposure details (e.g., n exposed, trauma types, time of exposure)
9. Treatment characteristics (e.g., type, dose, duration, number of sessions)
10. Outcome assessment (e.g., definition, assessment tool)
11. Results (e.g., reported inferential statistics, confidence intervals, 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 non-randomised studies of interventions, the Newcastle-Ottawa Scale (NOS)[76] will be used. When using the NOS, studies can be awarded a maximum of nine stars 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 (JBI).[77] The quality assessments (both for randomised and non-randomised 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, very low (table 1). As a rule of thumb, evidence from randomised trials is of high quality whereas evidence from non-randomised 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 confounding would decrease the indicated effect.[78]

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.

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 non-randomised 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 (RR) or odds ratios (OR) with 95% confidence intervals will be calculated. For continuous outcome variables, mean differences or standardised mean differences with 95% confidence intervals will be calculated. Mean differences will be utilised when the studies included in the review measured treatment outcomes with the same scale. Standardised mean differences will be utilised 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 (CMA).[80]

As per guidelines from the Cochrane Handbook for Systematic Reviews of Interventions 6.0,[74] randomised trials and non-randomised studies of interventions will not be combined in one meta-analysis. Instead, randomised trials and non-randomised studies will be separately analysed. Additionally, non-randomised studies of interventions that were judged to have a high risk of bias will be excluded from the meta-analysis.[74] For any meta-analyses with ≥ 10 studies, funnel plot asymmetry will be evaluated and possible explanations for the asymmetry considered (e.g., 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 [%female]). 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 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist can be found in online supplementary 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 the 31st of August 2020 (CRD42020201891). 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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Patient and public involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplementary Table 1 The search strategy for MEDLINE Complete

Number	Search Terms
S44	S12 AND S26 AND S42 (only English publications)
S43	S12 AND S26 AND S42
S42	S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41
S41	TI psychoeducation or AB psychoeducation
S40	TI antipsychotic* or AB antipsychotic*
S39	TI antidepressant* or AB antidepressant*
S38	TI "mood stabilizers" or AB "mood stabilizers"
S37	TI "mood stabilisers" or AB "mood stabilisers"
S36	TI intervention* or AB intervention*
S35	TI therap* or AB therap*
S34	TI treatment* or AB treatment*
S33	(MH "treatment outcome")
S32	(MH "lithium")
S31	(MH "tranquilizing agents+")
S30	(MH "antidepressive agents+")
S29	(MH "drug therapy")
S28	(MH "cognitive behavioral therapy+")
S27	(MH "psychotherapy+")
S26	S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S25	TI psychological trauma or AB psychological trauma
S24	TI (early AND trauma*) or AB (early AND trauma*)
S23	TI (adverse AND child* AND experience*) or AB (adverse AND child* AND experience*)
S22	TI (child* AND neglect) or AB (child* AND neglect)
S21	TI (child* AND abuse) or AB (child* AND abuse)
S20	TI (child* AND maltreatment) or AB (child* AND maltreatment)
S19	TI (child* AND trauma) or AB (child* AND trauma)
S18	(MH "domestic violence")
S17	(MH "psychological trauma+")
S16	(MH "battered child syndrome")
S15	(MH "child abuse+")
S14	(MH "adverse childhood experiences")
S13	(MH "adult survivors of child adverse events+")
S12	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S11	TI BPAD OR AB BPAD
S10	TI BPD OR AB BPD
S9	TI BD OR AB BD
S8	TI hypomanic OR AB hypomanic
S7	TI hypomania OR AB hypomania
S6	TI manic OR AB manic
S5	TI mania OR AB mania
S4	TI cyclothymi* OR AB cyclothymi*
S3	TI bipolar OR AB bipolar

S2	(MH "cyclothymic disorder")
S1	(MH "bipolar and related disorders+")

Supplementary Table 2 The search strategy for Embase

Number	Search Terms
S47	#46 AND 'article'/it AND [english]/lim
S46	#12 AND #28 AND #45
S45	#29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44
S44	psychoeducation:ti,ab
S43	antipsychotic*:ti,ab
S42	antidepressant*:ti,ab
S41	'mood stabilizers':ti,ab
S40	'mood stabilisers':ti,ab
S39	intervention*:ti,ab
S38	therap*:ti,ab
S37	treatment*:ti,ab
S36	'treatment outcome'/de
S35	'lithium'/de
S34	'neuroleptic agent'/exp
S33	'antidepressant agent'/exp
S32	'drug therapy'/de
S31	'cognitive behavioral therapy'/exp
S30	'psychotherapy'/exp
S29	'intervention study'/de
S28	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
S27	psychological NEAR/5 trauma:ti,ab
S26	(early AND trauma*):ti,ab
S25	(adverse AND child* AND experience*):ti,ab
S24	(child* AND neglect):ti,ab
S23	(child* AND abuse):ti,ab
S22	(child* AND maltreatment):ti,ab
S21	(child* AND trauma):ti,ab
S20	'domestic violence'/de
S19	'psychotrauma'/exp
S18	'battered child syndrome'/de
S17	'child abuse survivor'/exp
S16	'child abuse'/exp
S15	'childhood trauma survivor'/de
S14	'childhood trauma'/de
S13	'childhood adversity'/de
S12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
S11	BPAD:ti,ab
S10	BPD:ti,ab
S9	BD:ti,ab
S8	hypomanic:ti,ab
S7	hypomania:ti,ab
S6	manic:ti,ab
S5	mania:ti,ab

