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Psychotherapy for depression in children and adolescents: study protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction: Depression is common among children and adolescents and is associated with significantly negative effects. A number of structured psychosocial treatments are administered for depression in children and adolescents; however, evidence of their effectiveness is not clear. We describe the protocol of a systematic review and network meta-analysis to evaluate the efficacy, quality of life, tolerability and acceptability of the use of psychological intervention for this young population.

Methods and analysis: We will search PubMed, EMBASE, CENTRAL (the Cochrane Central Register of Controlled Trials), Web of Science, PsycINFO, CINAHL, LiLACS, Dissertation Abstracts, European Association for Grey Literature Exploitation (EAGLE) and the National Technical Information Service (NTIS) from inception to July 2014. There will be no restrictions on language, publication year or publication type. Only randomised clinical trials (RCTs) with psychosocial treatments for depression in children and adolescents will be considered. The primary outcome of efficacy will be the mean overall change of the total score in continuous depression severity scales from baseline to end point. Data will be independently extracted by two reviewers. Traditional pairwise meta–analyses will be performed for studies that directly compared different treatment arms. Then we will perform a Bayesian network meta–analyses to compare the relative efficacy, quality of life, tolerability and acceptability of different psychological intervention. Subgroup analyses will be performed by the age of participants and the duration of psychotherapy, and sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination: No ethical issues are foreseen. The results will be published in a peer–reviewed journal and disseminated electronically and in print. The meta–analysis may be updated to inform and guide management of depression in children and adolescents.

Trials registration number: PROSPERO CRD42014010014.

Strengths and limitations of this study

- This Bayesian network meta-analysis can integrate direct evidence with indirect evidence from multiple treatment comparisons to estimate the interrelations across all treatments.
- We will comprehensively assess the efficacy, quality of life, tolerability, acceptability and suicide-related outcomes in acute treatment and follow-up.
- A series of subgroup and sensitivity analyses will address clinically relevant questions.
- This study should help guide clinical decision-making of psychotherapeutic interventions to better treat child and adolescent depression.

BACKGROUND

Depression is increasing rapidly, and ranks fourth on the list of disorders with the highest burden of disease worldwide.[1] The point prevalence of depression has been estimated to be approximately 2% in children (6–12 years) and 2–8% in adolescents (13–18 years), with a peak incidence around puberty.[2 3] The average duration of a depressive episode in children and adolescents is about 9 months.[4] However, 70% of patients whose symptoms remit develop subsequent depressive episodes within 5 years, and research also shows continuity between childhood depression and depression experienced in adulthood.[4 5] Compared with diagnosis of adults, diagnoses of depressed children and adolescents are more often missed[5] and have more frequent suicide attempts and thoughts, particularly in teenage girls.[6] There is also serious impairment in social functioning, including poor school achievement and relational problems with family members and peers.[7 8]

In the past two decades, the availability of effective treatments for depression in children and adolescents has increased, with two broad categories of treatment being used to treat this population: psychotherapy and pharmacotherapy (eg, tricyclic antidepressants (TCAs) and serotonin selective reuptake inhibitors (SSRIs)).[9 10] In the management of mild to moderate depression, the first

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treatment option is still psychotherapy no matter which method is used.[10 11] In the USA, approximately three quarters of children and adolescents treated for depression are reported to have received some form of psychotherapy, although approximately one-third of patients underwent only one or two treatment visits during the course of the survey year.[12] For pharmacotherapy, TCAs are unlikely to benefit children and adolescents with depression,[13] and treatment with SSRIs has been controversial because of evidence of a significant increase in the risk of suicidality compared to a placebo.[14 15] Thus, concerns about this issue have refocused attention on the prevalence of depression in young patients, particularly on the most prominent medication alternative, psychotherapy and on the question of how effective this treatment is with youth depression.[16]

