Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis

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ABSTRACT
Introduction Depressive disorder is common in children and adolescents, with important consequences and serious impairments in terms of personal and social functioning. While both pharmacological and psychological interventions have been shown to be effective, there is still uncertainty about the balance between these and what treatment strategy should be preferred in clinical practice. Therefore, we aim to compare and rank in a network meta-analysis (NMA) the commonly used psychological, pharmacological and combined interventions for depressive disorder in children and adolescents.

Methods and analysis We will update the literature search of two previous NMAs for the identification of trials of antidepressant and psychotherapy alone for depressive disorder in children and adolescents. For identification of trials of combination interventions, seven databases (PubMed, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), Web of Science, PsychINFO, CINAHL, LilACS) will be searched from date of inception. We will also search ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and check relevant reports on the US Food and Drug Administration website for unpublished data. Building on our previous findings in the field, we will include any commonly prescribed oral antidepressants and any manualised or structured psychotherapies, as well as their combinations. Randomised controlled trials assessing any active intervention against active comparator or pill placebo/psychological controls in acute treatment for depressive disorder in children and adolescents will be included. The primary outcomes will be efficacy (mean change in depressive symptoms), and acceptability of treatment (dropout rate due to any cause). The secondary outcomes will be remission rate, tolerability of treatment (dropouts for adverse events), as well as suicide-related outcomes (suicidal behaviour or ideation). We will perform Bayesian NMAs for all relative outcome measures. Subgroup analyses and sensitivity analyses will be conducted to assess the robustness of the findings.

Dissemination This NMA will provide the most up to date and clinically useful information about the comparative efficacy and acceptability of antidepressants, psychological intervention and their combination in the acute treatment of children and adolescents with depressive disorder. This is the newest NMA and therefore these results are very important in terms of evidence-based medicine. The results will be disseminated through peer-reviewed publication.

Protocol registration PROSPERO CRD42015020841.
BACKGROUND

Depressive disorder in children and adolescents is a major public health problem, affecting 1%–2% of children (6–12 years old) and 2%–5% of adolescents (13–18 years old), with a peak incidence around puberty. The course of depressive disorder in children and adolescents is often characterised by protracted episodes, frequent recurrence and comorbid psychiatric disorders. Compared with adults, the identification and diagnosis of depressive disorder in children and adolescents may be more often missed by clinicians due to undifferentiated signs and symptoms and atypical presentations. Thus, many such patients exhibit serious impairments in social functioning (e.g., poor school achievement; relational problems with family members and peers), and are significantly increased risk for suicidal behaviours and suicidal ideation. For example, a report from the American Academy of Child and Adolescent Psychiatry (AACAP) suggested that depressive disorder is contributed to over 500,000 suicide attempts by children and adolescents a year.

The past two decades have seen significant increases in the data for children and adolescents with depression and both pharmacological and psychological therapies have been effective. Among current psychological interventions, based on our previous findings, cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT) seem to be the best available psychotherapies for depression in children and adolescents. Multiple pharmacological therapies have also been studied for the treatment of depressive disorder in children and adolescents. The controversy about the use of antidepressants in this age group, due to the potentially increased risk of suicidality, has not been fully resolved. Recently, the findings of our previous studies have not been fully resolved. The controversy about the use of antidepressants in this age group, due to the potentially increased risk of suicidality, has not been fully resolved. The controversy about the use of antidepressants in this age group, due to the potentially increased risk of suicidality, has not been fully resolved. Recently, the findings of our previous studies have not been fully resolved. Therefore, the current protocol is to synthesise all this evidence and provide clinicians with a reliable treatment algorithm of the commonly used psychological and pharmacological interventions, as well as their combinations for the acute treatment of depressive disorder in children and adolescents.

METHODS

Criteria for included studies

Types of studies

Any RCTs, including the first phase of cross-over trials as well as cluster-randomised trials, will be included. Quasi-randomised trials (e.g., those allocating participants using alternate days of the week) will be excluded. For trials of antidepressants alone, only double-blind RCTs (patients and raters blinded) will be included. As it is difficult to use a double-blind design for patients in trials of psychotherapy alone or the combination of antidepressant and psychotherapy, we will only include trials in which raters were blinded or participants were assessed by self-rating depression scales.

