**ABSTRACT**

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

**Method and analysis** MEDLINE Complete, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials will be searched to identify randomised and nonrandomised studies of pharmacological and/or psychological interventions for bipolar disorder, which also assessed childhood trauma. To be eligible for inclusion, studies must have been conducted with adolescents or adults (≥10 years). Data will be screened and extracted by two independent reviewers. The methodological quality of the included studies will be assessed with the Cochrane Collaboration’s Risk of Bias tool and the Newcastle-Ottawa Scale. If deemed viable, a meta-analysis will be conducted using a random effects model. Heterogeneity of evidence will be estimated with the I² statistics.

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

**PROSPERO registration number** CRD42020201891.

**INTRODUCTION**

Bipolar disorder is a potentially debilitating illness that is characterised by manic and depressive episodes. A manic episode is typically marked by an unusually elevated or irritable mood, whereas low mood or a significant loss of interest or pleasure occurs in a depressive episode. Bipolar disorder may significantly impair social and occupational functioning as well as the quality of life (QoL) 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 with approximately 70% experiencing an affective relapse within 4 years. These findings highlight the clinical importance of recognising environmental risk factors, such as childhood trauma, that contribute to the outcomes in bipolar disorder.

Childhood trauma is commonly reported by individuals with a diagnosis of bipolar disorder. Therefore, there is a need to critically evaluate the influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults 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. 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. Additionally, this systematic review will be the first to investigate the role of childhood trauma in the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder.

**Strengths and limitations of this study**

- This will be the first systematic review to involve the critical evaluation of the influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder.
- The screening and data extraction process will be completed by two independent reviewers and reported according to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.
- Standardised methodological appraisal tools will be used to assess risk of bias of the studies included in the review.
- Heterogeneity of evidence is likely as inclusive study design criteria were set for the review.
- The systematic review may be limited by the lack of available evidence, precluding a meta-analysis from being conducted.
disorder with prevalence rates as high as 50% being documented in various cross-sectional studies. As an example, Sala et al. 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.

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

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

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

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

Recent data collected from a randomised controlled trial (RCT) conducted to test the effectiveness of adjunctive infliximab for the treatment of adult outpatients with bipolar disorder contradicted prior research. McIntyre et al. found that participants with a history of physical abuse showed a greater reduction in depression severity and, hence, a better treatment response than participants without a history of physical abuse. Potentially explaining McIntyre et al.’s findings, childhood trauma has repeatedly been linked to increased and persistent inflammation in bipolar disorder.

Therefore, an anti-inflammatory agent might target the underlying pathophysiological mechanisms, facilitating positive treatment effects.

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

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

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

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

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

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

METHODS AND ANALYSIS
Eligibility criteria
Relevant studies will be identified according to the following criteria:

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

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

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

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

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

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

**Types of outcome measures**

**Primary outcome—mean reduction in symptom severity**

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

**Secondary outcomes—related to symptomatic recovery**

1. Treatment response as defined by either:
   - a reduction of 50% (or greater) on the YMRS, the MADRS or any other validated scale assessing manic or depressive symptoms or
   - a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression—Improvement scale or
   - other criteria specifying treatment response as defined by the study authors.

2. Symptomatic remission as defined by either:
   - a score of ≤12 on the YMRS or ≤10 on the MADRS or
   - a score of 1 (normal, not at all ill) or 2 (borderline mentally ill) on the Clinical Global Impression—Severity scale or
   - other criteria specifying remission as defined by the study authors.

3. Relapse/recurrence defined as a new affective episode according to the DSM or ICD criteria and/or by:
   - a score of ≥12 on the YMRS indicating a hypomanic recurrence;
   - a score of ≥20 on the YMRS indicating a manic recurrence;
   - a score of ≥22 on the MADRS indicating a depressive recurrence;
   - a score of ≥20 on the YMRS and a score of ≥22 on the MADRS indicating a mixed recurrence or
   - other criteria specifying relapse/recurrence as defined by the study authors.

