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# BMJ Open

## 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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3 **The influence of childhood trauma on the treatment outcomes of pharmacological**  
4 **and/or psychological interventions for adolescents and adults with bipolar disorder:**  
5 **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 ( $\geq 10$  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.<sup>1 2</sup> Bipolar disorder may significantly impair social and occupational functioning<sup>3 4</sup> as well as the quality of life (QoL)<sup>1 5-7</sup> 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<sup>8</sup> with approximately 70% experiencing an affective relapse within four years.<sup>9-12</sup> These findings highlight the clinical importance of recognising environmental risk factors that contribute to the outcomes in bipolar disorder.<sup>13 14</sup>

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.<sup>15-17</sup> As an example, Sala et al.<sup>18</sup> 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.<sup>13 15 16 19</sup>

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

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

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24 Cakir et al.<sup>24</sup> reported that experiences of emotional or physical abuse during childhood were  
25 significantly related to inadequate response to long-term treatment with anticonvulsants  
26 among outpatients with bipolar disorder. Etain et al.<sup>25</sup> indicated a similar association between  
27 a history of childhood physical abuse and response to lithium treatment in euthymic bipolar  
28 disorder patients. That is, greater exposure to physical abuse was inversely correlated with  
29 participants' levels of response to lithium. In addition to the correlation with physical abuse,  
30 the researchers demonstrated that participants who were exposed to multiple types of  
31 childhood trauma were more likely to inadequately respond to lithium than participants without  
32 a history of any childhood trauma.

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45 Recent data collected from a randomised controlled trial conducted to test the effectiveness  
46 of adjunctive infliximab for the treatment of adult outpatients with bipolar disorder, contradicted  
47 prior research.<sup>26</sup> McIntyre et al.<sup>26</sup> found that participants with a history of physical abuse  
48 showed a greater reduction in depression severity and hence, a better treatment response  
49 than participants without a history of physical abuse. Potentially explaining McIntyre et al.'s<sup>26</sup>  
50 findings, childhood trauma has repeatedly been linked to increased and persistent  
51 inflammation in bipolar disorder.<sup>27 28</sup> Therefore, an anti-inflammatory agent might target the  
52 underlying pathophysiological mechanisms, facilitating positive treatment effects.



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5 While pharmacotherapy underpins the successful treatment of major psychiatric disorders,  
6 there is consensus that the optimal management of bipolar disorder relies on the integration  
7 of pharmacological and psychological interventions.<sup>29 30</sup> Conus et al.<sup>31</sup> retrospectively audited  
8 the files of 118 patients with bipolar disorder who were provided a comprehensive treatment  
9 program targeted at early intervention. The researchers reported that patients who  
10 experienced sexual and/or physical abuse in childhood and adolescence were more likely to  
11 disengage from treatment; notably however, there was no association between a history of  
12 childhood trauma and either symptomatic or functional remission at end of treatment.  
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24 As such, evidence supporting the differential treatment outcomes among people with bipolar  
25 disorder who were exposed to significant traumatic experiences in childhood remains  
26 contentious. Several potentially relevant mediators of this association have been suggested  
27 including treatment non-adherence,<sup>32-35</sup> difficulties with forming a therapeutic alliance,<sup>23 32 36</sup>  
28 insecure attachment styles,<sup>23 37 38</sup> and early maladaptive schemas (EMS);<sup>39-41</sup> though these  
29 factors have not yet been extensively investigated among survivors of childhood trauma who  
30 have a diagnosis of bipolar disorder.  
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41 Additionally, a wide range of treatment outcomes have been considered in clinical research  
42 on bipolar disorder. Although researchers have traditionally focused on outcomes related to  
43 symptomatic recovery, patients' functional and personal recovery has increasingly received  
44 attention.<sup>42</sup> The evaluation of treatment outcomes that capture the experiences of the  
45 individual more broadly is encouraged as some patients continue to report significant  
46 impairments in functioning and QoL even though they only have relatively mild symptoms.<sup>42</sup>  
47 Hence, symptom measures alone appear to be inadequate in assessing treatment  
48 effectiveness in bipolar disorder.  
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3 To date, there has been no systematic reviews focusing on the influence of childhood trauma  
4 on the treatment outcomes of pharmacological, psychological, and combined interventions for  
5 adolescents and adults with bipolar disorder. This is despite current research highlighting that  
6 experiences of childhood trauma may be highly relevant to the efficacy of treatments for  
7 bipolar disorder.<sup>43-45</sup> Therefore, exploring exposure to childhood trauma as a moderator of  
8 treatment outcomes may assist the development of individualised and targeted interventions  
9 for people with bipolar disorder, ultimately facilitating treatment success.<sup>23 43</sup>  
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## 20 **OBJECTIVES**

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22 The aim of this systematic review is to investigate whether a history of childhood trauma  
23 affects the treatment outcomes of pharmacological and/or psychological interventions for  
24 adolescents and adults with bipolar disorder. If sufficient data are available, it will be explored  
25 whether there are differential effects of (1) treatment type (pharmacological, psychological,  
26 combination), (2) disorder-related features (age at onset, number of episodes), and (3)  
27 demographic factors (age, gender) in the context of childhood trauma.  
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## 37 **METHODS AND ANALYSIS**

### 38 **Eligibility criteria**

39 Relevant studies will be identified according to the following criteria:  
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#### 45 **Types of participants**

46 Studies including adolescents and/or adults ( $\geq 10$  years)<sup>46</sup> with a diagnosis of bipolar disorder  
47 will be eligible for the review. Diagnoses of bipolar I disorder, bipolar II disorder, cyclothymic  
48 disorder, and bipolar disorder not elsewhere classified or not otherwise specified as set out by  
49 standardised diagnostic criteria such as the Diagnostic and Statistical Manual of Mental  
50 Disorders (DSM) or the International Classification of Diseases (ICD) will be included.  
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3 To be considered, studies must have confirmed participants' diagnosis of bipolar disorder  
4 either through a structured or semi-structured diagnostic interview such as the Structured  
5 Clinical Interview for DSM (SCID),<sup>47</sup> the MINI International Neuropsychiatric Interview  
6 (M.I.N.I.),<sup>48</sup> and the Child and Adolescent Psychiatric Assessment (CAPA)<sup>49</sup> or through  
7 psychiatrist judgement, including in chart review. No restrictions will be placed on the setting  
8 of the studies; both in-patient and out-patient samples will be eligible.  
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18 Studies also including children ( $\leq 10$  years) will only be eligible if the mean age of the sample  
19 is  $\geq 10$  years or the data for adolescent and adult participants are separately available.  
20 Additionally, studies that were conducted in heterogeneous clinical populations will only be  
21 included if more than 80% of the sample had bipolar disorder or the data for participants with  
22 bipolar disorder are separately available. However, studies that were conducted in populations  
23 exclusively consisting of individuals who were exposed to childhood trauma will be excluded.  
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### 33 Types of studies

34 To allow for a comprehensive evaluation of the available evidence,<sup>50</sup> liberal design criteria will  
35 be implemented. Both randomised and non-randomised studies of pharmacological and/or  
36 psychological interventions for bipolar disorder which included an assessment of childhood  
37 trauma will be eligible. Randomised controlled trials (RCTs), cluster RCTs, cross-over trials,  
38 controlled (non-randomised) trials, one-arm trials, interrupted time series (ITS) studies,  
39 controlled before-after (CBA) studies, uncontrolled before-after studies, cohort studies, case-  
40 control and cross-sectional studies with quantitative data will be included. Case series, case  
41 reports, and purely qualitative studies will be excluded.  
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### 54 Types of exposure measures

55 For the purpose of this review, childhood trauma is defined in the form of maltreatment and  
56 includes physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional  
57 neglect experienced during early life ( $\leq 18$  years). Participants' history of childhood trauma  
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3 may be assessed with validated measures such as the Childhood Trauma Questionnaire  
4 (CTQ)<sup>51</sup> or indicated through clinician interviews. Studies that assessed childhood trauma via  
5 in chart review will also be eligible. Additionally, studies that considered both childhood trauma  
6 and adulthood trauma will be included if the data for childhood trauma are separately available.  
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8 Studies that exclusively assessed trauma experienced in adulthood ( $\geq 18$  years), will be  
9 excluded from the review.  
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### 18 Types of interventions

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20 Included in the review will be any pharmacological and/or psychological interventions  
21 administered for the management of bipolar disorder. Pharmacological interventions include,  
22 but are not limited to, mood stabilisers, antidepressants, antipsychotics, and antiepileptics.  
23  
24 Psychological interventions refer, for instance, to psychoeducation, cognitive behavioural  
25 therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and family-focused therapy  
26 (FFT). Combined treatment approaches (e.g., pharmacological and adjunctive psychological  
27 interventions) will also be considered.  
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### 37 Types of outcome measures

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

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40 The primary outcome will be mean reduction in symptom severity as defined by change scores  
41 from baseline to end of treatment on: (a) the Young Mania Rating Scale (YMRS)<sup>52</sup> indicating  
42 mean reduction in mania severity; and (b) the Montgomery-Åsberg Depression Rating Scale  
43 (MADRS)<sup>53</sup> indicating mean reduction in depression severity. Other validated scales  
44 assessing manic or depressive symptoms will also be considered.  
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#### 54 *Secondary outcomes – related to symptomatic recovery*

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56 1. Treatment response as defined by either:  
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58 a. a reduction of 50% (or greater) on the YMRS, the MADRS, or any other validated scale  
59 assessing manic or depressive symptoms; or  
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3 b. a score of 1 (very much improved) or 2 (much improved) on the Clinical Global  
4 Impression – Improvement (CGI-I)<sup>54 55</sup> scale; or  
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7 c. other criteria specifying treatment response as defined by the study authors.  
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10 2. Symptomatic remission as defined by either:  
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12 a. a score of  $\leq 12$  on the YMRS;<sup>56-58</sup> or  
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14 b. a score of  $\leq 10$  on the MADRS;<sup>59 60</sup> or  
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16 c. a score of 1 (normal, not at all ill) or 2 (borderline mentally ill) on the Clinical Global  
17 Impression – Severity (CGI-S)<sup>54 55</sup> scale; or  
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19 d. other criteria specifying remission as defined by the study authors.  
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22 3. Relapse/recurrence defined as a new affective episode according to the DSM or ICD  
23 criteria and/or by:<sup>61-65</sup>  
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25 a. a score of  $\geq 12$  on the YMRS indicating a hypomanic recurrence;  
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27 b. a score of  $\geq 20$  on the YMRS indicating a manic recurrence;  
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29 c. a score of  $\geq 22$  on the MADRS indicating a depressive recurrence;  
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31 d. a score of  $\geq 20$  on the YMRS and a score of  $\geq 22$  on the MADRS indicating a mixed  
32 recurrence; or  
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34 e. other criteria specifying relapse/recurrence as defined by the study authors.  
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41 *Secondary outcomes – related to functional and personal recovery*

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43 1. Improvement in global functioning as defined by change scores from baseline to end of  
44 treatment on the Global Assessment of Functioning (GAF)<sup>66</sup> scale or any other validated  
45 scale assessing functioning.  
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48 2. Improvement in QoL as defined by change scores from baseline to end of treatment on  
49 the Quality of Life in Bipolar Disorder-Brief (QoL.BD-Brief)<sup>67</sup> scale or any other validated  
50 scale assessing QoL.  
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58 Types of publications  
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3 This review will be restricted to studies reported in English and published in peer-reviewed  
4 journals.  
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### 9 **Information sources and search strategy**

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11 MEDLINE Complete via Ebsco, Embase via embase.com, PsycINFO via Ebsco, and the  
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13 Cochrane Central Register of Controlled Trials (CENTRAL) via cochranelibrary.com will be  
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15 searched from database inception to December 2020 to identify relevant studies. The specific  
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17 search strategies were developed using standardised subject terms (e.g., medical subject  
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19 headings [MeSH] terms, Emtree terms) and keywords related to bipolar disorder, childhood  
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21 trauma, and pharmacological or psychological interventions. The PICO (Population,  
22  
23 Intervention, Comparison, Outcome) framework was used to develop the search terms. The  
24  
25 standardised subject terms were tailored to each individual database and truncation and  
26  
27 wildcards were applied as appropriate. Drafts of the search strategies for each database are  
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29 reported in online supplementary file 1.  
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35 The studies identified in the database searches will be checked against the eligibility criteria  
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37 outlined above. First, the titles and abstracts will be independently screened by two reviewers.  
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39 Subsequently, two reviewers will retrieve and assess the full texts of studies that appear  
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41 eligible for the review. Reasons for the exclusion of studies will be recorded. Discrepancies  
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43 between the reviewers will be discussed and assessed by a third author, if necessary. The  
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45 original study authors will be contacted for additional information if outcomes of interest are  
46  
47 not reported. Finally, the database searches will be supplemented by reviewing the reference  
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49 lists of all included publications for additional studies. Prior to the final data analysis, the  
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51 searches will be re-run to allow for the inclusion of newly published studies.  
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### 55 **Data management and extraction**

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57 The online reference management database Covidence<sup>68</sup> will be used to manage the records  
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59 during the review process. Covidence allows for publication screening, handling of duplicate  
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3 records, evaluation of risk of bias, and extraction of study characteristics and outcomes  
4 according to the eligibility criteria. The following data will be independently extracted by two  
5 reviewers:  
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- 8 1. Study characteristics (e.g., study author, year of publication)
- 9 2. Study design (e.g., randomised, non-randomised)
- 10 3. Sample characteristics (e.g., N, country/ies, setting)
- 11 4. Participant characteristics (e.g., age range, % gender, diagnoses)
- 12 5. Disorder-related features (e.g., age at onset, number of episodes)
- 13 6. Treatment characteristics (e.g., type, dose, duration, number of sessions)
- 14 7. Diagnostic assessment (e.g., assessment tool)
- 15 8. Childhood trauma assessment (e.g., definition, assessment tool)
- 16 9. Outcome assessment (e.g., definition, assessment tool)
- 17 10. Results (e.g., reported inferential statistics, confidence intervals, effect sizes)

### 32 **Assessment of methodological quality**

33 For randomised trials, the Cochrane Collaboration's Risk of Bias tool<sup>69 70</sup> will be used.  
34 Specifically, the included studies will be evaluated according to the following sources of bias:  
35 random sequence generation, allocation concealment, blinding of participants and personnel,  
36 blinding of outcome assessment, incomplete outcome data, selective reporting, and other  
37 sources of bias. Based on the available information, studies will be rated as low risk or high  
38 risk. If insufficient information is provided to evaluate risk of bias of a study, it will be rated as  
39 unclear and the study author will be contacted for further details.  
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51 For non-randomised studies of interventions, the Newcastle-Ottawa Scale (NOS)<sup>71</sup> will be  
52 used. When using the NOS, studies can be awarded a maximum of nine stars depending on  
53 sample selection, comparability of groups, and assessment of exposure or outcome. Where  
54 needed, the quality assessment with the NOS will be supplemented by using the critical  
55 appraisal tools developed by the Joanna Briggs Institute (JBI).<sup>72</sup> The quality assessments  
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(both for randomised and non-randomised studies) will be completed by two independent reviewers.

