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Outcomes reported in randomised clinical trials of major depressive disorder treatments in adolescents: a systematic scoping review protocol

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ABSTRACT

Introduction Major depressive disorder (MDD) is a common mental health condition in adolescents. Randomised clinical trials (RCTs) are the gold standard for assessing the safety and efficacy of interventions in this population. Heterogeneity in the outcomes measured and reported between RCTs limits the ability to compare, contrast, and combine trial results in a clinically meaningful way. There is currently no core outcome set (COS) available for use in RCTs evaluating interventions in adolescents with MDD. We will conduct a systematic scoping review of outcomes reported in adolescent depression RCTs to assess the variability of trial outcomes and to inform the development of a COS for adolescent MDD.

Methods and analysis We will apply methods based on the Joanna Briggs Institute scoping review methods manual. RCTs evaluating any treatment intervention for adolescent MDD published in the last 10 years will be located using an electronic bibliographic database search (MEDLINE, PsycINFO and Cochrane Central Register of Controlled Trials). Title and abstract screening, full-text screening, and data charting of eligible studies will be performed in duplicate. Outcomes identified will be mapped to an outcome-domain framework. Data analysis will include summary statistics of the characteristics of the included trials and outcomes.

Ethics and dissemination The results of this review will inform the development of a COS for adolescent MDD. The development and implementation of a COS for RCTs evaluating interventions in adolescents with MDD promise to help reduce variability in trial outcome selection, definition, measurement and reporting, ultimately facilitating evidence synthesis that will help to identify the best treatment practices for adolescents with MDD.

Strengths and limitations of this study

- Our systematic methods are based on the Joanna Briggs Institute scoping review methods manual and the guidelines provided by the Core Outcome Measures in Effectiveness Trials Initiative.
- We will employ a rigorous search strategy using validated search filters developed with research librarians.
- We will only include studies published in English within the past 10 years.
- As this is a scoping review to collect reported outcomes, quality of the evidence and risk of bias of included studies will not be assessed.

INTRODUCTION

Major depressive disorder (MDD) is a debilitating mental health condition that affects more than 300 million people worldwide.[1] MDD has been estimated to affect approximately 5% of adolescents,[2 3] and can profoundly impact psychosocial, family, and academic functioning.[2 4] Adolescents with MDD are at increased risk of suicide as well as depressive disorders and poor functional outcomes in adulthood.[5–9] Randomised clinical trials (RCTs) remain the gold standard for assessing interventions in this population and are essential given that the safety and efficacy profile of treatment interventions in adolescents may differ from the profiles observed in adult studies.[10] For example, tricyclic antidepressants, an effective pharmacological treatment for MDD in adults, demonstrated no efficacy in adolescents.[11] Unfortunately, recent meta-analyses of adolescent MDD trials have been characterised by high heterogeneity in reported outcome data,[12 13] which limits data synthesis and the interpretation and usability of trial results for clinical decision-making practices.

Variability in the selection and reporting of trial outcomes is a well-recognised challenge in biomedical research.[14–17] This contributes to considerable avoidable waste of the financial and human resources invested in these trials, including participant time and effort.[18] One proposed solution to this is the development and implementation of core outcome sets (COS).[14–16] A COS is an agreed minimum

set of outcomes that should be measured and reported in all trials in a specific condition ("what" to measure).[19] COS are also suitable for use in clinical audit and research studies other than RCTs.[19] Recommended practice for COS development includes collating candidate outcomes through systematic literature reviews of outcomes in published studies and consensus methods with the community of stakeholders as to what outcomes should be included in a COS, such as Delphi surveys and face-to-face meetings.[20] Once consensus on what to measure is achieved through the development of the COS, the corresponding outcome measurement instrument for each outcome, and the timing of its application ("how" and "when" to measure), can be evaluated and selected for use in the COS using separate methods.[21] The Core Outcome Measures in Effectiveness Trials (COMET) Initiative[19] currently houses over 1000 references related to COS across a wide variety of health conditions. However, no COS for use in studies of adolescents with MDD exists to date, and evidence users are left with a lack of consensus and variability in the field with respect to outcome selection, definition, measurement, and reporting.[22]

This paper outlines the methods for a systematic scoping review that will represent the first step of the development of a COS for RCTs evaluating interventions in adolescents with MDD.[23] This COS was registered with the COMET initiative in February 2018.[23] The objective of this scoping review is to identify and characterise outcomes reported in published adolescent MDD trials. These results will be used to evaluate the extent of outcome heterogeneity in RCTs in adolescents with MDD, and will provide an initial list of outcomes to consider in a COS for this population.