The aim of psychotherapy is to build a relationship with the client through a structured and purposeful encounter, and although a range of specific techniques are employed, life issues and problems can be discussed and addressed. Just as there are many approaches to psychological therapies, the assumed mechanism of action for each varies. However, common to most is the aim to increase awareness, with the implicit or explicit aim of changing thoughts, behaviours or emotions to improve the mental health and well-being of the client.[17] In clinical practice, depressed children and adolescents are more likely to show an irritable mood, rather than the sad mood that features in depressed adults,[9] and dramatic brain changes have been found between childhood and adult patients in previous studies.[18 19] Therefore, it is important to analyse psychotherapy use in children and adolescents separately from adults. Since the late 1990s, several rigorous studies have been conducted validating the efficacy of psychotherapeutic approaches in child and adolescent depression.[20–22] Currently, a number of structured psychosocial treatments are administered for depression in children and adolescents, such as cognitive-behavioural therapy (CBT), which has also been commonly used for adult patients.[23] Other types of psychotherapies include behavioural, cognitive, interpersonal, problem-solving, play, psychodynamic and family. So far, there have been only a few systematic reviews or meta-analyses for depression in children and adolescents, and the evidence of effectiveness of psychotherapy remains unclear.[16 24–27] One recent meta-analysis by Cox *et al*[17] found that the existing evidence is not sufficient to robustly determine the relative effectiveness of antidepressants and psychological therapies (alone or in combination) for treating depression in children and adolescents, and another meta-analysis showed a modest benefit from antidepressants with no additional benefit over medication from CBT for treatment-resistant depression in adolescents.[26] In addition, Hetrick *et al*'s[27] study found that the efficacy of psychotherapy varies with different therapeutic components (eg, behavioural therapy may lead to better treatment outcomes in young people).[27] However, these systematic reviews and meta-analyses have not focused on any head-to-head comparisons of different psychological interventions. Thus, the evidence of hierarchies for the efficacy and tolerability of these interventions in acute phase treatment and follow-up has never been assessed in the comprehensive setting of a systematic review and meta-analysis.

For these reasons, a better-designed approach utilising Bayesian network meta-analysis is urgently needed in this area, integrating direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator) from multiple treatment comparisons to estimate the interrelations across all treatments.[28] This approach enables a coherent analysis of random trials data for comparisons of multiple treatments without adversely affecting randomisation of treatments within each trial, and its usefulness has been previously demonstrated in several studies on various medical conditions and interventions, such as antidepressants or psychotherapy for depression in adults,[29 30] and antimanic drugs for mania in adults.[31] Recently, we have completed a network meta-analysis comparing first-generation and second-generation antidepressants for depression in children, adolescents and young adults. To further improve the management for depression in children and adolescents, we will conduct a systematic review and network meta-analysis to evaluate the efficacy, quality of life, tolerability and acceptability of the use of psychological intervention for this young population.

METHODS

Criteria for included studies

Types of studies

Any relevant randomised controlled trials (RCTs) will be included. Quasi-randomised trials (such as those allocating by using alternate days of the week) will be excluded. For trials that have a crossover design, only the results from the first randomisation period will be considered. Also, the cluster RCTs will be included.

Types of participants

Children or adolescents should be between the ages of 6 and 18 years when they initially participated in the primary studies. For the purpose of reducing clinical heterogeneity, investigators always use one strict diagnostic definition, such as Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) or International Classification of Diseases 10th revision (ICD-10), to diagnose major depression. However, it is most likely that this method could overlook a lot of important information from clinical settings, because some children and adolescents, who do not satisfy the typical criteria of major depression but suffer from depressive symptoms or subthreshold depression, can also have serious functional deterioration in social and educational situations. Therefore, the following broad criteria to identify the participants will be applied in our

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study:(1) major depression as diagnosed according to standardised criteria such as DSM-III,[32] DSM-III-R,[33] DSM-IV,[34] ICD-9,[35] ICD-10,[36] Research Diagnostic Criteria[37] and Feighner criteria,[38] (2) minor or intermittent depression, or dysthymia as diagnosed according to standardised criteria such as DSM-III, DSM-III-R, DSM-IV, ICD-9, ICD-10, Research Diagnostic Criteria and Feighner criteria, (3) depressive status, defined as scoring above a certain cut-off on a depression rating scale according to the original authors' definition, such as the Hamilton Rating Scale for Depression (HRSD),[39] Children's Depression Inventory (CDI),[40] Beck depression inventory (BDI),[41] Center for Epidemiologic Study Depression Scale(CES-D),[42] Children's Depression Rating Scale (CDRS)[43] or Children's Depression Rating Scale-Revised (CDRS-R).[44] Trials where adults and children or adolescents are treated will be eligible for inclusion, if data on the children or adolescents could be extracted separately or obtained from trial authors. The studies where participants had comorbid secondary medical or other mental health conditions, including comorbid with suicidal ideation/attempt will not be excluded; however, participants with a secondary diagnosis of Axis I psychiatric disorders (eg, schizophrenia and bipolar disorder) will be excluded because the effectiveness of psychotherapy might be affected by these comorbidities. Besides, studies in which participants have a diagnosis of resistant depression or psychotic depression will be excluded.