**Secondary outcomes—related to functional and personal recovery**

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

**Types of publications**

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

**Information sources and search strategy**

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

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

**Data management and extraction**

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

1. Study characteristics (eg, study author, year of publication).
2. Study design (eg, randomised, nonrandomised).
3. Sample characteristics (eg, N, country/ies, setting).
4. Participant characteristics (eg, mean age, % women, diagnoses).
5. Diagnostic assessment (eg, assessment tool).
6. Clinical features (eg, age at onset, % rapid cycling, number of episodes, number of suicide attempts).
7. Childhood trauma assessment (eg, definition, assessment tool).
8. Exposure details (eg, n exposed, trauma types, time of exposure).
9. Treatment characteristics (eg, type, dose, duration, number of sessions).
10. Outcome assessment (eg, definition, assessment tool).
11. Results (eg, reported inferential statistics, confidence intervals (CIs), effect sizes).

Assessment of methodological quality

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

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

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach will be used to assess the quality of evidence for each of the outcomes. In the GRADE approach, the quality of evidence is rated across all identified studies resulting in one of four grades: high, moderate, low and very low (Table 1). As a rule of thumb, evidence from randomised trials is of high quality whereas evidence from 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 confoundings would decrease the indicated effect.

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

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

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

Data synthesis and statistical analysis

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

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

Heterogeneity of evidence will be determined with Higgins I² statistics calculations. If substantial heterogeneity between the studies is indicated (I² > 50%), possible reasons for the variability will be considered by analysing the characteristics of the studies included. If meta-analyses are deemed sensible based on the heterogeneity analysis, a random effects model will be used. All statistical analyses will be conducted with the software Comprehensive Meta-Analysis.

As per guidelines from the Cochrane Handbook for Systematic Reviews of Interventions V.6.0, 50%, 74 randomised trials and nonrandomised studies of interventions will not be combined in one meta-analysis. Instead, randomised trials and nonrandomised studies will be separately analysed. Additionally, nonrandomised studies of interventions that were judged to have a high risk of bias will be excluded from the meta-analysis. For any meta-analysis with ≥10 studies, funnel plot asymmetry will be evaluated and possible explanations for
the asymmetry will be considered (eg, publication bias), if applicable.74

Subgroup analyses
Where substantial heterogeneity is indicated (I²≥50%) and sufficient data are available, subgroup and meta-regression analyses will be performed to explore potential effect modifiers. Individual subgroup analyses will be conducted for the following categorical variables: trauma type (physical, sexual, emotional); treatment type (pharmacological, psychological, combination) and demographic features (age group (adolescent, adult sample)). Meta-regression analyses will be conducted for continuous variables describing participants’ clinical (age at onset (mean years), rapid cycling (% rapid cycling), number of episodes, number of suicide attempts) and demographic features (age (mean years), gender (% women)). Other subgroups may be identified where necessary. Sensitivity analyses will be completed to determine the robustness of the meta-analyses.

Presentation and reporting of results
This systematic review will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.61 In accordance with the PRISMA guidelines, the study selection process will be detailed in a flowchart, including number of studies excluded at each stage of the review and reasons for exclusion. The PRISMA-Protocols checklist is reported in online supplemental file 2.

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

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

Author affiliations
1 IMPACT—The Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Deakin University, Geelong, Victoria, Australia
2 Orygen, Parkville, Victoria, Australia
3 Florey Institute for Neuroscience and Mental Health, The University of Melbourne, Melbourne, Victoria, Australia
4 Centre for Youth Mental Health, The University of Melbourne, Parkville, Victoria, Australia
5 Department of Psychiatry, Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia
6 School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia

Acknowledgements
The authors would like to thank Blair Kelly, Deakin University, for assistance with developing the search strategy.

Contributors
AW developed the research question, designed the search strategy, and drafted, edited and approved the final version of the manuscript. OMD, SC, MB and AT developed the research question, revised the search strategy and edited and approved the final version of the manuscript. SER edited and approved the final version of the manuscript.