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE)<sup>73</sup> 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<sup>73</sup>

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



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3 treatment type (pharmacological, psychological, combination). The following will be calculated  
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5 if sufficient data are available:  
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9 For categorical outcomes, risk ratios (RR) or odds ratios (OR) with 95% confidence intervals  
10 will be calculated. For continuous outcomes, mean differences or standardised mean  
11 differences with 95% confidence intervals will be calculated. Mean differences will be utilised  
12 when the studies included in the review measured treatment outcomes with the same scale.  
13 Standardised mean differences will be utilised when the studies included in the review  
14 measured treatment outcomes with different scales.  
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24 Heterogeneity of evidence will be determined with Higgins  $I^2$  statistics calculations. If  
25 substantial heterogeneity between the studies is indicated ( $I^2 \geq 50\%$ ),<sup>69 74</sup> possible reasons for  
26 the variability will be considered by analysing the characteristics of the studies included. If  
27 meta-analyses are deemed sensible based on the heterogeneity analysis, a random-effects  
28 model will be used, conducted with the software Comprehensive Meta-Analysis (CMA).<sup>75</sup>  
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37 As per guidelines from the Cochrane Handbook for Systematic Reviews of Interventions 6.0,<sup>69</sup>  
38 randomised trials and non-randomised studies of interventions will not be combined in one  
39 meta-analysis. Instead, randomised trials and non-randomised studies will be separately  
40 analysed. Additionally, non-randomised studies of interventions that were judged to have a  
41 high risk of bias will be excluded from the meta-analysis.<sup>69</sup> For any meta-analyses with  $\geq 10$   
42 studies, funnel plot asymmetry will be evaluated and possible explanations for the asymmetry  
43 considered (e.g., publication bias), if applicable.<sup>69</sup>  
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### 54 **Subgroup analysis**

55 Where substantial heterogeneity is indicated ( $I^2 \geq 50\%$ ) and sufficient data are available,  
56 subgroup analyses will be performed by treatment type (pharmacological, psychological,  
57 combination), disorder-related features (age at onset, number of episodes), and demographic  
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3 factors (age, gender). Sensitivity analyses will be conducted to determine the robustness of  
4  
5 the meta-analyses.  
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### 9 **Presentation and reporting of results**

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11 This systematic review will be reported following the Preferred Reporting Items for Systematic  
12 Review and Meta-Analysis (PRISMA) guidelines.<sup>76</sup> In accordance with the PRISMA  
13  
14 guidelines, the study selection process will be detailed in a flowchart, including number of  
15  
16 studies excluded at each stage of the review and reasons for exclusion. The Preferred  
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18 Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist can  
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20 be found in online supplementary file 2.  
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### 26 **Ethics and dissemination**

27  
28 Only previously published data will be used in this systematic review; hence, ethical approval  
29  
30 is not required. This review was registered with the International Prospective Register of  
31  
32 Systematic Reviews (PROSPERO) on the 31<sup>st</sup> of August 2020 (CRD42020201891). The  
33  
34 findings will be published in peer-reviewed journals and presented at relevant conferences.  
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36 Multiple publications may be derived from this protocol.  
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### 41 **Patient and public involvement**

42  
43 This research was done without patient involvement. Patients were not invited to comment on  
44  
45 the study design and were not consulted to develop patient relevant outcomes or interpret the  
46  
47 results. Patients were not invited to contribute to the writing or editing of this document for  
48  
49 readability or accuracy.  
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### 53 **CONCLUSION**

54  
55 This will be the first review to involve a systematic exploration of the available evidence  
56  
57 reporting the influence of childhood trauma on the treatment outcomes of pharmacological  
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59 and/or psychological interventions for adolescents and adults with bipolar disorder. The  
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3 findings will clarify the role that childhood trauma plays in the treatment of bipolar disorder and  
4 will consequently have the potential to inform clinical guidelines and practice.  
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16 and drafted, edited and approved the final version of the manuscript. **OMD, SMC, MB, and AT**  
17 developed the research question, revised the search strategy and edited and approved the  
18 final version of the manuscript. **SER** edited and approved the final version of the manuscript.  
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22 conduct, or reporting, or dissemination plans of this research.  
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50  
51  
52  
53  
54  
55  
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57  
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59  
60

**REFERENCES**

1. Grande I, Berk M, Birmaher B, et al. Bipolar disorder. *The Lancet* 2016;387:1561-72. doi: 10.1016/s0140-6736(15)00241-x
2. Chu CS, Stubbs B, Chen TY, et al. The effectiveness of adjunct mindfulness-based intervention in treatment of bipolar disorder: A systematic review and meta-analysis. *Journal of Affective Disorders* 2018;225:234-45. doi: 10.1016/j.jad.2017.08.025 [published Online First: 2017/08/26]
3. Simon GE, Bauer MS, Ludman EJ, et al. Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. *Journal of Clinical Psychiatry* 2007;68:1237-45. doi: 10.4088/jcp.v68n0811
4. Lee EJ, Hower H, Jones RN, et al. Course of longitudinal psychosocial functioning in bipolar youth transitioning to adults. *Journal of Affective Disorders* 2020;268:109-17. doi: <https://doi.org/10.1016/j.jad.2020.03.016>
5. Maripuu M, Norrback K-F, Adolfsson R. Quality of life for patients diagnosed with bipolar disorder: Lifestyle and treatment. *Neurology, Psychiatry and Brain Research* 2019;34:34-40. doi: <https://doi.org/10.1016/j.npbr.2019.09.002>
6. Morton E, Murray G, Michalak EE, et al. Quality of life in bipolar disorder: towards a dynamic understanding. *Psychol Med* 2018;48(7):1111-18. doi: 10.1017/s0033291717002495 [published Online First: 2017/09/19]
7. Pascual-Sánchez A, Jenaro C, Montes-Rodríguez JM. Quality of life in euthymic bipolar patients: A systematic review and meta-analysis. *J Affect Disord* 2019;255:105-15. doi: 10.1016/j.jad.2019.05.032 [published Online First: 2019/06/01]
8. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Arch Gen Psychiatry* 2008;65(4):386-94. doi: 10.1001/archpsyc.65.4.386 [published Online First: 2008/04/09]

- 1  
2  
3 9. Meyer TD, Hautzinger M. Cognitive behaviour therapy and supportive therapy for bipolar  
4  
5 disorders: Relapse rates for treatment period and 2-year follow-up. *Psychological*  
6  
7 *Medicine* 2012;42:1429–39. doi: 10.1017/S0033291711002522  
8
- 9  
10 10. Simhandl C, Konig B, Amann BL. A prospective 4-year naturalistic follow-up of treatment  
11  
12 and outcome of 300 bipolar I and II patients. *Journal of Clinical Psychiatry*  
13  
14 2014;75:254–62. doi: 10.4088/JCP.13m08601  
15
- 16 11. Simhandl C, Radua J, Konig B, et al. The prevalence and effect of life events in 222 bipolar  
17  
18 I and II patients: A prospective, naturalistic 4 year follow-up study. *Journal of Affective*  
19  
20 *Disorders* 2015;170:166-71. doi: 10.1016/j.jad.2014.08.043 [published Online First:  
21  
22 2014/09/23]  
23
- 24 12. Gignac A, McGirr A, Lam RW, et al. Course and outcome following a first episode of mania:  
25  
26 four-year prospective data from the Systematic Treatment Optimization Program  
27  
28 (STOP-EM). *J Affect Disord* 2015;175:411-17. doi: 10.1016/j.jad.2015.01.032  
29  
30 [published Online First: 2015/02/14]  
31  
32
- 33 13. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of  
34  
35 bipolar disorder. *Psychiatry and Clinical Neurosciences* 2017;71:6-17. doi:  
36  
37 10.1111/pcn.12433 [published Online First: 2016/08/09]  
38
- 39 14. Palmier-Claus JE, Berry K, Bucci S, et al. Relationship between childhood adversity and  
40  
41 bipolar affective disorder: Systematic review and meta-analysis. *The British Journal of*  
42  
43 *Psychiatry* 2016;209:454-59. doi: 10.1192/bjp.bp.115.179655 [published Online First:  
44  
45 2016/10/21]  
46
- 47 15. Alvarez MJ, Roura P, Oses A, et al. Prevalence and clinical impact of childhood trauma in  
48  
49 patients with severe mental disorders. *The Journal of Nervous and Mental Disease*  
50  
51 2011;199:156-61. doi: 10.1097/NMD.0b013e31820c751c [published Online First:  
52  
53 2011/02/25]  
54
- 55 16. Garno JL, Goldberg JF, Ramirez PM, et al. Impact of childhood abuse on the clinical  
56  
57 course of bipolar disorder. *British Journal of Psychiatry* 2005;186 doi:  
58  
59 10.1192/bjp.186.2.121  
60

- 1  
2  
3 17. Jansen K, Cardoso TA, Fries GR, et al. Childhood trauma, family history, and their  
4 association with mood disorders in early adulthood. *Acta Psychiatrica Scandinavica*  
5 2016;134:281-86. doi: 10.1111/acps.12551 [published Online First: 2016/01/31]  
6  
7  
8  
9 18. Sala R, Goldstein BI, Wang S, et al. Childhood maltreatment and the course of bipolar  
10 disorders among adults: Epidemiologic evidence of dose-response effects. *Journal of*  
11 *Affective Disorders* 2014;165:74-80. doi: 10.1016/j.jad.2014.04.035 [published Online  
12 First: 2014/06/03]  
13  
14  
15  
16  
17 19. Jaworska-Andryszewska P, Rybakowski JK. Childhood trauma in mood disorders:  
18 Neurobiological mechanisms and implications for treatment. *Pharmacological Reports*  
19 2019;71:112-20. doi: 10.1016/j.pharep.2018.10.004 [published Online First:  
20 2018/12/14]  
21  
22  
23  
24  
25 20. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in  
26 bipolar disorder: a systematic review and meta-analysis. *The Lancet Psychiatry*  
27 2016;3:342-49. doi: 10.1016/s2215-0366(15)00544-1  
28  
29  
30  
31  
32 21. Etain B, Aas M, Andreassen OA, et al. Childhood trauma is associated with severe clinical  
33 characteristics of bipolar disorders. *Journal of Clinical Psychiatry* 2013;74:991-98. doi:  
34 10.4088/JCP.13m08353 [published Online First: 2013/11/16]  
35  
36  
37  
38 22. Maniglio R. The impact of child sexual abuse on the course of bipolar disorder: A  
39 systematic review. *Bipolar Disorders* 2013;15:341-58. doi: 10.1111/bdi.12050  
40 [published Online First: 2013/01/26]  
41  
42  
43  
44 23. Cotter J, Kaess M, Yung AR. Childhood trauma and functional disability in psychosis,  
45 bipolar disorder and borderline personality disorder: A review of the literature. *Irish*  
46 *Journal of Psychological Medicine* 2015;32:21-30. doi: 10.1017/ipm.2014.74  
47 [published Online First: 2015/03/01]  
48  
49  
50  
51  
52 24. Cakir S, Tasdelen Durak R, Ozyildirim I, et al. Childhood trauma and treatment outcome  
53 in bipolar disorder. *Journal of Trauma and Dissociation* 2016;17:397-409. doi:  
54 10.1080/15299732.2015.1132489 [published Online First: 2015/12/20]  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
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46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
25. Etain B, Lajnef M, Brichant-Petitjean C, et al. Childhood trauma and mixed episodes are associated with poor response to lithium in bipolar disorders. *Acta Psychiatrica Scandinavica* 2017;135:319-27. doi: 10.1111/acps.12684 [published Online First: 2016/12/18]
  26. McIntyre RS, Subramaniapillai M, Lee Y, et al. Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: A randomized clinical trial. *JAMA Psychiatry* 2019;76:783–90. doi: 10.1001/jamapsychiatry.2019.0779 [published Online First: 2019/05/09]
  27. Berk M, Walker AJ, Nierenberg AA. Biomarker-guided anti-inflammatory therapies: from promise to reality check. *JAMA Psychiatry* 2019;76:779-80. doi: 10.1001/jamapsychiatry.2019.0673
  28. Lippard ETC, Nemeroff CB. The devastating clinical consequences of child abuse and neglect: Increased disease vulnerability and poor treatment response in mood disorders. *The American Journal of Psychiatry* 2020;177:20-36. doi: 10.1176/appi.ajp.2019.19010020 [published Online First: 2019/09/21]
  29. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry* 2015;49(12):1087-206. doi: 10.1177/0004867415617657 [published Online First: 2015/12/09]
  30. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar disorders* 2018;20:97-170. doi: 10.1111/bdi.12609 [published Online First: 2018/03/14]
  31. Conus P, Cotton S, Schimmelmann BG, et al. Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. *Bipolar Disorders* 2010;12:244-52. doi: 10.1111/j.1399-5618.2010.00813.x [published Online First: 2010/06/23]