METHODS AND ANALYSIS

Study design

A systematic scoping review is the most appropriate approach for addressing the aim of this study, as it uses a knowledge synthesis approach that maps concepts underpinning a research area and the main sources and types of evidence available.[24–26] This protocol is based on the recommendations provided by the Joanna Briggs Institute scoping review methods manual[24] and follows recommended systematic methods.[27]

Protocol

This protocol was drafted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols reporting guideline (online supplementary appendix A).[28] The final scoping review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews.[29] This project was registered with the COMET Initiative on 26 February 2018.[23] The protocol preprint was prospectively made available on the Open Science Framework on 8 May 2018.[30] Important protocol amendments, if made, will be documented on this webpage.[30] The review commenced in May 2018, after this protocol was submitted, and is anticipated to be completed by December 2018. Data charting and synthesis are ongoing.

Eligibility criteria

The eligibility criteria for the included studies are based on the PICOT framework:[31]

Population (P): adolescents aged 12–18 years[32] with a diagnosis of MDD as defined by the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders,[33] or depressive disorder as per International Statistical Classification of Diseases criteria,[34] will be eligible, made using a validated diagnostic interview and/or through a clinician diagnosis. Adolescents with comorbid psychiatric conditions will be included. RCTs that include participants with ages outside this range will be included if (1) the reported mean or median participant age falls within the range of 12–18 years, or (2) there is a subgroup analysis that contains adolescents aged between 12 and 18 years inclusive (eg, trials with a subgroup analysis of ages 13–15 years would be eligible, but a subgroup analysis of ages 16–20 years would not be eligible).

Intervention (I): all treatment interventions for MDD (ie, pharmacological and non-pharmacological) will be eligible.

Comparators (C): there will be no comparator restrictions.

Outcomes (O): all planned outcomes will be eligible, meaning all outcomes specified in the published methods to be collected for randomised group comparisons. Health status outcomes (eg, severity of depressive symptoms), as well as resource-use outcomes (eg, number of outpatient appointments, impact on family finances) and delivery of care outcomes (eg, acceptability of intervention, treatment adherence), will be included in this review following established taxonomy;[35] these are recommended for consideration for inclusion in COS. Treatment-emergent adverse events (AEs) detected through standard AE monitoring will not be included as these are not planned outcomes of interest (eg, headaches self-reported at a study visit during AE assessment) and are specific to the intervention of interest.

Studies will be eligible if published within the last 10 years (2008–2017 inclusive) to capture recently conducted and reported trials. There will be no restrictions on when the outcomes were measured or duration of follow-up after the initiation of the intervention. Only RCTs published in English will be included for feasibility. Trials from any country or setting will be eligible. Pilot and feasibility RCTs, as well as interim reports, will be eligible for inclusion, only when a final trial report is not available for inclusion to avoid double counting of any outcomes.

Information sources and search strategy

We will locate studies for inclusion using an electronic bibliographic database search applied to MEDLINE (MEDical Literature Analysis and Retrieval System), PsycINFO, and the Cochrane Central Register of

Controlled Trials. The search strategy was collaboratively developed by review team authors experienced with electronic bibliographic database search strategies (AM, EJM, MO, NJB) including a child and adolescent psychiatrist (PS), in consultation with an experienced research librarian (AMa). Search strategy development was informed by an analysis of the MeSH (Medical Subject Headings) terms and text words contained in the title, abstract, and keyword headings from a sample of relevant articles identified from informal literature searching.[36–39] The proposed search strategy was then reviewed by a second expert research librarian (TAW). The final search strategy found in online supplementary appendix B incorporated feedback from TAW, who reviewed the final version using the Peer Review of Electronic Search Strategies guideline and required no further revisions.[40] MEDLINE and PsycINFO search strategies use validated search filters to identify RCTs.[41] Trained team members (AM, LS) will perform the final searches and deduplicate the results using EndNote X8.[42]

Source selection

Initial screening

Titles and abstracts will first be screened to assess eligibility. Two trained reviewers will screen independently and in duplicate. All discrepancies identified will be reviewed by a third reviewer, so that clarifications with respect to study eligibility can be made as needed and any obviously irrelevant reports can be removed at this stage. The two reviewers will complete training and reliability testing on a random sample of the search results (eg, 100 candidate articles) until sufficient inter-rater reliability is achieved (eg, ≥80% agreement). Studies included by both reviewers and those with unresolved discrepant decisions will move to full-text screening.

Full-text screening

Two trained reviewers will screen the full text of studies for eligibility independently and in duplicate. All discrepancies will be resolved through discussion with a third reviewer. The reviewers will complete training and reliability testing on a random sample of documents included from initial screening until sufficient inter-rater reliability is achieved (eg, ≥80% agreement). Reasons for study exclusion will be logged using Research Electronic Data Capture (REDCap) data management software.[43] When necessary, we will contact authors to clarify eligibility criteria. Included studies will move to data charting. The final list of included articles will be reviewed by a child and adolescent psychiatrist (PS) and any additional RCTs identified meeting study eligibility criteria will also be included.