Funding
AW is supported by a Deakin University Centre of Research Excellence in Psychiatric Treatment Postgraduate Research Scholarship. SER is supported by an Australian Government Research Training Programme Scholarship. OMD is supported by a NHMRC R.D. Wright Biomedical Career Development Fellowship (APP1145653). SC is supported by a NHMRC Senior Research Fellowship (APP1136344). MB is supported by a NHMRC Senior Principal Research Fellowship (APP1156072).

Competing interests
AW has received grant/research support from Deakin University and the Centre of Research Excellence for the Development of Innovative Therapies. SER has received grant/research support from Deakin University. OMD has received grant/research support from the Brain and Behavior Foundation, Simmons Autism Foundation, Stanley Medical Research Institute, Deakin University, Lilly, NHMRC and Australian Society for Bipolar and Depressive Disorders (ASBDD)/Servier. OMD has also received in-kind support from BioMedica Nutraceuticals, NutritionCare and Biocuticals. MB has received grant/research support from the NIH, Cooperative Research Centre, Simmons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer and Servier. AT has received travel/grant support from NHMRC, AMP Foundation, Stroke Foundation, Hunter Medical Research Institute, Helen Macpethson Smith Trust, Schizophrenia Fellowship NSW, SMHR, ISAD, the University of Newcastle and Deakin University.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
This content has been supplied by the author(s).

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Anna Wrobel http://orcid.org/0000-0002-1864-0394
Samantha E Russell http://orcid.org/0000-0001-6672-7550
Olivia M Dean http://orcid.org/0000-0002-2776-3935
Sue Cotton http://orcid.org/0000-0002-9386-8348
Michael Berk http://orcid.org/0000-0002-5554-6946

REFERENCES
1 Grande I, Berk M, Birmaher B, et al. Bipolar disorder. Lancet 2016;387:1561–72.
2 Chu C-S, Stubbs B, Chen T-Y, et al. The effectiveness of adjunct mindfulness-based intervention in treatment of bipolar disorder: a systematic review and meta-analysis. J Affect Disord 2018;225:234–45.
McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet* 2020;396:1841–56.

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 5th edn. Arlington, VA: Author, 2013.

Simon GE, Birmaher B, Lewin AJ, et al. Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. *J Clin Psychiatry* 2007;68:1237–45.

Lee EJ, Hower H, Jones RN, et al. Course of longitudinal psychosocial functioning in bipolar youth transitioning to adults. *J Affect Disord* 2020;268:109–17.

Maripuu M, Norrback K-F, Adolfsson R. Quality of life for patients diagnosed with bipolar disorder: lifestyle and treatment. *Neurol Psychiatry Brain Res* 2019;34:34–40.

Morton E, Murphy G, Michalak EE, et al. Quality of life in bipolar disorder: towards a dynamic understanding. *Psychol Med* 2018;48:1111–8.

Pascual-Sánchez A, Jenaro C, Montes-Rodríguez JM. Quality of life in euthymic bipolar patients: a systematic review and meta-analysis. *J Affect Disord* 2015;175:105–15.

Judd LL, Schettjer PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Arch Gen Psychiatry* 2008;65:386–94.

Meyer TD, Hautzinger M. Cognitive behaviour therapy and supportive therapy for bipolar disorders: relapse rates for treatment period and 2-year follow-up. *Psychol Med* 2012;42:1429–39.

Simhandl C, König B, Amann BL. A prospective 4-year naturalistic follow-up of treatment and outcome of 300 bipolar I and II patients. *J Clin Psychiatry* 2014;75:294–82.

Simhandl C, Rauch H, König B, et al. The prevalence and effect of life events in 222 bipolar I and II patients: a prospective, naturalistic 4-year follow-up study. *J Affect Disord* 2015;170:166–71.

Gignac A, McGrir A, Lam RW, et al. Outcome and course following a first episode of mania: four-year prospective data from the systematic treatment optimization program (STOP-EM). *J Affect Disord* 2015;175:411–7.

Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of bipolar disorder. *Psychiatr Clin Neurosci* 2017;71:16–17.

Palmer-Claus JE, Berry K, Bucci S, et al. Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *Br J Psychiatry* 2016;209:454–9.