Types of participants

We will include studies that enrolled participants aged less than 18 years of age when they are initially enrolled in the studies, of both sexes with a diagnosis of depressive disorder, including of major depressive disorder (MDD), dysthymia and other specified types, based on standardised diagnostic criteria (e.g., the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases). While it is accepted that subclinical depression still has a significant impact on an individuals' social and educational functioning, we will not include studies of this population. Similarly, studies where depressive disorder was not formally diagnosed will also be excluded for the same rationale that its clinical response.

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heterogeneity could violate the transitivity assumption in NMA (ie, one can compare indirectly intervention B and C via intervention A). We will also exclude trials in which participants are described as having psychotic depression or treatment-resistant depression, as their treatment response differs from patients without treatment resistance or symptoms of psychosis. Trials focusing on child or adolescent bipolar disorder will also be excluded, but not those involving patients with other comorbid psychiatric disorders as diagnosed according to standardised criteria (eg, anxiety disorder or attention deficit hyperactivity disorder). Where a study includes both adults and children/adolescents and the randomisation had been stratified according this variable, the data will be included if data on the depressed youths can be separately extracted from the manuscript or can be obtained from the authors. Studies conducted in both inpatient and outpatient settings will be included. RCTs recruiting participants with an overall sample size of fewer than 10 patients will be excluded.

Types of interventions

For pharmacological interventions, we will include any commonly prescribed oral antidepressants (fixed or flexible doses). These will include tricyclic antidepressants (TCAs; amitriptyline, clomipramine, nortriptyline, desipramine, imipramine, etc), selective serotonin reuptake inhibitors (SSRIs; escitalopram, fluoxetine, paroxetine, sertraline, etc) and serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine), as well as novel agents mirtazapine and nefazodone. In terms of psychological interventions, we will include any manualised or structured psychotherapies, for example, behaviour therapy, CBT, cognitive therapy, family therapy, interpersonal therapy, play therapy, problem-solving therapy, psychodynamic therapy and supportive therapy. Table 1 provides the detailed description of psychotherapies. Also, we will include the combination of both above-mentioned psychological interventions and pharmacological interventions. For the pharmacological interventions, the control condition is always a pill placebo, while the psychological control conditions are waiting-list (WL), treatment as usual (TAU), psychological placebo or attention-placebo or no-treatment (NT).

All RCTs comparing any active intervention (psychological interventions, pharmacological interventions or their combinations) with either active comparators or control conditions for acute treatment of depressive disorder in children and adolescents will be included. The acute phase will be defined as from 4 to 16 weeks. We will exclude trials with treatment duration of less than 4 weeks, because the onset of benefit for most antidepressants often takes at least 4 weeks. If a study presents data for more than one time point within our predefined acute phase window or beyond 16 weeks, the 8 week (or the closest to 8 week) will be taken as the time. Trials comparing the same antidepressant at different therapeutic doses will be merged in the same node in the network analysis so long as they are within the dose range licensed by drug regulatory agencies. Also, trials comparing the same type of psychological interventions, but at different numbers of therapeutic sessions, different delivery format (group, individual), different treatment medium (face-to-face, internet-based) and different treatment conditions (with or without family involvement) will be considered as the same node in the network analysis. We anticipate that any patient who meets all inclusion criteria, in principal, is equally likely to be randomised to any of the interventions in the synthesis comparator set.

We have generated an ideal network plot that is a fully connected network with all expected interventions (figure 1).

Types of outcome measures

Primary outcomes

1. Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self-rated or assessor-rated), for example, Children’s Depression Rating Scale (CDRS-R) and Hamilton Depression Rating Scale (HAMD) from baseline to endpoint.

2. Acceptability of treatment, defined as the proportion of patients who drop out of the study by any cause during the delivery of the intervention.