Data charting

All studies included from full-text screening will undergo data charting in duplicate by two trained reviewers using a standardised charting form developed using REDCap data management software.[43] Disagreements will be resolved through a third team member, when necessary.

The following data will be charted: publication identifiers (eg, journal, year, first author), study characteristics (eg, participant age group, total sample size, intervention type, length of follow-up, region(s) of study setting and funding source type). We will chart the following data for each outcome: definition of outcome, definition of meaningful change, outcome type (eg, single vs composite) and outcome measurement instrument(s) used. We note that other terms for outcome may be used in the included studies, such as endpoint or outcome measure.[44] In the context of adolescent MDD, an example of an outcome would be 'severity of MDD symptoms', and an example of an outcome measurement instrument would be the "Children's Depression Rating Scale-Revised".[45] We will also chart which outcomes were categorised as primary, secondary, or were not specified as either primary or secondary. We will classify an outcome as a "primary outcome" when studies explicitly report at least one of the following: (1) a study outcome is explicitly referred to as a "primary outcome"; (2) outcome data were used to calculate sample size or (3) study objective explicitly included examining an intervention effect on that outcome.[46] Notably, multiple primary outcomes are commonly reported in depression RCTs.[47]

After data charting, the identified outcomes will be synthesised and grouped through assignment to thematic "outcome terms'" as appropriate, consistent with the development of other COS.[20 46] For example, the outcomes "psychosocial improvement" and "level of functioning at school, home, and in the community" could be grouped under the outcome term "social functioning".[37 48] For composite outcomes, each individual component of the composite outcome, if reported, will be grouped under its appropriate outcome term.[46] All outcome terms will then be assigned (herein referred to as "outcome mapping") to an existing or adapted outcome framework, such as those described by COMET Handbook and elsewhere.[20 49] Outcome grouping and outcome mapping will be performed in consultation with child and adolescent psychiatrists and/or methodological experts.

Pilot testing

We will pilot the full-text review and data charting forms on a sample of 10 relevant documents before full-text review begins. We will also conduct a preliminary analysis to pilot the data summary process.

Risk of bias assessment or quality appraisal

As this is a scoping review, we will not conduct risk of bias assessments or quality appraisals of included sources. This approach is consistent with the Joanna Briggs Institute manual.[24]

Synthesis of results

Data analysis will include quantitative measures (counts and frequencies) of study and outcome characteristics (eg, number of included papers, total number of outcomes, total number of outcome measurement instruments, median number of outcomes per study). Tables will be used to display, for example, the characteristics of the included studies and outcomes, as well as the variation in outcome definitions. We will present the results of mapping outcome terms using, for example, a modified outcome matrix model inspired by the Outcome Reporting for Brief Intervention Trials project[50] and adopted in other COS developments.[46]

Patient and public involvement

Due to the methodological focus of this scoping review, patients and/or public were not involved in this study. Patients will be involved in later stages of the COS development process.[20]

DISCUSSION

This review will identify and map all outcomes reported in recent RCTs for the treatment of adolescent MDD. This comprehensive list of outcomes will provide the basis for the development of a COS for adolescent MDD. Methods outlining the development of the COS will be published separately.

Implications

The conduct of high-quality clinical trials that measure meaningful and clearly defined outcomes that facilitate evidence synthesis efforts is critical to identify the best treatments for adolescents with MDD. Research findings on adolescent MDD may be difficult to interpret, replicate, or include in evidence synthesis efforts due, in part, from the heterogeneity of the outcomes measured and reported in clinical trials. This systematic scoping review will identify the extent of outcome heterogeneity in published RCTs in adolescents with MDD and will help inform the development of a COS. Additional candidate outcomes for the COS, such as those that are important to patients and their families, but that have not been measured in RCTs to date, or new outcomes being measured in upcoming or ongoing RCTs, or those that may not have been identified in this review related to search limitations, may be identified during later stages of the COS development process by engaging with stakeholders.

Notably, there is currently a COS being developed for adult depression,[22] for which there may be different outcomes of interest compared with the adolescent population (eg, related to developmental differences and differences in treatment response). Future studies will be needed to identify the outcomes relevant to childhood depression that are outside the scope of this review, and to generate a developmentally sensitive COS and corresponding outcome measurement instruments for this younger population. The development and uptake of a COS for adolescent MDD promise to help improve the standardisation of outcome selection, and in turn, improve clinical decision-making and reduce research waste.[20 51]

Dissemination

The results of this scoping review will be published in a peer-review journal. We will circulate the publication to the COMET Initiative and other relevant mailing lists and social media platforms.

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