Types of interventions

RCTs comparing one psychological intervention with another or either of the control conditions for depression in children and adolescents will be included. For psychotherapy, CBT, behavioural therapy (BT), cognitive therapy (CT), interpersonal therapy, problem-solving therapy, play therapy, supportive counselling, psychodynamic therapy and family therapy will be included regardless of their treatment session and duration. The psychotherapy will be shown in table 1. We will view these psychological interventions as independent nodes in this network meta-analysis regardless of the treatment medium (face-to-face, website, telephone or other). If sufficient numbers of studies compared between different treatments in the same type of psychotherapy as currently described are detected, we will consider viewing it as another new node because it seems that the effect of each type of psychotherapy is unique.

In terms of control conditions, waiting-list control (WL), non-treatment control, treatment as usual (TAU) and (psychological or pill) placebo will be included. TAU is not considered to be psychotherapy but may have some treatment effects. Placebo may also have some potential treatment effects, whereas non-treatment and WL do not have any active treatment effects. Therefore, we will also view these control conditions as independent nodes in this network meta-analysis, except that the non-treatment and waiting list will be regarded as one node. Regular reviews of mental health symptoms and interventions, such as psychodrama and art exercise, will be regarded as psychological placebos because they involve time spent with the patient but without a focus on improving depressive symptoms.[24]

Trials in which psychotherapy is used as a combination strategy (such as combining different psychological interventions or psychotherapy and antidepressants) will be excluded, while studies with concomitant use of an auxiliary psychotropic agent (eg, benzodiazepine for insomnia) will be included.

Types of outcome measures

Acute phase treatment

We will assess the effects of acute phase treatment post-treatment in order to examine the possible maximum effects of psychotherapy.

Overall efficacy

1. The primary outcome of efficacy will mean overall change in the total score in continuous depression severity scales from baseline to end point, which will be assessed in the first instance by change in HRDS. If data are not available, we will use change in BDI or CDI and then other depressive rating scales.
2. Secondary outcome of efficacy will be the proportion of patients who respond to treatment, which is defined as substantial overall improvement from baseline as defined by the original investigators, such as more than a 50% reduction on a depression continuous measure (ie, '1=very much improved' or '2=Much improved' according to the Clinical Global Improvement (CGI) Scale or other criteria).[42] When 'response' is not reported, we will use 'remission' if available. Remission is defined as a reduction to the normal range (such as HRSD score ≤9, BDI score ≤10, CDI ≤12) and variably across studies.[45]

Overall acceptability

All-cause discontinuation as a proxy measure of treatment acceptability is defined as the proportion of patients who drop out for any reason.

Overall tolerability

Side effects discontinuation as a measure of treatment tolerability is defined as the proportion of patients who drop out for any reason.

Quality of life/functioning improvement

Quality of life/functioning improvement (QoL/functioning) means overall change in the total score in continuous quality of life scales from baseline to end point, for example, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[46] and the Short Form 36 Health Survey (SF-36),[47] etc, or functioning improvement scales, for example, Sheehan Disability Scale (SDS).[48] As measures of QoL/functioning vary across

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Table 1 Description of intervention strategies

Psychological intervention	Abbreviation	Description
Cognitive behavioural therapy	CBT	CBT uses some kind of cognitive restructuring training and promotes behavioural change
Behavioural therapy	BT	It uses some kind of behavioural training and thus promotes cognitive change. It may include relaxation therapy, biofeedback, coping skills, behavioural activation or social skills training
Cognitive therapy	CT	It uses some kind of cognitive restructuring training but does not promote behavioural change
Interpersonal therapy	IPT	IPT is a brief and highly-structured manual-based psychotherapy that focuses on the participants' social relationships and current evaluation of these relationships
Problem-solving therapy	PST	PST focuses on the problems participants currently face and on helping them find solutions to these problems
Play therapy	–	It uses techniques to engage participants in recreational activities to help them cope with their problems and fears
Non-directive supportive therapy	SUP	SUP is an unstructured therapy without specific psychological techniques that helps people to express their experiences and emotions and offer empathy. These nondirective therapies are commonly described in the literature as either counselling or supportive therapy
Psychodynamic therapy	DYN	DYN refers to a technique designed to help a person understand the origin and nature of long-standing problems, including psychological trauma
Family therapy	–	It works with families and couples in intimate relationships to nurture change and development. It tends to view change in terms of the systems of interaction between family members

studies, we will pool such measures together to create an omnibus effect size for each psychotherapy.