- 1  
2  
3 32. Lawson DM, Davis D, Brandon S. Treating complex trauma: critical interventions with  
4 adults who experienced ongoing trauma in childhood. *Psychotherapy (Chic)*  
5 2013;50:331-35. doi: 10.1037/a0032677 [published Online First: 2013/09/05]  
6  
7  
8  
9 33. Lecomte T, Spidel A, Leclerc C, et al. Predictors and profiles of treatment non-adherence  
10 and engagement in services problems in early psychosis. *Schizophrenia Research*  
11 2008;102:295-302. doi: 10.1016/j.schres.2008.01.024 [published Online First:  
12 2008/02/26]  
13  
14  
15  
16  
17 34. Spidel A, Greaves C, Yuille J, et al. A comparison of treatment adherence in individuals  
18 with a first episode of psychosis and inpatients with psychosis. *International Journal of*  
19 *Law and Psychiatry* 2015;39:90-98. doi: 10.1016/j.ijlp.2015.01.026 [published Online  
20 First: 2015/02/24]  
21  
22  
23  
24  
25  
26 35. Rakofsky JJ, Levy ST, Dunlop BW. Conceptualizing treatment nonadherence in patients  
27 with bipolar disorder and PTSD. *CNS Spectrums* 2011;16:11-20. doi:  
28 10.1017/S1092852912000119 [published Online First: 2011/01/01]  
29  
30  
31  
32 36. Lafrenaye-Dugas AJ, Godbout N, Hebert M. Cumulative childhood trauma and therapeutic  
33 alliance: The moderator role of attachment in adult patients consulting in sex therapy.  
34 *Journal of Sex & Marital Therapy* 2018;44:667-78. doi:  
35 10.1080/0092623X.2018.1447057 [published Online First: 2018/03/06]  
36  
37  
38  
39  
40 37. Cotter J, Yung AR. Exploring the impact of adverse childhood experiences on symptomatic  
41 and functional outcomes in adulthood: Advances, limitations and considerations. *Irish*  
42 *Journal of Psychological Medicine* 2018;35:5-7. doi: 10.1017/ipm.2017.53 [published  
43 Online First: 2017/10/18]  
44  
45  
46  
47  
48 38. Gumley AI, Taylor HE, Schwannauer M, et al. A systematic review of attachment and  
49 psychosis: Measurement, construct validity and outcomes. *Acta Psychiatrica*  
50 *Scandinavica* 2014;129:257-74. doi: 10.1111/acps.12172 [published Online First:  
51 2013/07/10]  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 39. Nordahl HM, Holthe H, Haugum JA. Early maladaptive schemas in patients with or without  
4 personality disorders: does schema modification predict symptomatic relief? *Clinical*  
5 *Psychology & Psychotherapy* 2005;12:142-49. doi: 10.1002/cpp.430  
6  
7  
8  
9  
10 40. van Vreeswijk MF, Spinhoven P, Eurelings-Bontekoe EH, et al. Changes in symptom  
11 severity, schemas and modes in heterogeneous psychiatric patient groups following  
12 short-term schema cognitive-behavioural group therapy: A naturalistic pre-treatment  
13 and post-treatment design in an outpatient clinic. *Clinical Psychology & Psychotherapy*  
14 2014;21:29-38. doi: 10.1002/cpp.1813 [published Online First: 2012/08/31]  
15  
16  
17  
18  
19  
20 41. Özdin S, Sarisoy G, Şahin AR, et al. Early maladaptive schemas in patients with bipolar  
21 and unipolar disorder. *International Journal of Psychiatry in Clinical Practice*  
22 2018;22:151-56. doi: 10.1080/13651501.2017.1387268  
23  
24  
25  
26  
27 42. Murray G, Leitan ND, Thomas N, et al. Towards recovery-oriented psychosocial  
28 interventions for bipolar disorder: Quality of life outcomes, stage-sensitive treatments,  
29 and mindfulness mechanisms. *Clinical Psychology Review* 2017;52:148-63. doi:  
30 10.1016/j.cpr.2017.01.002 [published Online First: 2017/01/28]  
31  
32  
33  
34  
35 43. Aas M, Henry C, Andreassen OA, et al. The role of childhood trauma in bipolar disorders.  
36 *International Journal of Bipolar Disorder* 2016;4:2-10. doi: 10.1186/s40345-015-0042-  
37 0 [published Online First: 2016/01/15]  
38  
39  
40  
41 44. Maes M, Congio A, Moraes JB, et al. Early life trauma predicts affective phenomenology  
42 and the effects are partly mediated by staging coupled with lowered lipid-associated  
43 antioxidant defences. *Biomol Concepts* 2018;9:115-30. doi: 10.1515/bmc-2018-0010  
44 [published Online First: 2018/11/25]  
45  
46  
47  
48  
49 45. Ventimiglia I, Van der Watt ASJ, Kidd M, et al. Association between trauma exposure and  
50 mood trajectories in patients with mood disorders. *Journal of Affective Disorders*  
51 2020;262:237-46. doi: 10.1016/j.jad.2019.10.057 [published Online First: 2019/11/14]  
52  
53  
54  
55  
56 46. Organization. WH. Health for the world's adolescents: a second chance in the second  
57 decade. Geneva: World Health Organization, 2014.  
58  
59  
60

- 1  
2  
3 47. First MB, Williams, J. B. W, Karg, R. S., Spitzer, R. L. Structured Clinical Interview for  
4  
5 DSM-5 - Research Version. Arlington, VA: American Psychiatric Association, 2015.  
6  
7 48. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric  
8  
9 Interview (M.I.N.I.): the development and validation of a structured diagnostic  
10  
11 psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 Suppl 20:22-  
12  
13 33;quiz 34-57. [published Online First: 1999/01/09]  
14  
15 49. Angold A, Costello EJ. A test-retest reliability study of child-reported psychiatric symptoms  
16  
17 and diagnoses using the Child and Adolescent Psychiatric Assessment (CAPA-C).  
18  
19 *Psychol Med* 1995;25(4):755-62. doi: 10.1017/s0033291700034991 [published Online  
20  
21 First: 1995/07/01]  
22  
23 50. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic reviews of effectiveness.  
24  
25 In: Aromataris E, Munn Z, eds. Joanna Briggs Institute Reviewer's Manual: The Joanna  
26  
27 Briggs Institute, 2017.  
28  
29 51. Bernstein DP, Fink L, Handelsman L, et al. Initial reliability and validity of a new  
30  
31 retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*  
32  
33 1994;151:1132-36. doi: 10.1176/ajp.151.8.1132 [published Online First: 1994/08/01]  
34  
35 52. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: Reliability, validity and  
36  
37 sensitivity. *The British Journal of Psychiatry* 1978;133:429-35. doi:  
38  
39 10.1192/bjp.133.5.429 [published Online First: 1978/11/01]  
40  
41 53. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change.  
42  
43 *The British Journal of Psychiatry* 1979;134:382-89. doi: 10.1192/bjp.134.4.382  
44  
45 [published Online First: 1979/04/01]  
46  
47 54. Spearing MK, Post RM, Leverich GS, et al. Modification of the clinical global impressions  
48  
49 (CGI) scale for use in bipolar illness (BP): The CGI-BP. *Psychiatry Research*  
50  
51 1997;73:159-71. doi: 10.1016/s0165-1781(97)00123-6 [published Online First:  
52  
53 1998/03/03]  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 55. Guy W. Clinical Global Impressions - ECDEU Assessment Manual for  
4 Psychopharmacology Revised (DHEW Publ No ADM 76-338). Rockville, MD: National  
5 Institute of Mental Health 1976.  
6  
7  
8  
9  
10 56. Patel NC, Patrick DM, Youngstrom EA, et al. Response and remission in adolescent  
11 mania: Signal detection analyses of the young mania rating scale. *Journal of the*  
12 *American Academy of Child & Adolescent Psychiatry* 2007;46(5):628-35. doi:  
13 10.1097/chi.0b013e3180335ae4  
14  
15  
16  
17  
18 57. Masand PS, Eudicone J, Pikalov A, et al. Criteria for defining symptomatic and sustained  
19 remission in bipolar I disorder: a post-hoc analysis of a 26-week aripiprazole study  
20 (study CN138-010). *Psychopharmacol Bull* 2008;41(2):12-23. [published Online First:  
21 2008/08/01]  
22  
23  
24  
25  
26 58. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a  
27 double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. *Arch Gen*  
28 *Psychiatry* 2000;57(9):841-9. doi: 10.1001/archpsyc.57.9.841 [published Online First:  
29 2000/09/15]  
30  
31  
32  
33  
34 59. Hawley CJ, Gale TM, Sivakumaran T. Defining remission by cut off score on the MADRS:  
35 selecting the optimal value. *J Affect Disord* 2002;72(2):177-84. doi: 10.1016/s0165-  
36 0327(01)00451-7 [published Online First: 2002/08/30]  
37  
38  
39  
40 60. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the  
41 Montgomery-Asberg depression rating scale corresponding to the definition of  
42 remission on the Hamilton rating scale for depression. *J Psychiatr Res* 2004;38(6):577-  
43 82. doi: 10.1016/j.jpsychires.2004.03.007 [published Online First: 2004/10/02]  
44  
45  
46  
47  
48 61. Castle D, White C, Chamberlain J, et al. Group-based psychosocial intervention for bipolar  
49 disorder: randomised controlled trial. *British Journal of Psychiatry* 2010;196(5):383-88.  
50 doi: 10.1192/bjp.bp.108.058263 [published Online First: 2018/01/02]  
51  
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54 62. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group  
55 psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease  
56  
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3 is in remission. *Arch Gen Psychiatry* 2003;60(4):402-7. doi:  
4 10.1001/archpsyc.60.4.402 [published Online First: 2003/04/16]  
5  
6  
7 63. Reinares M, Pacchiarotti I, Solé B, et al. A prospective longitudinal study searching for  
8 predictors of response to group psychoeducation in bipolar disorder. *Journal of*  
9 *Affective Disorders* 2020;274:1113-21. doi: <https://doi.org/10.1016/j.jad.2020.02.047>  
10  
11  
12  
13 64. Gorwood P, Weiller E, Lemming O, et al. Escitalopram prevents relapse in older patients  
14 with major depressive disorder. *The American Journal of Geriatric Psychiatry*  
15 2007;15(7):581-93. doi: 10.1097/01.JGP.0000240823.94522.4c  
16  
17  
18  
19 65. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral  
20 antidepressant treatment for relapse prevention in patients with treatment-resistant  
21 depression: a randomized clinical trial. *JAMA Psychiatry* 2019;76(9):893-903. doi:  
22 10.1001/jamapsychiatry.2019.1189  
23  
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25  
26  
27  
28 66. Association. AP. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition,  
29 Text Revisions (DSM-IV-TR) ed. Washington, DC: American Psychiatric Association  
30 2000.  
31  
32  
33  
34 67. Michalak EE, Murray G. Development of the QoL.BD: a disorder-specific scale to assess  
35 quality of life in bipolar disorder. *Bipolar Disord* 2010;12(7):727-40. doi:  
36 10.1111/j.1399-5618.2010.00865.x [published Online First: 2010/11/03]  
37  
38  
39  
40 68. Innovation VH. Covidence systematic review software. Melbourne, Australia: Veritas  
41 Health Innovation.  
42  
43  
44 69. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of  
45 Interventions version 6.0 (updated July 2019): Cochrane 2019.  
46  
47  
48 70. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for  
49 assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi:  
50 10.1136/bmj.d5928  
51  
52  
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54 71. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing  
55 the quality of nonrandomised studies in meta-analyses.  
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3 72. Institute TJB. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic  
4  
5       Reviews.  
6  
7 73. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality  
8  
9       of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-26. doi:  
10  
11       10.1136/bmj.39489.470347.AD  
12  
13 74. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses.  
14  
15       *BMJ* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557  
16  
17 75. Comprehensive Meta-Analysis [program]. 3.0 version. Englewood, NJ: Biostat, Inc.  
18  
19 76. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and  
20  
21       meta-analyses: The PRISMA Statement. *PLOS Medicine* 2009;6(7):e1000097. doi:  
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23       10.1371/journal.pmed.1000097  
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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