S4	cyclothymi*:ti,ab
S3	bipolar:ti,ab
S2	'mania'/exp
S1	'bipolar disorder'/exp

Supplementary Table 3 The search strategy for PsycINFO

Number	Search Terms
S232	S15 AND S33 AND S230 (only English publications; academic journals)
S231	S15 AND S33 AND S230
S230	S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89 or S90 or S91 or S92 or S93 or S94 or S95 or S96 or S97 or S98 or S99 or S100 or S101 or S102 or S103 or S104 or S105 or S106 or S107 or S108 or S109 or S110 or S111 or S112 or S113 or S114 or S115 or S116 or S117 or S118 or S119 or S120 or S121 or S122 or S123 or S124 or S125 or S126 or S127 or S128 or S129 or S130 or S131 or S132 or S133 or S134 or S135 or S136 or S137 or S138 or S139 or S140 or S141 or S142 or S143 or S144 or S145 or S146 or S147 or S148 or S149 or S150 or S151 or S152 or S153 or S154 or S155 or S156 or S157 or S158 or S159 or S160 or S161 or S162 or S163 or S164 or S165 or S166 or S167 or S168 or S169 or S170 or S171 or S172 or S173 or S174 or S175 or S176 or S177 or S178 or S179 or S180 or S181 or S182 or S183 or S184 or S185 or S186 or S187 or S188 or S189 or S190 or S191 or S192 or S193 or S194 or S195 or S196 or S197 or S198 or S199 or S200 or S201 or S202 or S203 or S204 or S205 or S206 or S207 or S208 or S209 or S210 or S211 or S212 or S213 or S14 or S215 or S216 or S217 or S218 or S219 or S220 or S221 or S222 or S223 or S224 or S225 or S226 or S227 or S228 or S229
S229	TI psychoeducation or AB psychoeducation
S228	TI antipsychotic* or AB antipsychotic*
S227	TI antidepressant* or AB antidepressant*
S226	TI "mood stabilizers" or AB "mood stabilizers"
S225	TI "mood stabilisers" or AB "mood stabilisers"
S224	TI intervention* or AB intervention*
S223	TI therap* or AB therap*
S222	TI treatment* or AB treatment*
S221	DE "Lithium"
S220	DE "Tetrabenazine"
S219	DE "Sulpiride"
S218	DE "Spiroperidol"
S217	DE "Risperidone"
S216	DE "Reserpine"
S215	DE "Quetiapine"
S214	DE "Olanzapine"
S213	DE "Nialamide"
S212	DE "Molindone"
S211	DE "Clozapine"
S210	DE "Aripiprazole"
S209	DE "Thiothixene"
S208	DE "Pimozide"
S207	DE "Phenothiazine Derivatives"

S206	DE "Neuroleptic Drugs"
S205	DE "Minor Tranquilizers"
S204	DE "Meprobamate"
S203	DE "Haloperidol"
S202	DE "Doxepin"
S201	DE "Benactyzine"
S200	DE "Amitriptyline"
S199	DE "Tranquilizing Drugs"
S198	DE "Zimeldine"
S197	DE "Venlafaxine"
S196	DE "Tricyclic Antidepressant Drugs"
S195	DE "Trazodone"
S194	DE "Tranylcypromine"
S193	DE "Sulpiride"
S192	DE "Sertraline"
S191	DE "Serotonin Norepinephrine Reuptake Inhibitors"
S190	DE "Pipradrol"
S189	DE "Pheniprazine"
S188	DE "Phenelzine"
S187	DE "Paroxetine"
S186	DE "Nomifensine"
S185	DE "Nialamide"
S184	DE "Nefazodone"
S183	DE "Molindone"
S182	DE "Moclobemide"
S181	DE "Mianserin"
S180	DE "Methylphenidate"
S179	DE "Lithium Carbonate"
S178	DE "Isocarboxazid"
S177	DE "Iproniazid"
S176	DE "Fluvoxamine"
S175	DE "Fluoxetine"
S174	DE "Citalopram"
S173	DE "Bupropion"
S172	DE "Antidepressant Drugs"
S171	DE "Drug Therapy"
S170	DE "Virtual Reality Exposure Therapy"
S169	DE "Prolonged Exposure Therapy"
S168	DE "In Vivo Exposure"
S167	DE "Implosive Therapy"
S166	DE "Imaginal Exposure"
S165	DE "Systematic Desensitization Therapy"
S164	DE "Response Cost"
S163	DE "Reciprocal Inhibition Therapy"
S162	DE "Implosive Therapy"
S161	DE "Exposure Therapy"
S160	DE "Dialectical Behavior Therapy"