Suicide-related outcomes

We consider suicide-related outcomes as both a dichotomous and continuous outcome. If data are available, we will extract the number of participants with suicidal behaviour/ideation during the acute treatment, as measured on a standardised, validated and reliable rating scale such as the Suicidal Ideation Questionnaire-Junior High School version.[49] In addition, we will also collect data on suicidal ideation as a continuous outcome where a standardised, validated and reliable rating scale has been used.

Follow-up measure

After the acute phase treatment, we will assess the effects at the end of follow-up (maximum of up to 12 months) in order to examine the possible delayed or maintenance effects of psychotherapy. If some participants took further treatments, including continuous treatment, booster sessions or any other psychotherapies or antidepressants during the follow-up period, we will exclude them in the follow-up analysis. Therefore, the number of participants who did not take further treatments will be used as a measure of follow-up efficacy of the acute phase interventions. Owing to the variability in follow-up points, and the fact that some studies assessed outcomes at multiple follow-up time points, we will collect data at the last time points as an outcome measure.

Overall efficacy

1. The primary outcome of efficacy in the long term will be defined as the mean overall change in continuous depression severity scales, which is similar to the acute phase treatment measurement.
2. The secondary outcome of efficacy will be defined as 'response', which is similar to the acute phase treatment measurement.

Overall acceptability

All-cause discontinuation as a proxy measure of treatment acceptability is defined as the proportion of patients who drop out for any reason.

Overall tolerability

Side effects discontinuation as a measure of treatment tolerability is defined as the proportion of patients who drop out for any reason.

Quality of life/functioning improvement

QoL/functioning will be the mean overall change in continuous quality of life scales or functioning improvement scales, which is similar to the acute phase treatment measurement.

Suicide-related outcomes

We consider suicide-related outcomes as both a dichotomous and continuous outcome. If data are available, we will extract the number of participants with suicidal behaviour/ideation during the acute treatment, as measured on a standardised, validated and reliable rating

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scale such as the Suicidal Ideation Questionnaire-Junior High School version.[49] In addition, we will also collect data on suicidal ideation as a continuous outcome where a standardised, validated and reliable rating scale has been used.

Search strategy

All published, unpublished and ongoing RCTs that compared one psychological intervention with another or either of the control conditions in the treatment of depression in children and adolescents will be identified. We will identify relevant trials from systematic searches in the following electronic databases: MEDLINE/PubMed, EMBASE, CENTRAL (the Cochrane Central Register of Controlled Trials), Web of Science, PsycINFO, CINAHL and LiLACS. A comprehensive search of unpublished theses and dissertations via ProQuest Dissertation Abstracts, European Association for Grey Literature Exploitation (EAGLE) and National Technical Information Service (NTIS) will be completed. We will search clinicaltrials.gov for ongoing trial registers. We will also check relevant reports on the US Food and Drug Administration (FDA) website, the WHO's trial portal, and hand-search major psychiatric and medical journals. The search deadline will be from inception up to July 2013. No language restrictions will be applied. Details of search strategies can be found in online supplementary appendix table 1. Electronic databases will be searched using the following strategy: additional relevant studies will be obtained by scanning reference lists of trials identified in the initial searches and relevant review papers. In addition, all relevant authors will be contacted to supplement incomplete information.

Study selection and data extraction

Selection of trials

Titles and abstracts of references identified by the electronic search strategies described above will be independently examined by two reviewers (BQ and YL). 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 by the same eligibility criteria. The inter-rater reliability of the two raters will be calculated. Besides, the references of relevant review papers and included trials will be checked by BQ and YZ. Any disagreement will be resolved by consensus between the two reviewers and, if need be, with another reviewer (XZ). The reasons for exclusion of trials will be reported in the characteristics of excluded studies tables.

Quality assessment

Two reviewers (BQ and YL) will independently assess the methodological quality of the included studies. 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.[50] The following items will be assessed:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants, personnel and outcome assessors (assessments should be made for each main outcome or class of outcomes).
4. Incomplete outcome data (assessments should be made for each main outcome or class of outcomes).
5. Selective outcome reporting.
6. Other sources of bias.

The inter-rater reliability of the total score of study quality assessment will be examined. Any disagreement will be resolved by consensus between the two raters and, if need be, with another reviewer (XZ).