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3 S2 (MH "cyclothymic disorder")  
4 S1 (MH "bipolar and related disorders+")  
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For peer review only



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

## Supplementary Material

*BMJ Open*

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

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For peer review only

**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"

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3	S206	DE "Neuroleptic Drugs"
4	S205	DE "Minor Tranquilizers"
5	S204	DE "Meprobamate"
6	S203	DE "Haloperidol"
7	S202	DE "Doxepin"
8	S201	DE "Benactyzine"
9	S200	DE "Amitriptyline"
10	S199	DE "Tranquilizing Drugs"
11	S198	DE "Zimeldine"
12	S197	DE "Venlafaxine"
13	S196	DE "Tricyclic Antidepressant Drugs"
14	S195	DE "Trazodone"
15	S194	DE "Tranylcypromine"
16	S193	DE "Sulpiride"
17	S192	DE "Sertraline"
18	S191	DE "Serotonin Norepinephrine Reuptake Inhibitors"
19	S190	DE "Pipradrol"
20	S189	DE "Pheniprazine"
21	S188	DE "Phenelzine"
22	S187	DE "Paroxetine"
23	S186	DE "Nomifensine"
24	S185	DE "Nialamide"
25	S184	DE "Nefazodone"
26	S183	DE "Molindone"
27	S182	DE "Moclobemide"
28	S181	DE "Mianserin"
29	S180	DE "Methylphenidate"
30	S179	DE "Lithium Carbonate"
31	S178	DE "Isocarboxazid"
32	S177	DE "Iproniazid"
33	S176	DE "Fluvoxamine"
34	S175	DE "Fluoxetine"
35	S174	DE "Citalopram"
36	S173	DE "Bupropion"
37	S172	DE "Antidepressant Drugs"
38	S171	DE "Drug Therapy"
39	S170	DE "Virtual Reality Exposure Therapy"
40	S169	DE "Prolonged Exposure Therapy"
41	S168	DE "In Vivo Exposure"
42	S167	DE "Implosive Therapy"
43	S166	DE "Imaginal Exposure"
44	S165	DE "Systematic Desensitization Therapy"
45	S164	DE "Response Cost"
46	S163	DE "Reciprocal Inhibition Therapy"
47	S162	DE "Implosive Therapy"
48	S161	DE "Exposure Therapy"
49	S160	DE "Dialectical Behavior Therapy"
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3	S159 DE "Conversion Therapy"
4	S158 DE "Aversion Therapy"
5	S157 DE "Behavior Therapy"
6	S156 DE "Prolonged Exposure Therapy"
7	S155 DE "Cognitive Processing Therapy"
8	S154 DE "Acceptance and Commitment Therapy"
9	S153 DE "Workplace Intervention"
10	S152 DE "School Based Intervention"
11	S151 DE "Group Intervention"
12	S150 DE "Family Intervention"
13	S149 DE "Early Intervention"
14	S148 DE "Crisis Intervention"
15	S147 DE "Intervention"
16	S146 DE "Video-Based Interventions"
17	S145 DE "Treatment Planning"
18	S144 DE "Treatment Outcomes"
19	S143 DE "Treatment Guidelines"
20	S142 DE "Trauma Treatment"
21	S141 DE "Trauma-Informed Care"
22	S140 DE "Therapeutic Processes"
23	S139 DE "Symptoms Based Treatment"
24	S138 DE "Spiritual Care"
25	S137 DE "Speech Therapy"
26	S136 DE "Sociotherapy"
27	S135 DE "Social Casework"
28	S134 DE "Sex Therapy"
29	S133 DE "Self-Help Techniques"
30	S132 DE "Respite Care"
31	S131 DE "Pain Management"
32	S130 DE "Relaxation Therapy"
33	S129 DE "Rehabilitation"
34	S128 DE "Psychoeducation"
35	S127 DE "Private Practice"
36	S126 DE "Physical Treatment Methods"
37	S125 DE "Personal Therapy"
38	S124 DE "Partial Hospitalization"
39	S123 DE "Outpatient Treatment"
40	S122 DE "Multisystemic Therapy"
41	S121 DE "Multimodal Treatment Approach"
42	S120 DE "Movement Therapy"
43	S119 DE "Mindfulness-Based Interventions"
44	S118 DE "Mind Body Therapy"
45	S117 DE "Milieu Therapy"
46	S116 DE "Mental Health Programs"
47	S115 DE "Medical Treatment (General)"
48	S114 DE "Maintenance Therapy"
49	S113 DE "Life Sustaining Treatment"
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3	S112	DE "Language Therapy"
4	S111	DE "Involuntary Treatment"
5	S110	DE "Intervention"
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7	S109	DE "Interdisciplinary Treatment Approach"
8	S108	DE "Integrated Services"
9	S107	DE "Institutionalization"
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11	S106	DE "Hydrotherapy"
12	S105	DE "Human Services"
13	S104	DE "Human Potential Movement"
14	S103	DE "Hospice"
15	S102	DE "Horticulture Therapy"
16	S101	DE "Health Care Services"
17		
18	S100	DE "Habilitation"
19	S99	DE "Disease Management"
20	S98	DE "Cross Cultural Treatment"
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22	S97	DE "Creative Arts Therapy"
23	S96	DE "Counseling"
24	S95	DE "Computer Assisted Therapy"
25	S94	DE "Cognitive Techniques"
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27	S93	DE "Cognitive Stimulation Therapy"
28	S92	DE "Cognitive Behavior Therapy"
29	S91	DE "Client Treatment Matching"
30	S90	DE "Client Transfer"
31	S89	DE "Caregiving"
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33	S88	DE "Bibliotherapy"
34	S87	DE "Behavior Modification"
35	S86	DE "Anxiety Management"
36	S85	DE "Alternative Medicine"
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38	S84	DE "Aftercare"
39	S83	DE "Adventure Therapy"
40	S82	DE "Adjunctive Treatment"
41	S81	DE "Addiction Treatment"
42	S80	DE "Treatment"
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44	S79	DE "Transactional Analysis"
45	S78	DE "Supportive Psychotherapy"
46	S77	DE "Strategic Therapy"
47	S76	DE "Solution Focused Therapy"
48	S75	DE "Relationship Therapy"
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50	S74	DE "Reality Therapy"
51	S73	DE "Rational Emotive Behavior Therapy"
52	S72	DE "Psychotherapeutic Techniques"
53	S71	DE "Psychotherapeutic Counseling"
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55	S70	DE "Psychodynamic Psychotherapy"
56	S69	DE "Psychodrama"
57	S68	DE "Psychoanalysis"
58	S67	DE "Primal Therapy"
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60	S66	DE "Persuasion Therapy"

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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"

## Supplementary Material

BMJ Open

1		
2		
3	S20	DE "Physical Abuse"
4	S19	DE "Emotional Abuse"
5	S18	DE "Child Neglect"
6	S17	DE "Child Abuse"
7	S16	DE "Childhood Adversity"
8	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
9	S14	TI BPAD OR AB BPAD
10	S13	TI BPD OR AB BPD
11	S12	TI BD OR AB BD
12	S11	TI hypomanic OR AB hypomanic
13	S10	TI hypomania OR AB hypomania
14	S9	TI manic OR AB manic
15	S8	TI mania OR AB mania
16	S7	TI cyclothymi* OR AB cyclothymi*
17	S6	TI bipolar OR AB bipolar
18	S5	DE "Mania"
19	S4	DE "Cyclothymic Disorder"
20	S3	DE "Bipolar II Disorder"
21	S2	DE "Bipolar I Disorder"
22	S1	DE "Bipolar Disorder"
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**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

For peer review only

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**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.
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
	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
	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Contributions			
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	
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

## Supplementary material

BMJ Open

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 $\tau$ )	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.**

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.

# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-044569.R1
Article Type:	Protocol
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<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	PSYCHIATRY, MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY

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3 1 **The influence of childhood trauma on the treatment outcomes of pharmacological**  
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5 2 **and/or psychological interventions for adolescents and adults with bipolar disorder:**  
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7 3 **protocol for a systematic review and meta-analysis**  
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11 5 Anna L. Wrobel<sup>1,6</sup>, Samantha E. Russell<sup>1</sup>, Olivia M. Dean<sup>1,2</sup>, Sue M. Cotton<sup>5,6</sup>, Michael  
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13 6 Berk<sup>1,2,3,5,6</sup>, Alyna Turner<sup>1,4</sup>  
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41 19 Word count: 3993 (excluding title page, abstract, references and tables)  
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3 24 **ABSTRACT**  
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5 25 **Introduction:** Despite available pharmacological and psychological treatments, remission  
6  
7 26 rates for bipolar disorder remain relatively low. Current research implicates the experience of  
8  
9 27 childhood trauma as a potential moderator of poor treatment outcomes amongst individuals  
10  
11 28 with bipolar disorder. To date, the evidence reporting the influence of childhood trauma on the  
12  
13 29 treatment outcomes of pharmacological and/or psychological interventions for adolescents  
14  
15 30 and adults with bipolar disorder has not been systematically reviewed.  
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17  
18 31 **Method and analysis:** MEDLINE Complete, Embase, PsycINFO, and the Cochrane Central  
19  
20 32 Register of Controlled Trials (CENTRAL) will be searched to identify randomised and non-  
21  
22 33 randomised studies of pharmacological and/or psychological interventions for bipolar disorder  
23  
24 34 which also assessed childhood trauma. To be eligible for inclusion, studies must have been  
25  
26 35 conducted with adolescents or adults ( $\geq 10$  years). Data will be screened and extracted by two  
27  
28 36 independent reviewers. The methodological quality of the included studies will be assessed  
29  
30 37 with the Cochrane Collaboration's Risk of Bias tool and the Newcastle-Ottawa scale. If  
31  
32 38 deemed viable, a meta-analysis will be conducted using a random-effects model.  
33  
34 39 Heterogeneity of evidence will be estimated with the  $I^2$  statistics.  
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37 40 **Ethics and dissemination:** This systematic review will use only previously published data.  
38  
39 41 Therefore, ethical approval is not required. The results will be written in concordance with the  
40  
41 42 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines,  
42  
43 43 published in peer-reviewed journals, and presented at relevant conferences.  
44

45 44 **PROSPERO registration number:** CRD42020201891  
46

47 45  
48  
49 46 **Keywords:** bipolar disorder, childhood trauma, treatment outcomes, pharmacotherapy,  
50  
51 47 psychotherapy, systematic review, meta-analysis  
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3 48 **ARTICLE SUMMARY**  
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5 49 **Strengths and limitations of this study**  
6

- 7 50 • This will be the first systematic review to involve the critical evaluation of the influence of  
8 childhood trauma on the treatment outcomes of pharmacological and/or psychological  
9 51 interventions for adolescents and adults with bipolar disorder.  
10 52  
11 53 • The screening and data extraction process will be completed by two independent  
12 reviewers and reported according to PRISMA guidelines.  
13 54  
14 55 • Standardised methodological appraisal tools will be used to assess risk of bias of the  
15 studies included in the review.  
16 56  
17 57 • Heterogeneity of evidence is likely as inclusive study design criteria were set for the review.  
18 58  
19 59 • The systematic review may be limited by the lack of available evidence, precluding a meta-  
20 analysis from being conducted.  
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## 60 INTRODUCTION

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

71  
72 Childhood trauma is commonly reported by individuals with a diagnosis of bipolar disorder with  
73 prevalence rates as high as 50% being documented in various cross-sectional studies.<sup>17-19</sup> As  
74 an example, Sala et al.<sup>20</sup> analysed data collected from a large community sample and reported  
75 that 54.3% of adults with bipolar disorder also had a history of childhood trauma. Specifically,  
76 21.7% had experienced physical abuse, 26.0% sexual abuse, 38.4% emotional abuse, 13.6%  
77 physical neglect, and 14.7% emotional neglect. This high prevalence is noteworthy as  
78 experiences of childhood trauma have been recognised to affect the clinical presentation of  
79 several major psychiatric disorders including bipolar disorder.<sup>15 17 18 21</sup>

80  
81 In a comprehensive meta-analysis, Agnew-Blais and Danese<sup>22</sup> indicated an association  
82 between childhood trauma and more severe clinical characteristics of bipolar disorder.  
83 Broadly, the researchers reported that individuals with a history of childhood trauma were  
84 more likely to present with an earlier age at onset, rapid cycling, psychotic features, psychiatric  
85 comorbidities, suicide attempts, and a greater number of affective episodes. Agnew-Blais and  
86 Danese<sup>22</sup> further highlighted that childhood trauma was related to the experience of more  
87 severe manic, depressive, and psychotic symptoms among patients with bipolar disorder.