Secondary outcomes

1. Efficacy (as dichotomous outcome), measured by the total number of patients who achieved the criteria of remission, defined as being below the threshold in depression rating score (eg, less than 28 for CDRS-R), while these thresholds are different across trials.

2. Tolerability of treatment, defined as the proportion of patients who discontinued treatment due to any adverse events during the delivery of the intervention.

3. Suicide-related outcome, estimated by the reported cases of definitive suicidal behaviour or suicidal ideation during the acute phase of treatment. The definition of suicide-related outcome is based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA). For the antidepressants trials, the data on suicidality mainly referred to the Columbia reanalysis data reported in the Food and Drug Administration (FDA) report. If trials are not included in this report, we will attempt to extract the data on suicide-related outcome from the Medicines and Healthcare products Regulatory Agency database or the pharmaceutical company website. For the psychological trials and the combination trials, we will mainly extract the data on suicidality from original text and from related reviews.

4. Global functional improvement, estimated by overall change scores on global assessment of functioning scales, for example, Children’s Global Assessment Scale (CGAS) and Global Assessment of Functioning Scale (CGAF), or quality of life scales, for
example, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). When data are reported on more than one measure, we will first choose data from the CGAS, then the GAF and finally the Q-LES-Q and others.

Where depression symptoms are measured using more than one depression scale in a trial, we will extract data from the depressive scales on the basis of a hierarchy of rating scales. The hierarchy will be based on psychometric properties and appropriateness for use with children and adolescents and for consistency of use across trials (referred from the Zhou et al study, table 2). We will also establish a hierarchy of informants of depressive rating scales, with the clinician report first in the hierarchy, and then the child or adolescent self-report.

**DATA SOURCES AND SEARCH STRATEGY**

For the identification of trials of antidepressant and psychotherapy alone for depressive disorder in children and adolescents, we will update the literature search of our two previous NMAs. Other eligible trials of the combinations of antidepressant and psychotherapy will be identified by searching PubMed, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), Web of Science, PsycINFO, ProQuest, CINAHL, LilACS from date of inception with Medical Subject Headings (MeSH)
and text words: (depress* or dysthymi* or mood disorder* or affective disorder*) and (adolesc* or child* or boy* or girl* or juvenil* or minors or paediatri* or pediatri* or pubescen* or school* or student* or teen* or young or youth*) and (‘selective serotonin reuptake inhibitor*’ or SSRIs or ‘serotonin norepinephrine reuptake inhibitor*’ or SNRIs or ‘citalopram or fluoxetine or paroxetine or sertraline or escitalopram or fluvoxamine or venlafaxine or duloxetine ‘noradrenergic and specific serotonergic antidepressants’ or NaSSA or mirtazapine or TCA or tricyclic or amitriptyline or clomipramine or desipramine or imipramine or nortriptyline) and (psychotherapy* or behavio* or ‘family therap*’ or CBT or cognitive or interpersonal or IPT or ‘play therap*’ or supportive or problem-solving or psychodynamic). We will also search ClinicalTrials.gov in USA and other international trial registers via the International Clinical Trials Registry Platform (ICTRP) in WHO. We will also check relevant reports on the US FDA website and hand-search key journals, conference proceedings, such as, J Child Adolesc Psychopharmacol, J Am Acad Child Adolesc Psychiatry, Child Adolesc Psychiatry Ment Health, Psychopharmacol Bull, Arch Gen Psychiatry, Am J Psychiatry, Eur Psychiatry, Depress Anxiety. There will be no restrictions on language