Data extraction

Two independent reviewers (BQ and YL) will extract the data from the original reports using standardised data extraction forms, which include f study characteristics (such as first listed author, publication year, journal, country, institution and sponsor), patient characteristics (such as diagnostic criteria for depression, the type of patients, the number of patients and patients' baseline), intervention details (such as psychotherapy type, session of psychotherapy, the duration of treatment, treatment setting and pattern) and outcome measures (such as the patients of intention-to-treat (ITT) analysis, acute treatment outcomes and follow-up outcomes). Any disagreements will be resolved by a third review author (XZ).

Statistical analysis

First, traditional pairwise meta-analyses will be performed for studies that directly compared different treatment arms. Then we will perform a Bayesian network meta-analysis to assess the relative outcomes of different psychotherapies and control conditions with each other from all direct and indirect comparisons. Dichotomous outcomes will be analysed on an ITT basis: dropouts will always be included in this analysis. When data on dropouts are carried forward and included in the evaluation (Last Observation Carried Forward, LOCF), they will be analysed according to the primary studies. Scores from continuous outcomes will not be analysed on an ITT basis. Continuous outcomes will therefore be analysed on an end point basis, including only participants with a final assessment or with a LOCF to the final assessment.

Traditional pairwise meta-analyses

Traditional pairwise meta-analyses will be performed using Review Manager (V.5.2). Using the DerSimonian method and the Laird random-effects model, the pooled estimates of standardised mean difference (SMD) with 95% CIs will be calculated for the continuous outcomes, and ORs with 95% CIs will be calculated for the dichotomous outcomes. Heterogeneity of treatment effects across studies will be assessed by I^2 and the Q-statistic test.[50]

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Bayesian network meta-analyses

Network meta-analyses will be performed using the WinBUGS software package (V.1.4.3, MRC Biostatistics Unit, Cambridge, UK) with random-effects models for multiarm trials.[28 51] The other analyses will be performed and presented by the Stata V.11.0 and R V.2.11.1 software packages. Network meta-analyses will be performed on two different evidence networks. The primary analysis is based on a network where the psychological interventions mentioned above will be treated as a separate node regardless of group or individual treatment. A secondary evidence network of drug class will also be constructed to view the group psychotherapy or individual psychotherapy in the same intervention as a separate node. 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. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic will be assessed.[52] Convergence will be found to be adequate after running 50 000 samples for both chains. These samples will then be discarded as 'burn-in,' and posterior summaries will be based on 100 000 subsequent simulations. All results will be reported as posterior medians of SMD or with corresponding 95% credible intervals (CrIs), which can be interpreted like conventional 95% CIs. When a loop connected three treatments, it was possible to evaluate the inconsistency between direct and indirect evidence. The node splitting method will be used to calculate the inconsistency of the model, which separates evidence on a particular comparison into direct and indirect evidence.[53]

The probability of each treatment being the most effective (best, second-best, third-best and so on) will be calculated and graphically ranked with rankograms.[54] Probability values will be summarised and reported as surface under the cumulative ranking curve (SUCRA), a simple transformation of the mean rank used to provide a hierarchy of the treatments that accounts for the location and the variance of all relative treatment effects.[55] The larger the SUCRA value, the better the rank of the treatment with a SUCRA of 1.0 if an intervention always ranks first and 0.0 if it always ranks last.

Subgroup analysis

Where possible, we will perform the following subgroups analysis: (1) for the age of participants (eg, children aged 6–12 years or adolescents from 13 to 18 years); and (2) for the duration of psychotherapy (eg, short-term treatment of six or fewer weeks or long-term treatment of more than 6 weeks).

Sensitivity analyses

We will perform the following sensitivity analyses: (1) by limiting the studies to be included to those of higher quality; (2) by limiting studies to those that employed standardised criteria for major depression; (3) by excluding studies with comorbid physical or mental disorders that were not a primary diagnosis (if possible, excluding only participants who had a comorbid diagnosis); (4) by excluding studies with a concomitant use of psychotropic agents (if possible, excluding only participants who had a concomitant use of psychotropic agents); (5) by excluding studies with small sample sized trials; and (6) by excluding studies with mild and intermittent depression patients.

Funnel plot analysis and meta-regression analysis

We will perform funnel plot analyses to check for publication bias. Moreover, we will carry out meta-regression analyses to investigate the effect of sponsorship or year published on outcome estimate.

Ethics and dissemination

This systematic review and network meta-analysis will be published in a peer–reviewed journal. It will be disseminated electronically and in print. As no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required.

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