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5 89 The reviewers' findings are largely echoed in recent longitudinal studies. Andreu Pascual et  
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7 90 al.<sup>23</sup>, for example, prospectively followed a large group of young people with bipolar disorder.  
8  
9 91 The researchers demonstrated that the experience of at least one traumatic event in childhood  
10  
11 92 was related to an earlier symptom onset, more severe affective symptoms, greater suicidal  
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13 93 ideation, psychiatric comorbidities, and greater functional impairment. Additionally, Andreu  
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15 94 Pascual et al.<sup>23</sup> noted that people who were exposed to a traumatic event after achieving  
16  
17 95 symptomatic recovery, were more likely to experience an affective relapse.  
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22 97 Associations between the clinical presentation of bipolar disorder and specific types of  
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24 98 childhood trauma have also been reported. For instance, Etain et al.<sup>24</sup> implicated emotional  
25  
26 99 and sexual abuse as independent moderators of an earlier age at of onset as well as  
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28 100 individuals' history of suicide attempts. Maniglio<sup>25</sup> additionally summarised that sexual abuse  
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30 101 experienced in childhood was related to comorbid substance use disorders and the incidence  
31  
32 102 of psychotic symptoms. Due to the high prevalence of childhood trauma and its clear clinical  
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34 103 relevance, research has recently begun to focus on childhood trauma as a potential moderator  
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36 104 of treatment outcomes for both pharmacological and psychological interventions in bipolar  
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38 105 disorder.<sup>22 26</sup>  
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43 107 Cakir et al.<sup>27</sup> reported that experiences of emotional or physical abuse during childhood were  
44  
45 108 significantly related to inadequate response to long-term treatment with anticonvulsants  
46  
47 109 among outpatients with bipolar disorder. Etain et al.<sup>28</sup> indicated a similar association between  
48  
49 110 a history of childhood physical abuse and response to lithium treatment in euthymic bipolar  
50  
51 111 disorder patients. That is, greater exposure to physical abuse was inversely correlated with  
52  
53 112 participants' levels of response to lithium. In addition to the correlation with physical abuse,  
54  
55 113 the researchers demonstrated that participants who were exposed to multiple types of  
56  
57 114 childhood trauma were more likely to inadequately respond to lithium than participants without  
58  
59 115 a history of any childhood trauma.

116

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

125

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

134

135 As such, evidence supporting the differential treatment outcomes among people with bipolar  
136 disorder who were exposed to significant traumatic experiences in childhood remains  
137 contentious. Several potentially relevant mediators of this association have been suggested  
138 including treatment non-adherence,<sup>35-38</sup> difficulties with forming a therapeutic alliance,<sup>26 35 39</sup>  
139 insecure attachment styles,<sup>26 40 41</sup> and early maladaptive schemas (EMS),<sup>42-44</sup> though these  
140 factors have not yet been extensively investigated among survivors of childhood trauma who  
141 have a diagnosis of bipolar disorder.

142

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3 143 Additionally, a wide range of treatment outcomes have been considered in clinical research  
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5 144 on bipolar disorder. Although researchers have traditionally focused on outcomes related to  
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7 145 symptomatic and functional recovery, patients' personal recovery has increasingly received  
8  
9 146 attention.<sup>45</sup> Personal recovery is frequently conceptualised as the process an individual  
10  
11 147 undergoes to psychologically adapt to their disorder; a definition that expands patients'  
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13 148 recovery beyond the reduction of psychiatric symptoms and impairments in functioning.<sup>45 46</sup>  
14  
15 149 The evaluation of treatment outcomes that capture the experiences of the individual more  
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17 150 broadly is encouraged as some patients continue to report significant impairments in  
18  
19 151 functioning and QoL even though they only have relatively mild symptoms.<sup>45</sup> Hence, symptom  
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21 152 measures alone appear to be inadequate in assessing treatment effectiveness in bipolar  
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23 153 disorder.  
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27  
28 155 To date, there has been no systematic reviews focusing on the influence of childhood trauma  
29  
30 156 on the treatment outcomes of pharmacological, psychological, and combined interventions for  
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32 157 adolescents and adults with bipolar disorder. This is despite current research demonstrating  
33  
34 158 that experiences of childhood trauma may be highly relevant to the efficacy of treatments for  
35  
36 159 bipolar disorder.<sup>47-49</sup> Research that aims to improve the prediction of treatment outcomes can  
37  
38 160 greatly benefit patients with psychiatric disorders as this knowledge may reduce the burden  
39  
40 161 associated with receiving inappropriate and/or suboptimal treatments and decrease patients'  
41  
42 162 risk of experiencing a chronic illness course.<sup>50</sup>  
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46  
47 164 Exploring the influence of exposure to childhood trauma on patients' treatment outcomes may  
48  
49 165 thus assist the development of individualised interventions for people with bipolar disorder,  
50  
51 166 promoting treatment success and ultimately facilitating recovery.<sup>26 47</sup> Clarification on the role  
52  
53 167 that childhood trauma plays in the treatment of bipolar disorder has clear translational value  
54  
55 168 with the potential to inform clinical guidelines and practice. A systematic exploration of the  
56  
57 169 available evidence is particularly suitable for this endeavour because it allows for data to be  
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170 collated from a variety of sources and illustrate areas of research that are underscored by a  
171 limited number of patients and/or conflicting evidence.

172

## 173 **OBJECTIVES**

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

180

## 181 **METHODS AND ANALYSIS**

### 182 **Eligibility criteria**

183 Relevant studies will be identified according to the following criteria:

184

#### 185 Types of participants

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

193

194 To be considered, studies must have confirmed participants' diagnosis of bipolar disorder  
195 either through a structured or semi-structured diagnostic interview such as the Structured  
196 Clinical Interview for DSM (SCID),<sup>52</sup> the MINI International Neuropsychiatric Interview  
197 (M.I.N.I.),<sup>53</sup> and the Child and Adolescent Psychiatric Assessment (CAPA)<sup>54</sup> or through

1  
2  
3 198 psychiatrist judgement, including in chart review. No restrictions will be placed on the setting  
4  
5 199 of the studies; both in-patient and out-patient samples will be eligible.  
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9 201 Studies also including children ( $\leq 10$  years) will only be eligible if the mean age of the sample  
10  
11 202 is  $\geq 10$  years or the data for adolescent and adult participants are separately available.  
12  
13 203 Additionally, studies that were conducted in heterogeneous clinical populations will only be  
14  
15 204 included if more than 80% of the sample had bipolar disorder or the data for participants with  
16  
17 205 bipolar disorder are separately available. However, studies that were conducted in populations  
18  
19 206 exclusively consisting of individuals who were exposed to childhood trauma will be excluded.  
20  
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22 207

#### 23 24 208 Types of studies

25  
26 209 To allow for a comprehensive evaluation of the available evidence,<sup>55</sup> broad design criteria will  
27  
28 210 be implemented. Both randomised and non-randomised studies of pharmacological and/or  
29  
30 211 psychological interventions for bipolar disorder which included an assessment of childhood  
31  
32 212 trauma will be eligible. Randomised controlled trials (RCTs), cluster RCTs, cross-over trials,  
33  
34 213 controlled (non-randomised) trials, one-arm trials, interrupted time series (ITS) studies,  
35  
36 214 controlled before-after (CBA) studies, uncontrolled before-after studies, cohort studies, case-  
37  
38 215 control and cross-sectional studies with quantitative data will be included. Case series, case  
39  
40 216 reports, and purely qualitative studies will be excluded.  
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#### 44 45 218 Types of exposure measures

46  
47 219 For the purpose of this review, childhood trauma is defined in the form of maltreatment and  
48  
49 220 includes physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional  
50  
51 221 neglect experienced during childhood and early adolescence ( $\leq 18$  years). Participants' history  
52  
53 222 of childhood trauma may be assessed with validated measures such as the Childhood Trauma  
54  
55 223 Questionnaire (CTQ)<sup>56</sup> or indicated through clinician interviews. Studies that assessed  
56  
57 224 childhood trauma via in chart review will also be eligible. Additionally, studies that considered  
58  
59 225 both childhood trauma and adulthood trauma will be included if the data for childhood trauma  
60

226 are separately available. Studies that exclusively assessed trauma experienced in adulthood  
227 ( $\geq 18$  years), will be excluded from the review.

228

229 Types of interventions

230 Included in the review will be any pharmacological and/or psychological interventions  
231 administered for the management of bipolar disorder. Pharmacological interventions include,  
232 but are not limited to, mood stabilisers, antidepressants, antipsychotics, and antiepileptics.  
233 Psychological interventions refer, for instance, to psychoeducation, cognitive behavioural  
234 therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and family-focused therapy  
235 (FFT). Combined treatment approaches (e.g., pharmacological and adjunctive psychological  
236 interventions) will also be considered. Studies that exclusively investigated lifestyle  
237 interventions, however, will be excluded from this review.

238

239 Types of outcome measures

240 *Primary outcome – mean reduction in symptom severity*

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

246

247 *Secondary outcomes – related to symptomatic recovery*

248 1. Treatment response as defined by either:

249 a. a reduction of 50% (or greater) on the YMRS, the MADRS, or any other validated scale  
250 assessing manic or depressive symptoms; or

251 b. a score of 1 (very much improved) or 2 (much improved) on the Clinical Global  
252 Impression – Improvement (CGI-I)<sup>59 60</sup> scale; or

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



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3 254 2. Symptomatic remission as defined by either:  
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5 255 a. a score of  $\leq 12$  on the YMRS;<sup>61-63</sup> or  
6  
7 256 b. a score of  $\leq 10$  on the MADRS;<sup>64 65</sup> or  
8  
9 257 c. a score of 1 (normal, not at all ill) or 2 (borderline mentally ill) on the Clinical Global  
10  
11 258 Impression – Severity (CGI-S)<sup>59 60</sup> scale; or  
12  
13 259 d. other criteria specifying remission as defined by the study authors.  
14  
15 260 3. Relapse/recurrence defined as a new affective episode according to the DSM or ICD  
16  
17 261 criteria and/or by:<sup>66-70</sup>  
18  
19 262 a. a score of  $\geq 12$  on the YMRS indicating a hypomanic recurrence;  
20  
21 263 b. a score of  $\geq 20$  on the YMRS indicating a manic recurrence;  
22  
23 264 c. a score of  $\geq 22$  on the MADRS indicating a depressive recurrence;  
24  
25 265 d. a score of  $\geq 20$  on the YMRS and a score of  $\geq 22$  on the MADRS indicating a mixed  
26  
27 266 recurrence; or  
28  
29 267 e. other criteria specifying relapse/recurrence as defined by the study authors.  
30  
31  
32  
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34

35 269 *Secondary outcomes – related to functional and personal recovery*

- 36  
37 270 1. Improvement in global functioning as defined by change scores from baseline to end of  
38  
39 271 treatment on the Global Assessment of Functioning (GAF)<sup>71</sup> scale or any other validated  
40  
41 272 scale assessing functioning.  
42  
43 273 2. Improvement in QoL as defined by change scores from baseline to end of treatment on  
44  
45 274 the Quality of Life in Bipolar Disorder-Brief (QoL.BD-Brief)<sup>72</sup> scale or any other validated  
46  
47 275 scale assessing QoL.  
48  
49  
50

51 277 **Types of publications**

52  
53 278 This review will be restricted to studies reported in English and published in peer-reviewed  
54  
55 279 journals.  
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57

58 280

59  
60 281 **Information sources and search strategy**

1  
2  
3 282 MEDLINE Complete via Ebsco, Embase via embase.com, PsycINFO via Ebsco, and the  
4  
5 283 Cochrane Central Register of Controlled Trials (CENTRAL) via cochranelibrary.com will be  
6  
7 284 searched from database inception to December 2020 to identify relevant studies. The specific  
8  
9 285 search strategies were developed using standardised subject terms (e.g., medical subject  
10  
11 286 headings [MeSH] terms, Emtree terms) and keywords related to bipolar disorder, childhood  
12  
13 287 trauma, and pharmacological or psychological interventions. The PICO (Population,  
14  
15 288 Intervention, Comparison, Outcome) framework was used to develop the search terms. The  
16  
17 289 standardised subject terms were tailored to each individual database and truncation and  
18  
19 290 wildcards were applied as appropriate. Drafts of the search strategies for each database are  
20  
21 291 reported in online supplementary file 1.  
22  
23  
24  
25

26 293 The studies identified in the database searches will be checked against the eligibility criteria  
27  
28 294 outlined above. First, the titles and abstracts will be independently screened by two reviewers.  
29  
30 295 Subsequently, two reviewers will retrieve and assess the full texts of studies that appear  
31  
32 296 eligible for the review. Reasons for the exclusion of studies will be recorded. Discrepancies  
33  
34 297 between the reviewers will be discussed and assessed by a third author, if necessary. The  
35  
36 298 original study authors will be contacted for additional information if outcomes of interest are  
37  
38 299 not reported. Finally, the database searches will be supplemented by reviewing the reference  
39  
40 300 lists of all included publications for additional studies. Prior to the final data analysis, the  
41  
42 301 searches will be re-run to allow for the inclusion of newly published studies.  
43  
44  
45  
46

### 47 303 **Data management and extraction**

48  
49 304 The online reference management database Covidence<sup>73</sup> will be used to manage the records  
50  
51 305 during the review process. Covidence allows for publication screening, handling of duplicate  
52  
53 306 records, evaluation of risk of bias, and extraction of study characteristics and outcomes  
54  
55 307 according to the eligibility criteria. The following data will be independently extracted by two  
56  
57 308 reviewers:  
58  
59

60 309 1. Study characteristics (e.g., study author, year of publication)

- 310 2. Study design (e.g., randomised, non-randomised)
- 311 3. Sample characteristics (e.g., N, country/ies, setting)
- 312 4. Participant characteristics (e.g., mean age, %female, diagnoses)
- 313 5. Diagnostic assessment (e.g., assessment tool)
- 314 6. Clinical features (e.g., age at onset, %rapid cycling, number of episodes, number of suicide  
315 attempts)
- 316 7. Childhood trauma assessment (e.g., definition, assessment tool)
- 317 8. Exposure details (e.g., n exposed, trauma types, time of exposure)
- 318 9. Treatment characteristics (e.g., type, dose, duration, number of sessions)
- 319 10. Outcome assessment (e.g., definition, assessment tool)
- 320 11. Results (e.g., reported inferential statistics, confidence intervals, effect sizes)

321

### 322 **Assessment of methodological quality**

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

330

331 For non-randomised studies of interventions, the Newcastle-Ottawa Scale (NOS)<sup>76</sup> will be  
332 used. When using the NOS, studies can be awarded a maximum of nine stars depending on  
333 sample selection, comparability of groups, and assessment of exposure or outcome. Where  
334 needed, the quality assessment with the NOS will be supplemented by using the critical  
335 appraisal tools developed by the Joanna Briggs Institute (JBI).<sup>77</sup> The quality assessments  
336 (both for randomised and non-randomised studies) will be completed by two independent  
337 reviewers.