Alvarez M-J, Roupa P, Osés A, et al. Prevalence and clinical impact of childhood trauma in patients with severe mental disorders. *J Nerv Ment Dis* 2011;199:156–61.

Garno JL, Goldberg JF, Ramirez PM, et al. Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry* 2005;186:121–5.

Jansen K, Cardoso TA, Fries GR, et al. Childhood trauma, family history, and their association with mood disorders in early adulthood. *Acta Psychiatr Scand* 2016;134:281–6.

Sala R, Goldstein BI, W alker AJ, Nierenberg AA. Biomarker-guided anti-inflammatory therapies: from promise to reality check. *JAMA Psychiatry* 2019;76:779–80.

Lippard ETC, Nemeroff CB. The devastating clinical consequences of child abuse and neglect: increased disease vulnerability and poor treatment response in mood disorders. *Am J Psychiatry* 2020;177:20–36.

Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust NZ J Psychiatry* 2015;49:1087–206.

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian network for mood and anxiety treatments (CANNAM) and International Society for bipolar disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018;20:937–170.

Conus P, Cotton S, Schimmelmann BG, et al. Pretreatment and outcome correlates of first sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. *Bipolar Disord* 2010;12:244–52.

Lawson DM, Davis B, Brandon S. Treating complex trauma: critical interventions with adults who experienced ongoing trauma in childhood. *Psychotherapy* 2013;50:331–5.

Lecomte T, Spidel A, Leclerc C, et al. Predictors and profiles of treatment non-adherence and engagement in services problems in early psychosis. *Soc Psychiatry Psychiatr Epidemiol* 2002;37:295–302.

Spidel A, Greaves C, Yule F, et al. A comparison of treatment adherence in individuals with a first episode of psychosis and inpatients with psychosis. *Int J Law Psychiatry* 2015;39:90–8.

Rakofsky JJ, Levy ST, Dunlop BW. Conceptualizing treatment nonadherence in patients with bipolar disorder and PTSD. *CNS Spectr* 2011;16:11–20.

Lafrenaye-Dugas A-J, Godbout N, Hébert M. Cumulative childhood trauma and therapeutic alliance: the moderator role of attachment in adult patients consulting in sex therapy. *J Sex Marital Ther* 2018;44:667–78.

Colter J, Yung AR. Exploring the impact of adverse childhood experiences on symptomatic and functional outcomes in adulthood: advances, limitations and considerations. *J Psych Med* 2018;35:5–7.

Gumley AI, Taylor HEF, Schwannauer M, et al. A systematic review of attachment and psychosis: measurement, construct validity and outcomes. *Acta Psychiatr Scand* 2014;129:254–6.

Nordahl HM, Holte H, Haugum JA. Early maladaptive schemas in patients with or without personality disorders: does schema modification predict symptomatic relief? *Clin Psychol Psychother* 2005;12:142–9.

van Vreeswijk MF, Spinhoven P, Eurelings-Bontekoe EHM, et al. Changes in symptom severity, schemas and modes in heterogeneous psychiatric patient groups following short-term schema cognitive-behavioural group therapy: a naturalistic pre-treatment and post-treatment design in an outpatient clinic. *Clin Psychol Psychother* 2014;21:29–38.

Ozdem S, Sarisoy G, Sahin AR, et al. Early maladaptive schemas in patients with bipolar and unipolar disorder. *Int J Psychiatry Clin Pract* 2018;22:151–6.

Murray G, Leitan ND, Thomas N, et al. Towards recovery-oriented psychosocial interventions for bipolar disorder: quality of life outcomes, stage-sensitive treatments, and mindfulness mechanisms. *Clin Psychol Rev* 2017;52:148–63.

Cavelti M, Kyrgis S, Beck EM, et al. Assessing recovery from schizophrenia as an individual process. A review of self-report instruments. *Eur Psychiatry* 2012;27:19–32.

Aas M, Henry C, Andreason OA, et al. The role of childhood trauma in bipolar disorders. *Int J Law Psychiatry* 2016;4:2–10.