S159	DE "Conversion Therapy"
S158	DE "Aversion Therapy"
S157	DE "Behavior Therapy"
S156	DE "Prolonged Exposure Therapy"
S155	DE "Cognitive Processing Therapy"
S154	DE "Acceptance and Commitment Therapy"
S153	DE "Workplace Intervention"
S152	DE "School Based Intervention"
S151	DE "Group Intervention"
S150	DE "Family Intervention"
S149	DE "Early Intervention"
S148	DE "Crisis Intervention"
S147	DE "Intervention"
S146	DE "Video-Based Interventions"
S145	DE "Treatment Planning"
S144	DE "Treatment Outcomes"
S143	DE "Treatment Guidelines"
S142	DE "Trauma Treatment"
S141	DE "Trauma-Informed Care"
S140	DE "Therapeutic Processes"
S139	DE "Symptoms Based Treatment"
S138	DE "Spiritual Care"
S137	DE "Speech Therapy"
S136	DE "Sociotherapy"
S135	DE "Social Casework"
S134	DE "Sex Therapy"
S133	DE "Self-Help Techniques"
S132	DE "Respite Care"
S131	DE "Pain Management"
S130	DE "Relaxation Therapy"
S129	DE "Rehabilitation"
S128	DE "Psychoeducation"
S127	DE "Private Practice"
S126	DE "Physical Treatment Methods"
S125	DE "Personal Therapy"
S124	DE "Partial Hospitalization"
S123	DE "Outpatient Treatment"
S122	DE "Multisystemic Therapy"
S121	DE "Multimodal Treatment Approach"
S120	DE "Movement Therapy"
S119	DE "Mindfulness-Based Interventions"
S118	DE "Mind Body Therapy"
S117	DE "Milieu Therapy"
S116	DE "Mental Health Programs"
S115	DE "Medical Treatment (General)"
S114	DE "Maintenance Therapy"
S113	DE "Life Sustaining Treatment"

S112	DE "Language Therapy"
S111	DE "Involuntary Treatment"
S110	DE "Intervention"
S109	DE "Interdisciplinary Treatment Approach"
S108	DE "Integrated Services"
S107	DE "Institutionalization"
S106	DE "Hydrotherapy"
S105	DE "Human Services"
S104	DE "Human Potential Movement"
S103	DE "Hospice"
S102	DE "Horticulture Therapy"
S101	DE "Health Care Services"
S100	DE "Habilitation"
S99	DE "Disease Management"
S98	DE "Cross Cultural Treatment"
S97	DE "Creative Arts Therapy"
S96	DE "Counseling"
S95	DE "Computer Assisted Therapy"
S94	DE "Cognitive Techniques"
S93	DE "Cognitive Stimulation Therapy"
S92	DE "Cognitive Behavior Therapy"
S91	DE "Client Treatment Matching"
S90	DE "Client Transfer"
S89	DE "Caregiving"
S88	DE "Bibliotherapy"
S87	DE "Behavior Modification"
S86	DE "Anxiety Management"
S85	DE "Alternative Medicine"
S84	DE "Aftercare"
S83	DE "Adventure Therapy"
S82	DE "Adjunctive Treatment"
S81	DE "Addiction Treatment"
S80	DE "Treatment"
S79	DE "Transactional Analysis"
S78	DE "Supportive Psychotherapy"
S77	DE "Strategic Therapy"
S76	DE "Solution Focused Therapy"
S75	DE "Relationship Therapy"
S74	DE "Reality Therapy"
S73	DE "Rational Emotive Behavior Therapy"
S72	DE "Psychotherapeutic Techniques"
S71	DE "Psychotherapeutic Counseling"
S70	DE "Psychodynamic Psychotherapy"
S69	DE "Psychodrama"
S68	DE "Psychoanalysis"
S67	DE "Primal Therapy"
S66	DE "Persuasion Therapy"