338

339 The Grading of Recommendation, Assessment, Development and Evaluation (GRADE)<sup>78</sup>

340 approach will be used to assess the quality of evidence for each of the outcomes. In the

341 GRADE approach, the quality of evidence is rated across all identified studies resulting in one

342 of four grades: high, moderate, low, very low (table 1). As a rule of thumb, evidence from

343 randomised trials is of high quality whereas evidence from non-randomised studies of

344 interventions is of low quality.<sup>78</sup> However, the quality of evidence can be rated down due to

345 risk of bias, inconsistency of results, indirectness of evidence, imprecision, or publication

346 bias.<sup>78</sup> The quality of evidence can be rated up if studies report a large magnitude of effect or

347 a clear dose-response gradient or in situations where all residual confounding would decrease

348 the indicated effect.<sup>78</sup>

349

**Table 1** Quality of Evidence Grades as stipulated in the GRADE handbook<sup>78</sup>

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.

350

### 351 **Data synthesis and statistical analysis**

352 For each of the outcomes included in the review, the results will be synthesised using

353 tabulation and visual displays via forest plots, as appropriate. Randomised trials and non-

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

355 treatment type (pharmacological, psychological, combination). A narrative evaluation of these

1  
2  
3 356 results will additionally be provided. The following will be calculated if sufficient data are  
4  
5 357 available:

6  
7 358

8  
9 359 For categorical outcome variables, risk ratios (RR) or odds ratios (OR) with 95% confidence  
10  
11 360 intervals will be calculated. For continuous outcome variables, mean differences or  
12  
13 361 standardised mean differences with 95% confidence intervals will be calculated. Mean  
14  
15 362 differences will be utilised when the studies included in the review measured treatment  
16  
17 363 outcomes with the same scale. Standardised mean differences will be utilised when the  
18  
19 364 studies included in the review measured treatment outcomes with different scales.

20  
21  
22 365

23  
24 366 Heterogeneity of evidence will be determined with Higgins  $I^2$  statistics calculations. If  
25  
26 367 substantial heterogeneity between the studies is indicated ( $I^2 \geq 50\%$ ),<sup>74 79</sup> possible reasons for  
27  
28 368 the variability will be considered by analysing the characteristics of the studies included. If  
29  
30 369 meta-analyses are deemed sensible based on the heterogeneity analysis, a random-effects  
31  
32 370 model will be used. All statistical analyses will be conducted with the software Comprehensive  
33  
34 371 Meta-Analysis (CMA).<sup>80</sup>

35  
36  
37 372

38  
39 373 As per guidelines from the Cochrane Handbook for Systematic Reviews of Interventions 6.0,<sup>74</sup>  
40  
41 374 randomised trials and non-randomised studies of interventions will not be combined in one  
42  
43 375 meta-analysis. Instead, randomised trials and non-randomised studies will be separately  
44  
45 376 analysed. Additionally, non-randomised studies of interventions that were judged to have a  
46  
47 377 high risk of bias will be excluded from the meta-analysis.<sup>74</sup> For any meta-analyses with  $\geq 10$   
48  
49 378 studies, funnel plot asymmetry will be evaluated and possible explanations for the asymmetry  
50  
51 379 considered (e.g., publication bias), if applicable.<sup>74</sup>

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54 380

### 55 381 **Subgroup analyses**

56  
57 382 Where substantial heterogeneity is indicated ( $I^2 \geq 50\%$ ) and sufficient data are available,  
58  
59 383 subgroup and meta-regression analyses will be performed to explore potential effect

1  
2  
3 384 modifiers. Individual subgroup analyses will be conducted for the following categorical  
4  
5 385 variables: trauma type (physical, sexual, emotional); treatment type (pharmacological,  
6  
7 386 psychological, combination); and demographic features (age group [adolescent, adult  
8  
9 387 sample]). Meta-regression analyses will be conducted for continuous variables describing  
10  
11 388 participants' clinical (age at onset [mean years], rapid cycling [%rapid cycling], number of  
12  
13 389 episodes, number of suicide attempts) and demographic features (age [mean years], gender  
14  
15 [%female]). Other subgroups may be identified where necessary. Sensitivity analyses will be  
16 390 completed to determine the robustness of the meta-analyses.  
17  
18 391  
19  
20 392

### 21 22 393 **Presentation and reporting of results**

23  
24 394 This systematic review will be reported following the Preferred Reporting Items for Systematic  
25  
26 395 Review and Meta-Analysis (PRISMA) guidelines.<sup>81</sup> In accordance with the PRISMA  
27  
28 396 guidelines, the study selection process will be detailed in a flowchart, including number of  
29  
30 397 studies excluded at each stage of the review and reasons for exclusion. The Preferred  
31  
32 398 Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist  
33  
34 399 can be found in online supplementary file 2.  
35  
36  
37 400

### 38 39 401 **Ethics and dissemination**

40  
41 402 Only previously published data will be used in this systematic review; hence, ethical approval  
42  
43 403 is not required. This review was registered with the International Prospective Register of  
44  
45 404 Systematic Reviews (PROSPERO) on the 31<sup>st</sup> of August 2020 (CRD42020201891). The  
46  
47 405 findings will be published in peer-reviewed journals and presented at relevant conferences.  
48  
49 406 Multiple publications may be derived from this protocol.  
50  
51  
52 407

### 53 54 408 **Patient and public involvement**

55  
56 409 This research was done without patient involvement. Patients were not invited to comment on  
57  
58 410 the study design and were not consulted to develop patient relevant outcomes or interpret the  
59  
60

1  
2  
3 411 results. Patients were not invited to contribute to the writing or editing of this document for  
4  
5 412 readability or accuracy.  
6

7 413

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12

13 416

14  
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16  
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18  
19 419 developed the research question, revised the search strategy and edited and approved the  
20  
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48  
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50  
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58  
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60

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3 439 Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary  
4  
5 440 Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry  
6  
7 441 Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and  
8  
9 442 served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative  
10  
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16  
17 446 University of Newcastle and Deakin University.  
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20 447

21  
22 448 **Patient and public involvement:** Patients or the public were not involved in the design, or  
23  
24 449 conduct, or reporting, or dissemination plans of this research.  
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56  
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60



450 **REFERENCES**

- 451 1. Grande I, Berk M, Birmaher B, et al. Bipolar disorder. *The Lancet* 2016;387:1561-72. doi:  
452 10.1016/s0140-6736(15)00241-x
- 453 2. Chu CS, Stubbs B, Chen TY, et al. The effectiveness of adjunct mindfulness-based  
454 intervention in treatment of bipolar disorder: A systematic review and meta-analysis.  
455 *Journal of Affective Disorders* 2018;225:234-45. doi: 10.1016/j.jad.2017.08.025  
456 [published Online First: 2017/08/26]
- 457 3. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *The Lancet*  
458 2020;396(10265):1841-56. doi: [https://doi.org/10.1016/S0140-6736\(20\)31544-0](https://doi.org/10.1016/S0140-6736(20)31544-0)
- 459 4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders  
460 (5th ed.): Arlington, VA: Author 2013.
- 461 5. Simon GE, Bauer MS, Ludman EJ, et al. Mood symptoms, functional impairment, and  
462 disability in people with bipolar disorder: specific effects of mania and depression.  
463 *Journal of Clinical Psychiatry* 2007;68:1237-45. doi: 10.4088/jcp.v68n0811
- 464 6. Lee EJ, Hower H, Jones RN, et al. Course of longitudinal psychosocial functioning in bipolar  
465 youth transitioning to adults. *Journal of Affective Disorders* 2020;268:109-17. doi:  
466 <https://doi.org/10.1016/j.jad.2020.03.016>
- 467 7. Maripuu M, Norrback K-F, Adolfsson R. Quality of life for patients diagnosed with bipolar  
468 disorder: Lifestyle and treatment. *Neurology, Psychiatry and Brain Research*  
469 2019;34:34-40. doi: <https://doi.org/10.1016/j.npbr.2019.09.002>
- 470 8. Morton E, Murray G, Michalak EE, et al. Quality of life in bipolar disorder: towards a dynamic  
471 understanding. *Psychol Med* 2018;48(7):1111-18. doi: 10.1017/s0033291717002495  
472 [published Online First: 2017/09/19]
- 473 9. Pascual-Sánchez A, Jenaro C, Montes-Rodríguez JM. Quality of life in euthymic bipolar  
474 patients: A systematic review and meta-analysis. *J Affect Disord* 2019;255:105-15. doi:  
475 10.1016/j.jad.2019.05.032 [published Online First: 2019/06/01]
- 476 10. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective  
477 episodes in bipolar disorders and rapid episode relapse/recurrence. *Arch Gen*

- 1  
2  
3 478 *Psychiatry* 2008;65(4):386-94. doi: 10.1001/archpsyc.65.4.386 [published Online First:  
4  
5 479 2008/04/09]  
6  
7 480 11. Meyer TD, Hautzinger M. Cognitive behaviour therapy and supportive therapy for bipolar  
8  
9 481 disorders: Relapse rates for treatment period and 2-year follow-up. *Psychological*  
10  
11 482 *Medicine* 2012;42:1429–39. doi: 10.1017/S0033291711002522  
12  
13 483 12. Simhandl C, Konig B, Amann BL. A prospective 4-year naturalistic follow-up of treatment  
14  
15 484 and outcome of 300 bipolar I and II patients. *Journal of Clinical Psychiatry*  
16  
17 485 2014;75:254–62. doi: 10.4088/JCP.13m08601  
18  
19 486 13. Simhandl C, Radua J, Konig B, et al. The prevalence and effect of life events in 222 bipolar  
20  
21 487 I and II patients: A prospective, naturalistic 4 year follow-up study. *Journal of Affective*  
22  
23 488 *Disorders* 2015;170:166-71. doi: 10.1016/j.jad.2014.08.043 [published Online First:  
24  
25 489 2014/09/23]  
26  
27 490 14. Gignac A, McGirr A, Lam RW, et al. Course and outcome following a first episode of mania:  
28  
29 491 four-year prospective data from the Systematic Treatment Optimization Program  
30  
31 492 (STOP-EM). *J Affect Disord* 2015;175:411-17. doi: 10.1016/j.jad.2015.01.032  
32  
33 493 [published Online First: 2015/02/14]  
34  
35 494 15. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of  
36  
37 495 bipolar disorder. *Psychiatry and Clinical Neurosciences* 2017;71:6-17. doi:  
38  
39 496 10.1111/pcn.12433 [published Online First: 2016/08/09]  
40  
41 497 16. Palmier-Claus JE, Berry K, Bucci S, et al. Relationship between childhood adversity and  
42  
43 498 bipolar affective disorder: Systematic review and meta-analysis. *The British Journal of*  
44  
45 499 *Psychiatry* 2016;209:454-59. doi: 10.1192/bjp.bp.115.179655 [published Online First:  
46  
47 500 2016/10/21]  
48  
49 501 17. Alvarez MJ, Roura P, Oses A, et al. Prevalence and clinical impact of childhood trauma in  
50  
51 502 patients with severe mental disorders. *The Journal of Nervous and Mental Disease*  
52  
53 503 2011;199:156-61. doi: 10.1097/NMD.0b013e31820c751c [published Online First:  
54  
55 504 2011/02/25]  
56  
57  
58  
59  
60