Table 2  Hierarchy of depression symptom severity measurement scales

| Hierarchy | Depression symptom severity measurement scales                              | Abbreviation |
|-----------|---------------------------------------------------------------------------|--------------|
| 1         | Children's Depression Rating Scale                                        | CDRS         |
| 2         | Hamilton Depression Rating Scale                                          | HAMD         |
| 3         | Montgomery Asberg Depression Rating Scale                                 | MADRS        |
| 4         | Beck Depression Inventory                                                 | BDI          |
| 5         | Children's Depression Inventory                                           | CDI          |
| 6         | Schedule for Affective Disorders and Schizophrenia for School Aged Children | K-SADS       |
| 7         | Mood and Feeling Questionnaire                                            | MFQ          |
| 8         | Reynolds Adolescent Depression Scale                                      | RADS         |
| 9         | Bellevue Index of Depression                                              | BID          |
| 10        | Child Depression Scale                                                    | CDS          |
| 11        | Centre for Epidemiologic Studies Depression Scale                         | CESD         |
| 12        | Child Assessment Schedule                                                 | CAS          |
| 13        | Child Behaviour Checklist-Depression                                       | CBCL-D       |
or publication year. Additional relevant studies will be obtained by scanning reference lists of trials identified in the initial searches and relevant review papers. We will also inquire at the relative pharmaceutical companies (eg, GlaxoSmithKline, Lilly, Organon, Forest Pharmaceuticals, Bristol-Myers Squibb) and search their websites for unpublished data. All relevant experts and principal manufacturers will be contacted to supplement incomplete reports of the original papers or to provide new data for unpublished studies.

**Study selection and data extraction**

**Selection of trials**

Titles and abstracts identified from the search strategies will be independently examined by two reviewers (XZ and YZ). If both reviewers judge that the trial does not meet eligibility criteria, we will exclude it. Then, we will obtain the full-texts of all remaining articles and determine whether to include them according to inclusion criteria described above. We will calculate the inter-rater reliability of the two raters. Any disagreements will be resolved by a third review author (AC or PX) or by consultation with the authors of the articles. The reasons for exclusion of trials will be reported in the characteristics of excluded studies list.

**Data extraction**

Two independent reviewers (XZ and YZ) will extract the data from each included trial using standardised data extraction forms, including study characteristics (eg, first listed author, publication year, title, publication type, publication journal, country and sponsor), patient characteristics (eg, diagnostic criteria, comorbidities, the age of patients, patient setting, the number of patients, the gender of patients and severity of depression at baseline), intervention details (eg, the type of intervention, the treatment duration, the dose of antidepressant agent, the length and number of sessions of psychotherapy, treatment delivery and treatment medium of psychotherapy) and outcome measures (primary outcomes and secondary outcomes). We will assess and report the reliability of the reviewers’ data extraction on each coded variable. Any disagreements will be resolved by a third review author (AC or PX). Where necessary, the authors of the studies will be contacted for further information.

**Risk of bias assessment**

We will assess risk of bias as ‘low risk’, ‘unclear risk’ or ‘high risk’, in accordance with the Cochrane Collaboration’s Risk of Bias tool as described in the Cochrane Handbook for Systematic Reviews of Interventions. The following items will be assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias (eg, sponsorship bias/researcher allegiance bias). Two independent review authors (XZ and YZ) will assess the risk of bias in selected studies. Degree of agreement between the two independent raters will be reported. Any disagreements will be resolved by a third review author (AC or PX). Where necessary, the authors of the studies will be contacted for further information. Studies will be classified as having high risk of bias if two or more domains were rated as high risk of bias; low if five or more were rated as low risk of bias and none was rated as high risk of bias, and all other cases will be assumed to pertain to moderate risk.

**Statistical analysis**

NMA combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum power. First, we will perform pairwise meta-analyses of direct evidence using the random-effects model with Stata V.14.0. Second, we will also perform a random-effects NMA within a Bayesian framework using Markov chain Monte Carlo in WinBUGS V.1.4.3. Where different measures are used to assess the same outcome, continuous outcomes data will be pooled with standardised mean difference (SMD) and dichotomous outcomes will be analysed by calculating the OR. In the presence of minimally informative priors, credible intervals (CrIs) can be interpreted similarly to CIs.

Missing dichotomous outcome data will be managed according to the intention to treat (ITT) principle, and all the dropouts after randomisation will be considered to be non-responders. Missing continuous outcome data will be analysed using the completer data. When p values, t values, CIs or SEs are reported in articles, SD will be calculated from their values. Where SDs are missing, attempts will be made to obtain these data through contacting trial authors. When this fails, they will be borrowed from the other trials in the network or from other published reports.