S65	DE "Network Therapy"
S64	DE "Narrative Therapy"
S63	DE "Logotherapy"
S62	DE "Interpersonal Psychotherapy"
S61	DE "Integrative Psychotherapy"
S60	DE "Insight Therapy"
S59	DE "Individual Psychotherapy"
S58	DE "Hypnotherapy"
S57	DE "Humanistic Psychotherapy"
S56	DE "Guided Imagery"
S55	DE "Group Psychotherapy"
S54	DE "Gestalt Therapy"
S53	DE "Geriatric Psychotherapy"
S52	DE "Feminist Therapy"
S51	DE "Eye Movement Desensitization Therapy"
S50	DE "Expressive Psychotherapy"
S49	DE "Experiential Psychotherapy"
S48	DE "Existential Therapy"
S47	DE "Emotion Focused Therapy"
S46	DE "Eclectic Psychotherapy"
S45	DE "Couples Therapy"
S44	DE "Conversion Therapy"
S43	DE "Client Centered Therapy"
S42	DE "Child Psychotherapy"
S41	DE "Brief Relational Therapy"
S40	DE "Brief Psychotherapy"
S39	DE "Autogenic Training"
S38	DE "Analytical Psychotherapy"
S37	DE "Affirmative Therapy"
S36	DE "Adolescent Psychotherapy"
S35	DE "Adlerian Psychotherapy"
S34	DE "Psychotherapy"
S33	S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32
S32	TI psychological trauma or AB psychological trauma
S31	TI (early AND trauma*) or AB (early AND trauma*)
S30	TI (adverse AND child* AND experience*) or AB (adverse AND child* AND experience*)
S29	TI (child* AND neglect) or AB (child* AND neglect)
S28	TI (child* AND abuse) or AB (child* AND abuse)
S27	TI (child* AND maltreatment) or AB (child* AND maltreatment)
S26	TI (child* AND trauma) or AB (child* AND trauma)
S25	DE "Domestic Violence"
S24	DE "Emotional Trauma"
S23	DE "Battered Child Syndrome"
S22	DE "Verbal Abuse"
S21	DE "Sexual Abuse"

S20	DE "Physical Abuse"
S19	DE "Emotional Abuse"
S18	DE "Child Neglect"
S17	DE "Child Abuse"
S16	DE "Childhood Adversity"
S15	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14	TI BPAD OR AB BPAD
S13	TI BPD OR AB BPD
S12	TI BD OR AB BD
S11	TI hypomanic OR AB hypomanic
S10	TI hypomania OR AB hypomania
S9	TI manic OR AB manic
S8	TI mania OR AB mania
S7	TI cyclothymi* OR AB cyclothymi*
S6	TI bipolar OR AB bipolar
S5	DE "Mania"
S4	DE "Cyclothymic Disorder"
S3	DE "Bipolar II Disorder"
S2	DE "Bipolar I Disorder"
S1	DE "Bipolar Disorder"

Supplementary Table 4 The search strategy for CENTRAL

Number	Search Terms
S44	#12 AND #26 AND #42 (in Trials)
S43	#12 AND #26 AND #42
S42	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
S41	(psychoeducation):ti,ab
S40	(antipsychotic*):ti,ab
S39	(antidepressant*):ti,ab
S38	("mood stabilizers"):ti,ab
S37	("mood stabilisers"):ti,ab
S36	(intervention*):ti,ab
S35	(therap*):ti,ab
S34	(treatment*):ti,ab
S33	MeSH descriptor: [Treatment Outcome] this term only
S32	MeSH descriptor: [Lithium] this term only
S31	MeSH descriptor: [Tranquilizing Agents] explode all trees
S30	MeSH descriptor: [Antidepressive Agents] explode all trees
S29	MeSH descriptor: [Drug Therapy] this term only
S28	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees
S27	MeSH descriptor: [Psychotherapy] explode all trees
S26	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
S25	(psychological NEAR/5 trauma):ti,ab
S24	((early AND trauma*)):ti,ab
S23	((adverse AND child* AND experience*)):ti,ab
S22	((child* AND neglect)):ti,ab
S21	((child* AND abuse)):ti,ab
S20	((child* AND maltreatment)):ti,ab
S19	((child* AND trauma)):ti,ab
S18	MeSH descriptor: [Domestic Violence] this term only
S17	MeSH descriptor: [Psychological Trauma] explode all trees
S16	MeSH descriptor: [Battered Child Syndrome] this term only
S15	MeSH descriptor: [Child Abuse] explode all trees
S14	MeSH descriptor: [Adverse Childhood Experiences] this term only
S13	MeSH descriptor: [Adult Survivors of Child Adverse Events] explode all trees
S12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
S11	(BPAD):ti,ab
S10	(BPD):ti,ab
S9	(BD):ti,ab
S8	(hypomanic):ti,ab
S7	(hypomania):ti,ab
S6	(manic):ti,ab
S5	(mania):ti,ab
S4	(cyclothymi*):ti,ab
S3	(bipolar):ti,ab
S2	MeSH descriptor: [Cyclothymic Disorder] this term only

S1	MeSH descriptor: [Bipolar and Related Disorders] explode all trees

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 16
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	17
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11-12

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp File 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12-13
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13-14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	14-15
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14-15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15-16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14-15
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14-15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.