- 1  
2  
3 505 18. Garno JL, Goldberg JF, Ramirez PM, et al. Impact of childhood abuse on the clinical  
4  
5 506 course of bipolar disorder. *British Journal of Psychiatry* 2005;186 doi:  
6  
7 507 10.1192/bjp.186.2.121  
8  
9 508 19. Jansen K, Cardoso TA, Fries GR, et al. Childhood trauma, family history, and their  
10  
11 509 association with mood disorders in early adulthood. *Acta Psychiatrica Scandinavica*  
12  
13 510 2016;134:281-86. doi: 10.1111/acps.12551 [published Online First: 2016/01/31]  
14  
15 511 20. Sala R, Goldstein BI, Wang S, et al. Childhood maltreatment and the course of bipolar  
16  
17 512 disorders among adults: Epidemiologic evidence of dose-response effects. *Journal of*  
18  
19 513 *Affective Disorders* 2014;165:74-80. doi: 10.1016/j.jad.2014.04.035 [published Online  
20  
21 514 First: 2014/06/03]  
22  
23 515 21. Jaworska-Andryszewska P, Rybakowski JK. Childhood trauma in mood disorders:  
24  
25 516 Neurobiological mechanisms and implications for treatment. *Pharmacological Reports*  
26  
27 517 2019;71:112-20. doi: 10.1016/j.pharep.2018.10.004 [published Online First:  
28  
29 518 2018/12/14]  
30  
31 519 22. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in  
32  
33 520 bipolar disorder: a systematic review and meta-analysis. *The Lancet Psychiatry*  
34  
35 521 2016;3:342-49. doi: 10.1016/s2215-0366(15)00544-1  
36  
37 522 23. Andreu Pascual M, Levenson JC, Merranko J, et al. The Effect of Traumatic Events on the  
38  
39 523 Longitudinal Course and Outcomes of Youth with Bipolar Disorder. *Journal of Affective*  
40  
41 524 *Disorders* 2020;274:126-35. doi: <https://doi.org/10.1016/j.jad.2020.05.131>  
42  
43 525 24. Etain B, Aas M, Andreassen OA, et al. Childhood trauma is associated with severe clinical  
44  
45 526 characteristics of bipolar disorders. *Journal of Clinical Psychiatry* 2013;74:991-98. doi:  
46  
47 527 10.4088/JCP.13m08353 [published Online First: 2013/11/16]  
48  
49 528 25. Maniglio R. The impact of child sexual abuse on the course of bipolar disorder: A  
50  
51 529 systematic review. *Bipolar Disorders* 2013;15:341-58. doi: 10.1111/bdi.12050  
52  
53 530 [published Online First: 2013/01/26]  
54  
55 531 26. Cotter J, Kaess M, Yung AR. Childhood trauma and functional disability in psychosis,  
56  
57 532 bipolar disorder and borderline personality disorder: A review of the literature. *Irish*

- 1  
2  
3 533 *Journal of Psychological Medicine* 2015;32:21-30. doi: 10.1017/ipm.2014.74  
4  
5 534 [published Online First: 2015/03/01]  
6  
7 535 27. Cakir S, Tasdelen Durak R, Ozyildirim I, et al. Childhood trauma and treatment outcome  
8  
9 536 in bipolar disorder. *Journal of Trauma and Dissociation* 2016;17:397-409. doi:  
10 537 10.1080/15299732.2015.1132489 [published Online First: 2015/12/20]  
11  
12  
13 538 28. Etain B, Lajnef M, Brichant-Petitjean C, et al. Childhood trauma and mixed episodes are  
14  
15 539 associated with poor response to lithium in bipolar disorders. *Acta Psychiatrica*  
16  
17 540 *Scandinavica* 2017;135:319-27. doi: 10.1111/acps.12684 [published Online First:  
18  
19 541 2016/12/18]  
20  
21  
22 542 29. McIntyre RS, Subramaniapillai M, Lee Y, et al. Efficacy of adjunctive infliximab vs placebo  
23  
24 543 in the treatment of adults with bipolar I/II depression: A randomized clinical trial. *JAMA*  
25  
26 544 *Psychiatry* 2019;76:783-90. doi: 10.1001/jamapsychiatry.2019.0779 [published  
27  
28 545 Online First: 2019/05/09]  
29  
30  
31 546 30. Berk M, Walker AJ, Nierenberg AA. Biomarker-guided anti-inflammatory therapies: from  
32  
33 547 promise to reality check. *JAMA Psychiatry* 2019;76:779-80. doi:  
34  
35 548 10.1001/jamapsychiatry.2019.0673  
36  
37 549 31. Lippard ETC, Nemeroff CB. The devastating clinical consequences of child abuse and  
38  
39 550 neglect: Increased disease vulnerability and poor treatment response in mood  
40  
41 551 disorders. *The American Journal of Psychiatry* 2020;177:20-36. doi:  
42  
43 552 10.1176/appi.ajp.2019.19010020 [published Online First: 2019/09/21]  
44  
45 553 32. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of  
46  
47 554 Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*  
48  
49 555 2015;49(12):1087-206. doi: 10.1177/0004867415617657 [published Online First:  
50  
51 556 2015/12/09]  
52  
53  
54 557 33. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety  
55  
56 558 Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018  
57  
58 559 guidelines for the management of patients with bipolar disorder. *Bipolar disorders*  
59  
60 560 2018;20:97-170. doi: 10.1111/bdi.12609 [published Online First: 2018/03/14]

- 1  
2  
3 561 34. Conus P, Cotton S, Schimmelmann BG, et al. Pretreatment and outcome correlates of  
4  
5 562 past sexual and physical trauma in 118 bipolar I disorder patients with a first episode  
6  
7 563 of psychotic mania. *Bipolar Disorders* 2010;12:244-52. doi: 10.1111/j.1399-  
8  
9 564 5618.2010.00813.x [published Online First: 2010/06/23]
- 11 565 35. Lawson DM, Davis D, Brandon S. Treating complex trauma: critical interventions with  
12  
13 566 adults who experienced ongoing trauma in childhood. *Psychotherapy (Chic)*  
14  
15 567 2013;50:331-35. doi: 10.1037/a0032677 [published Online First: 2013/09/05]
- 17 568 36. Lecomte T, Spidel A, Leclerc C, et al. Predictors and profiles of treatment non-adherence  
18  
19 569 and engagement in services problems in early psychosis. *Schizophrenia Research*  
20  
21 570 2008;102:295-302. doi: 10.1016/j.schres.2008.01.024 [published Online First:  
22  
23 571 2008/02/26]
- 25 572 37. Spidel A, Greaves C, Yuille J, et al. A comparison of treatment adherence in individuals  
26  
27 573 with a first episode of psychosis and inpatients with psychosis. *International Journal of*  
28  
29 574 *Law and Psychiatry* 2015;39:90-98. doi: 10.1016/j.ijlp.2015.01.026 [published Online  
30  
31 575 First: 2015/02/24]
- 33 576 38. Rakofsky JJ, Levy ST, Dunlop BW. Conceptualizing treatment nonadherence in patients  
34  
35 577 with bipolar disorder and PTSD. *CNS Spectrums* 2011;16:11-20. doi:  
36  
37 578 10.1017/S1092852912000119 [published Online First: 2011/01/01]
- 39 579 39. Lafrenaye-Dugas AJ, Godbout N, Hebert M. Cumulative childhood trauma and therapeutic  
40  
41 580 alliance: The moderator role of attachment in adult patients consulting in sex therapy.  
42  
43 581 *Journal of Sex & Marital Therapy* 2018;44:667-78. doi:  
44  
45 582 10.1080/0092623X.2018.1447057 [published Online First: 2018/03/06]
- 47 583 40. Cotter J, Yung AR. Exploring the impact of adverse childhood experiences on symptomatic  
48  
49 584 and functional outcomes in adulthood: Advances, limitations and considerations. *Irish*  
50  
51 585 *Journal of Psychological Medicine* 2018;35:5-7. doi: 10.1017/ipm.2017.53 [published  
52  
53 586 Online First: 2017/10/18]
- 55 587 41. Gumley AI, Taylor HE, Schwannauer M, et al. A systematic review of attachment and  
56  
57 588 psychosis: Measurement, construct validity and outcomes. *Acta Psychiatrica*

- 1  
2  
3 589 *Scandinavica* 2014;129:257-74. doi: 10.1111/acps.12172 [published Online First:  
4  
5 590 2013/07/10]  
6  
7 591 42. Nordahl HM, Holthe H, Haugum JA. Early maladaptive schemas in patients with or without  
8  
9 592 personality disorders: does schema modification predict symptomatic relief? *Clinical*  
10  
11 593 *Psychology & Psychotherapy* 2005;12:142-49. doi: 10.1002/cpp.430  
12  
13 594 43. van Vreeswijk MF, Spinhoven P, Eurelings-Bontekoe EH, et al. Changes in symptom  
14  
15 595 severity, schemas and modes in heterogeneous psychiatric patient groups following  
16  
17 596 short-term schema cognitive-behavioural group therapy: A naturalistic pre-treatment  
18  
19 597 and post-treatment design in an outpatient clinic. *Clinical Psychology & Psychotherapy*  
20  
21 598 2014;21:29-38. doi: 10.1002/cpp.1813 [published Online First: 2012/08/31]  
22  
23 599 44. Özdin S, Sarisoy G, Şahin AR, et al. Early maladaptive schemas in patients with bipolar  
24  
25 600 and unipolar disorder. *International Journal of Psychiatry in Clinical Practice*  
26  
27 601 2018;22:151-56. doi: 10.1080/13651501.2017.1387268  
28  
29 602 45. Murray G, Leitan ND, Thomas N, et al. Towards recovery-oriented psychosocial  
30  
31 603 interventions for bipolar disorder: Quality of life outcomes, stage-sensitive treatments,  
32  
33 604 and mindfulness mechanisms. *Clinical Psychology Review* 2017;52:148-63. doi:  
34  
35 605 10.1016/j.cpr.2017.01.002 [published Online First: 2017/01/28]  
36  
37 606 46. Cavelti M, Kvrđic S, Beck EM, et al. Assessing recovery from schizophrenia as an  
38  
39 607 individual process. A review of self-report instruments. *European Psychiatry*  
40  
41 608 2012;27:19-32. doi: 10.1016/j.eurpsy.2011.01.007 [published Online First:  
42  
43 609 2011/12/02]  
44  
45 610 47. Aas M, Henry C, Andreassen OA, et al. The role of childhood trauma in bipolar disorders.  
46  
47 611 *International Journal of Bipolar Disorder* 2016;4:2-10. doi: 10.1186/s40345-015-0042-  
48  
49 612 0 [published Online First: 2016/01/15]  
50  
51 613 48. Maes M, Congio A, Moraes JB, et al. Early life trauma predicts affective phenomenology  
52  
53 614 and the effects are partly mediated by staging coupled with lowered lipid-associated  
54  
55 615 antioxidant defences. *Biomol Concepts* 2018;9:115-30. doi: 10.1515/bmc-2018-0010  
56  
57 616 [published Online First: 2018/11/25]  
58  
59  
60

- 1  
2  
3 617 49. Ventimiglia I, Van der Watt ASJ, Kidd M, et al. Association between trauma exposure and  
4  
5 618 mood trajectories in patients with mood disorders. *Journal of Affective Disorders*  
6  
7 619 2020;262:237-46. doi: 10.1016/j.jad.2019.10.057 [published Online First: 2019/11/14]  
8  
9 620 50. McMahon FJ. Prediction of treatment outcomes in psychiatry-where do we stand ?  
10  
11 621 *Dialogues Clin Neurosci* 2014;16:455-64. doi: 10.31887/DCNS.2014.16.4/fmcmahon  
12  
13 622 51. Organization. WH. Health for the world's adolescents: a second chance in the second  
14  
15 623 decade. Geneva: World Health Organization, 2014.  
16  
17 624 52. First MB, Williams, J. B. W, Karg, R. S., Spitzer, R. L. Structured Clinical Interview for  
18  
19 625 DSM-5 - Research Version. Arlington, VA: American Psychiatric Association, 2015.  
20  
21 626 53. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric  
22  
23 627 Interview (M.I.N.I.): the development and validation of a structured diagnostic  
24  
25 628 psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 Suppl 20:22-  
26  
27 629 33;quiz 34-57. [published Online First: 1999/01/09]  
28  
29 630 54. Angold A, Costello EJ. A test-retest reliability study of child-reported psychiatric symptoms  
30  
31 631 and diagnoses using the Child and Adolescent Psychiatric Assessment (CAPA-C).  
32  
33 632 *Psychol Med* 1995;25(4):755-62. doi: 10.1017/s0033291700034991 [published Online  
34  
35 633 First: 1995/07/01]  
36  
37 634 55. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic reviews of effectiveness.  
38  
39 635 In: Aromataris E, Munn Z, eds. Joanna Briggs Institute Reviewer's Manual: The Joanna  
40  
41 636 Briggs Institute, 2017.  
42  
43 637 56. Bernstein DP, Fink L, Handelsman L, et al. Initial reliability and validity of a new  
44  
45 638 retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*  
46  
47 639 1994;151:1132-36. doi: 10.1176/ajp.151.8.1132 [published Online First: 1994/08/01]  
48  
49 640 57. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: Reliability, validity and  
50  
51 641 sensitivity. *The British Journal of Psychiatry* 1978;133:429-35. doi:  
52  
53 642 10.1192/bjp.133.5.429 [published Online First: 1978/11/01]  
54  
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3 643 58. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change.  
4  
5 644 *The British Journal of Psychiatry* 1979;134:382-89. doi: 10.1192/bjp.134.4.382  
6  
7 645 [published Online First: 1979/04/01]  
8  
9 646 59. Spearing MK, Post RM, Leverich GS, et al. Modification of the clinical global impressions  
10  
11 647 (CGI) scale for use in bipolar illness (BP): The CGI-BP. *Psychiatry Research*  
12  
13 648 1997;73:159-71. doi: 10.1016/s0165-1781(97)00123-6 [published Online First:  
14  
15 649 1998/03/03]  
16  
17 650 60. Guy W. Clinical Global Impressions - ECDEU Assessment Manual for  
18  
19 651 Psychopharmacology Revised (DHEW Publ No ADM 76-338). Rockville, MD: National  
20  
21 652 Institute of Mental Health 1976.  
22  
23 653 61. Patel NC, Patrick DM, Youngstrom EA, et al. Response and remission in adolescent  
24  
25 654 mania: Signal detection analyses of the young mania rating scale. *Journal of the*  
26  
27 655 *American Academy of Child & Adolescent Psychiatry* 2007;46(5):628-35. doi:  
28  
29 656 10.1097/chi.0b013e3180335ae4  
30  
31 657 62. Masand PS, Eudicone J, Pikalov A, et al. Criteria for defining symptomatic and sustained  
32  
33 658 remission in bipolar I disorder: a post-hoc analysis of a 26-week aripiprazole study  
34  
35 659 (study CN138-010). *Psychopharmacol Bull* 2008;41(2):12-23. [published Online First:  
36  
37 660 2008/08/01]  
38  
39 661 63. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a  
40  
41 662 double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. *Arch Gen*  
42  
43 663 *Psychiatry* 2000;57(9):841-9. doi: 10.1001/archpsyc.57.9.841 [published Online First:  
44  
45 664 2000/09/15]  
46  
47 665 64. Hawley CJ, Gale TM, Sivakumaran T. Defining remission by cut off score on the MADRS:  
48  
49 666 selecting the optimal value. *J Affect Disord* 2002;72(2):177-84. doi: 10.1016/s0165-  
50  
51 667 0327(01)00451-7 [published Online First: 2002/08/30]  
52  
53 668 65. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the  
54  
55 669 Montgomery-Asberg depression rating scale corresponding to the definition of  
56  
57  
58  
59  
60