In the analysis of NMA , the pooled estimates will be obtained using the Markov Chains Monte Carlo method. Two Markov chains will be run simultaneously with different arbitrarily chosen initial values and non-informative priors will be used for the parameters. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic will be assessed. We will also estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA can also be interpreted as the percentage of efficacy/safety of a treatment that would be ranked first without uncertainty.

**Measures for transitivity assumption**

We will assess whether the included interventions are transitive by evaluating NMA. This can be done by checking the consistency of the estimates across different comparisons. If the estimates are consistent across comparisons, the intervention can be considered transitive. If there are differences in the estimates across comparisons, the intervention cannot be considered transitive.

In the analysis of NMA , the pooled estimates will be obtained using the Markov Chains Monte Carlo method. Two Markov chains will be run simultaneously with different arbitrarily chosen initial values and non-informative priors will be used for the parameters. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic will be assessed. We will also estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA can also be interpreted as the percentage of efficacy/safety of a treatment that would be ranked first without uncertainty.
psychotherapy in children and adolescents include bipolarity, psychotic features, subthreshold depression. We have assured transitivity in our network with regard to these variables by limiting our samples to participants with non-psychotic unipolar depressive disorders. Other clinical or methodological variables that may influence our primary outcomes of treatment efficacy or acceptability include: age, sex, depressive severity at baseline and the treatment duration.

Measures for heterogeneity
In standard pairwise meta-analyses, we will estimate a different heterogeneity variance for each pairwise comparisons; in NMA we will assume a common estimate for the heterogeneity variance across the different comparisons. We will assess statistically the presence of heterogeneity within each pairwise comparison using the $I^2$ statistic and its 95% CI that measures the percentage of variability that cannot be attributed to random error. The assessment for the presence of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter ($\tau^2$) estimated from the NMA models. We will also estimate a total $I^2$ value and predictive intervals for heterogeneity in the network.

Measures for inconsistency
NMA assumes that there is consistency in the network (ie, direct and indirect evidence are in agreement). However, the assumption of consistency can be violated either in the entire network or in certain parts (ie, loops of evidence) of the network. Therefore, consistency needs to be checked. We will evaluate the presence of local inconsistency and global inconsistency in Stata V.14.0 and will be duplicated in R software.

Measures for publication bias
We will use the contour-enhanced funnel plot and Egger’s test to assess risk of publication bias within each pairwise comparison. We will also use the comparison-adjusted funnel plots of all trials with placebo controls or inactive controls to investigate whether results in imprecise trials differ from those in more precise trials in NMA.

Subgroup analyses and sensitivity analyses
Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (1) age of participants (children vs adolescents); (2) sex ratio; (3) the severity of depressive symptoms at baseline; (4) the treatment duration; (5) severity of depressive symptom at baseline. If possible, we will do some extra subgroup analyses according to the results of heterogeneity and inconsistency. In the sensitivity analysis, trials where missing data have been imputed will be excluded, trials where high risk of bias rating have been assessed, and trials where only included patients comorbidity with other psychiatric disorders will be excluded. And, we will not only test whether the results change but also if transitivity (consistency/model fit) is affected. We will also examine some variables (eg, sample size of trials), as continuous measure in meta-regression analyses.

GRADE quality assessment
We will also assess the quality of evidence contributing to primary outcomes with the GRADE framework, which characterises the quality of a body of evidence on the basis of the study limitations, imprecision, heterogeneity or inconsistency, indirectness and publication bias. The starting point for confidence in each network estimate is high, but will be downgraded according to the assessments of these five aspects.

ETHICS AND DISSEMINATION
This NMA does not need ethical approval, as data used here are based on aggregated data in the public domain. Findings from the analysis will provide an overview and information on the relative efficacy and acceptability of antidepressant medications, psychological therapies and their combination for depressive disorder in children and adolescents. It is suggested that the findings will have significant implications for clinical practice and further research.

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