Maes M, Congio A, Moraes JB, et al. Early life trauma predicts affective phenomenology and the effects are partly mediated by stage coupling with lowered lipid-associated antioxidant defences. *Biomol Concepts* 2018;9:115–30.

Ventimiglia I, Van der Watt ASJ, Kidd M, et al. Association between trauma exposure and mood trajectories in patients with mood disorders. *J Affect Disord* 2020;262:237–46.

McMahon FJ. Prediction of treatment outcomes in psychiatry--where do we stand? *Dialogues Clin Neurosci* 2014;16:455–64.

World Health Organization. *Health for the world's adolescents: a second chance in the second decade.* Geneva: World Health Organization, 2014.

First MB, Williams JBW, Karg RS. Structured clinical interview for DSM-5 -- research version. Arlington, VA: American Psychiatric Association, 2015.

Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric interview (M.I.N.I.): the development and validation
of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22-33;quiz 34-57.

54 Angold A, Costello EJ. A test-retest reliability study of child-reported psychiatric symptoms and diagnoses using the child and adolescent psychiatric assessment (CAPA-C). Psychol Med 1995;25:755–62.

55 Tufanaru C, Munn Z, Aromataris E. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z, eds. Joanna Briggs Institute reviewer’s manual. The Joanna Briggs Institute, 2017.

56 Bernstein DP, Fink L, Handelsman L, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 1994;151:1132–6.

57 Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–35.

58 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.

59 Spearing MK, Post RM, Leverich GS, et al. Modification of the clinical global impressions (cGI) scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–71.

60 Guy W. Clinical global impressions – ECDEU assessment manual for psychopharmacology revised (DHEW Publ No ADM 76-338). Rockville, MD: National Institute of Mental Health, 1976.

61 Patel NC, Patrick DM, Youngstrom EA, et al. Response and remission in adolescent mania: signal detection analyses of the young mania rating scale. J Am Acad Child Adolesc Psychiatry 2004;38:577–82.

62 Montgomery SA, Asberg M. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. Arch Gen Psychiatry 2000;57:841–9.

63 Hawley CJ, Gale TM, Sivakumaran T, et al. Defining remission by cut off score on the MADRS: selecting the optimal value. J Affect Disord 2012;135:22–32.

64 Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. Arch Gen Psychiatry 2000;57:841–9.

65 Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. J Psychiatr Res 2004;38:577–82.

66 Castle D, White C, Chamberlain J, et al. Group-based psychosocial intervention for bipolar disorder: randomised controlled trial. Br J Psychiatry 2010;196:383–8.

67 Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003;60:402–7.

68 Reinares M, Pacchiarotti I, Solé B, et al. A prospective longitudinal study searching for predictors of response to group psychoeducation in bipolar disorder. J Affect Disord 2020;274:1113–21.

69 Gorwood P, Weiller E, Lemming O, et al. Escitalopram prevents relapse in older patients with major depressive disorder. Am J Geriatr Psychiatry 2007;15:581–93.

70 Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 2019;76:893–903.

71 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, text revisions (DSM-IV-TR). 4 edn. Washington, DC: American Psychiatric Association, 2000.

72 Michalak EE, Murray G, Collaborative RESearch Team to Study Psychosocial Issues in Bipolar Disorder (CREST.BD). Development of the QoL.BD: a disorder-specific scale to assess quality of life in bipolar disorder. Bipolar Disord 2010;12:727–40.

73 Innovation VH. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation, 2021.

74 Higgins JPT, Thomas J, Chandler J. Cochrane handbook for systematic reviews of interventions version 6.0. Cochrane, 2019.

75 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

76 Wells GA, Shea B, O’Connell D. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2012.

77 Institute TJB. The Joanna Briggs Institute critical appraisal tools for use in JBI systematic reviews, 2017.

78 Guyatt GH, Oxman AD, Vist GE, et al. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

79 Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

80 Biostat. Inc. Comprehensive meta-analysis [program], 3.0 version. Englewood, NJ: Biostat, Inc, 2021.

81 Mohr D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.