- 1  
2  
3 670 remission on the Hamilton rating scale for depression. *J Psychiatr Res* 2004;38(6):577-  
4  
5 671 82. doi: 10.1016/j.jpsychires.2004.03.007 [published Online First: 2004/10/02]  
6  
7 672 66. Castle D, White C, Chamberlain J, et al. Group-based psychosocial intervention for bipolar  
8  
9 673 disorder: randomised controlled trial. *British Journal of Psychiatry* 2010;196(5):383-88.  
10  
11 674 doi: 10.1192/bjp.bp.108.058263 [published Online First: 2018/01/02]  
12  
13 675 67. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group  
14  
15 676 psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease  
16  
17 677 is in remission. *Arch Gen Psychiatry* 2003;60(4):402-7. doi:  
18  
19 678 10.1001/archpsyc.60.4.402 [published Online First: 2003/04/16]  
20  
21 679 68. Reinares M, Pacchiarotti I, Solé B, et al. A prospective longitudinal study searching for  
22  
23 680 predictors of response to group psychoeducation in bipolar disorder. *Journal of*  
24  
25 681 *Affective Disorders* 2020;274:1113-21. doi: <https://doi.org/10.1016/j.jad.2020.02.047>  
26  
27 682 69. Gorwood P, Weiller E, Lemming O, et al. Escitalopram prevents relapse in older patients  
28  
29 683 with major depressive disorder. *The American Journal of Geriatric Psychiatry*  
30  
31 684 2007;15(7):581-93. doi: 10.1097/01.JGP.0000240823.94522.4c  
32  
33 685 70. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral  
34  
35 686 antidepressant treatment for relapse prevention in patients with treatment-resistant  
36  
37 687 depression: a randomized clinical trial. *JAMA Psychiatry* 2019;76(9):893-903. doi:  
38  
39 688 10.1001/jamapsychiatry.2019.1189  
40  
41 689 71. Association. AP. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition,  
42  
43 690 Text Revisions (DSM-IV-TR) ed. Washington, DC: American Psychiatric Association  
44  
45 691 2000.  
46  
47 692 72. Michalak EE, Murray G. Development of the QoL.BD: a disorder-specific scale to assess  
48  
49 693 quality of life in bipolar disorder. *Bipolar Disord* 2010;12(7):727-40. doi:  
50  
51 694 10.1111/j.1399-5618.2010.00865.x [published Online First: 2010/11/03]  
52  
53 695 73. Innovation VH. Covidence systematic review software. Melbourne, Australia: Veritas  
54  
55 696 Health Innovation.  
56  
57  
58  
59  
60

- 1  
2  
3 697 74. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of  
4  
5 698 Interventions version 6.0 (updated July 2019): Cochrane 2019.  
6  
7 699 75. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for  
8  
9 700 assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi:  
10 701 10.1136/bmj.d5928  
11  
12 702 76. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing  
13  
14 703 the quality of nonrandomised studies in meta-analyses, 2012.  
15  
16 704 77. Institute TJB. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic  
17  
18 705 Reviews.  
19  
20 706 78. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality  
21  
22 707 of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-26. doi:  
23  
24 708 10.1136/bmj.39489.470347.AD  
25  
26 709 79. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses.  
27  
28 710 *BMJ* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557  
29  
30 711 80. Comprehensive Meta-Analysis [program]. 3.0 version. Engelwood, NJ: Biostat, Inc.  
31  
32 712 81. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and  
33  
34 713 meta-analyses: The PRISMA Statement. *PLOS Medicine* 2009;6(7):e1000097. doi:  
35  
36 714 10.1371/journal.pmed.1000097  
37  
38  
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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+")

For peer review only

**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

Supplementary Material

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3	S4 cyclothymi*:ti,ab
4	S3 bipolar:ti,ab
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6	S2 'mania'/exp
7	S1 'bipolar disorder'/exp
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**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"

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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"



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3	S159 DE "Conversion Therapy"
4	S158 DE "Aversion Therapy"
5	S157 DE "Behavior Therapy"
6	S156 DE "Prolonged Exposure Therapy"
7	S155 DE "Cognitive Processing Therapy"
8	S154 DE "Acceptance and Commitment Therapy"
9	S153 DE "Workplace Intervention"
10	S152 DE "School Based Intervention"
11	S151 DE "Group Intervention"
12	S150 DE "Family Intervention"
13	S149 DE "Early Intervention"
14	S148 DE "Crisis Intervention"
15	S147 DE "Intervention"
16	S146 DE "Video-Based Interventions"
17	S145 DE "Treatment Planning"
18	S144 DE "Treatment Outcomes"
19	S143 DE "Treatment Guidelines"
20	S142 DE "Trauma Treatment"
21	S141 DE "Trauma-Informed Care"
22	S140 DE "Therapeutic Processes"
23	S139 DE "Symptoms Based Treatment"
24	S138 DE "Spiritual Care"
25	S137 DE "Speech Therapy"
26	S136 DE "Sociotherapy"
27	S135 DE "Social Casework"
28	S134 DE "Sex Therapy"
29	S133 DE "Self-Help Techniques"
30	S132 DE "Respite Care"
31	S131 DE "Pain Management"
32	S130 DE "Relaxation Therapy"
33	S129 DE "Rehabilitation"
34	S128 DE "Psychoeducation"
35	S127 DE "Private Practice"
36	S126 DE "Physical Treatment Methods"
37	S125 DE "Personal Therapy"
38	S124 DE "Partial Hospitalization"
39	S123 DE "Outpatient Treatment"
40	S122 DE "Multisystemic Therapy"
41	S121 DE "Multimodal Treatment Approach"
42	S120 DE "Movement Therapy"
43	S119 DE "Mindfulness-Based Interventions"
44	S118 DE "Mind Body Therapy"
45	S117 DE "Milieu Therapy"
46	S116 DE "Mental Health Programs"
47	S115 DE "Medical Treatment (General)"
48	S114 DE "Maintenance Therapy"
49	S113 DE "Life Sustaining Treatment"
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3	S112	DE "Language Therapy"
4	S111	DE "Involuntary Treatment"
5	S110	DE "Intervention"
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7	S109	DE "Interdisciplinary Treatment Approach"
8	S108	DE "Integrated Services"
9	S107	DE "Institutionalization"
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11	S106	DE "Hydrotherapy"
12	S105	DE "Human Services"
13	S104	DE "Human Potential Movement"
14	S103	DE "Hospice"
15	S102	DE "Horticulture Therapy"
16	S101	DE "Health Care Services"
17		
18	S100	DE "Habilitation"
19	S99	DE "Disease Management"
20	S98	DE "Cross Cultural Treatment"
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22	S97	DE "Creative Arts Therapy"
23	S96	DE "Counseling"
24	S95	DE "Computer Assisted Therapy"
25	S94	DE "Cognitive Techniques"
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27	S93	DE "Cognitive Stimulation Therapy"
28	S92	DE "Cognitive Behavior Therapy"
29	S91	DE "Client Treatment Matching"
30	S90	DE "Client Transfer"
31	S89	DE "Caregiving"
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33	S88	DE "Bibliotherapy"
34	S87	DE "Behavior Modification"
35	S86	DE "Anxiety Management"
36	S85	DE "Alternative Medicine"
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38	S84	DE "Aftercare"
39	S83	DE "Adventure Therapy"
40	S82	DE "Adjunctive Treatment"
41	S81	DE "Addiction Treatment"
42	S80	DE "Treatment"
43		
44	S79	DE "Transactional Analysis"
45	S78	DE "Supportive Psychotherapy"
46	S77	DE "Strategic Therapy"
47	S76	DE "Solution Focused Therapy"
48	S75	DE "Relationship Therapy"
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50	S74	DE "Reality Therapy"
51	S73	DE "Rational Emotive Behavior Therapy"
52	S72	DE "Psychotherapeutic Techniques"
53	S71	DE "Psychotherapeutic Counseling"
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55	S70	DE "Psychodynamic Psychotherapy"
56	S69	DE "Psychodrama"
57	S68	DE "Psychoanalysis"
58	S67	DE "Primal Therapy"
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60	S66	DE "Persuasion Therapy"

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3	S65 DE "Network Therapy"
4	S64 DE "Narrative Therapy"
5	S63 DE "Logotherapy"
6	S62 DE "Interpersonal Psychotherapy"
7	S61 DE "Integrative Psychotherapy"
8	S60 DE "Insight Therapy"
9	S59 DE "Individual Psychotherapy"
10	S58 DE "Hypnotherapy"
11	S57 DE "Humanistic Psychotherapy"
12	S56 DE "Guided Imagery"
13	S55 DE "Group Psychotherapy"
14	S54 DE "Gestalt Therapy"
15	S53 DE "Geriatric Psychotherapy"
16	S52 DE "Feminist Therapy"
17	S51 DE "Eye Movement Desensitization Therapy"
18	S50 DE "Expressive Psychotherapy"
19	S49 DE "Experiential Psychotherapy"
20	S48 DE "Existential Therapy"
21	S47 DE "Emotion Focused Therapy"
22	S46 DE "Eclectic Psychotherapy"
23	S45 DE "Couples Therapy"
24	S44 DE "Conversion Therapy"
25	S43 DE "Client Centered Therapy"
26	S42 DE "Child Psychotherapy"
27	S41 DE "Brief Relational Therapy"
28	S40 DE "Brief Psychotherapy"
29	S39 DE "Autogenic Training"
30	S38 DE "Analytical Psychotherapy"
31	S37 DE "Affirmative Therapy"
32	S36 DE "Adolescent Psychotherapy"
33	S35 DE "Adlerian Psychotherapy"
34	S34 DE "Psychotherapy"
35	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
36	S32 TI psychological trauma or AB psychological trauma
37	S31 TI (early AND trauma*) or AB (early AND trauma*)
38	S30 TI (adverse AND child* AND experience*) or AB (adverse AND child* AND experience*)
39	S29 TI (child* AND neglect) or AB (child* AND neglect)
40	S28 TI (child* AND abuse) or AB (child* AND abuse)
41	S27 TI (child* AND maltreatment) or AB (child* AND maltreatment)
42	S26 TI (child* AND trauma) or AB (child* AND trauma)
43	S25 DE "Domestic Violence"
44	S24 DE "Emotional Trauma"
45	S23 DE "Battered Child Syndrome"
46	S22 DE "Verbal Abuse"
47	S21 DE "Sexual Abuse"
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## Supplementary Material

BMJ Open

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3	S20	DE "Physical Abuse"
4	S19	DE "Emotional Abuse"
5	S18	DE "Child Neglect"
6	S17	DE "Child Abuse"
7	S16	DE "Childhood Adversity"
8	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
9	S14	TI BPAD OR AB BPAD
10	S13	TI BPD OR AB BPD
11	S12	TI BD OR AB BD
12	S11	TI hypomanic OR AB hypomanic
13	S10	TI hypomania OR AB hypomania
14	S9	TI manic OR AB manic
15	S8	TI mania OR AB mania
16	S7	TI cyclothymi* OR AB cyclothymi*
17	S6	TI bipolar OR AB bipolar
18	S5	DE "Mania"
19	S4	DE "Cyclothymic Disorder"
20	S3	DE "Bipolar II Disorder"
21	S2	DE "Bipolar I Disorder"
22	S1	DE "Bipolar Disorder"
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review only

**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

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

For peer review only

**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.
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
	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
	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Contributions			
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	
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

Supplementary material

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 $\tau$ )	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.**

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