BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016608
Article Type:	Protocol
Date Submitted by the Author:	25-Feb-2017
Complete List of Authors:	Zhou, Xinyu; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology and Psychiatry Cipriani, Andrea; University of Oxford, Department of Psychiatry; Warneford Hospital, Oxford Health NHS Foundation Trust Zhang, Yuqing; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology and Psychiatry Cuijpers, Pim; Vrije Universiteit Amsterdam, Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute Hetrick, Sarah; University of Melbourne, Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health Weisz, John; Harvard University, Department of Psychology Pu, Juncai; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology and Psychiatry Del Giovane, Cinzia; University of Modena and Reggio Emilia, Clinical and Diagnostic Medicine and Public Health Furukawa, Toshi; Kyoto University, Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health Barth, Jürgen; University Hospital and University of Zurich, Institute of Complementary and Integrative Medicine Coghill, David; University of Melbourne, Departments of Paediatrics and Psychiatry Leucht, Stefan; Technische Universität München, Department of Psychiatry and Psychotherapy Yang, Lining; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology and Psychiatry Ravindran, Arun ; University of Toronto, Department of Psychiatry Xie, Peng; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology and Psychiatry; Chongqing Medical University, Institute of Neuroscience and the Collaborative Innovation Center for Brain Science
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health, Pharmacology and therapeutics, Evidence based practice
Keywords:	Depression & mood disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY, antidepressant, psychotherapy, network meta-

	analysis, systematic review

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

Xinyu Zhou,[1] Andrea Cipriani,[2,3] Yuqing Zhang,[1] Pim Cuijpers,[4] Sarah E. Hetrick,[5] John R. Weisz,[6] Juncai Pu,[1] Cinzia Del Giovane,[7] Toshiaki A. Furukawa,[8] Jürgen Barth,[9] David Coghill,[10] Stefan Leucht[11] Lining Yang,[1] Arun V Ravindran,[12] Peng Xie[1]

[1] Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University, Chongqing, China

[2] Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

[3] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

[4] Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, The Netherlands

[5] Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health, University of Melbourne, Melbourne, Australia

[6] Department of Psychology, Harvard University, Cambridge, MA, USA

[7] Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy

[8] Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan

[9] Institute of Complementary and Integrative Medicine, University Hospital and University of Zurich, Zurich, Switzerland

[10] Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, Australia

[11] Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany

[12] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Direct correspondence to:

Prof. Peng Xie, Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuzhong District, Chongqing 400016, China; E-mail: xiepeng973@126.com

Xinyu Zhou and Andrea Cipriani contributed equally to this work.

Keywords: depression, child, adolescent, antidepressant, psychotherapy, network meta-analysis, systematic review

Word count: 3381.

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 young people.

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, PsycINFO, CINAHL, LiLACS) will be searched from date of inception. We will also search ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and check relevant reports on the US FDA 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 behavior 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. The results will be disseminated through peer-reviewed publication.

Protocol registration: PROSPERO CRD42015020841

Strengths and limitations of this study

1. The network meta-analysis can integrate direct evidence with indirect evidence from multiple treatment comparisons and multiple control approaches to estimate the interrelations across all treatments, which can guide treatment decisions and guideline development.

2. For the first time the efficacy, acceptability, tolerability, and suicide-related outcomes of pharmacological and psychological interventions, alone or in combination for depressive disorder in children and adolescents will be comprehensively assessed in a network meta-analysis.

3. We will employ validated local and global methods to evaluate consistency and we will explore whether treatment effects are robust in network subgroup analyses and sensitivity analyses. The quality of evidence for network estimates of the primary outcomes will be assessed 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.

Background

Depressive disorder in children and adolescents is a major public health problem, affecting 1% to 2% of children (6–12 years old) and 2% to 5% of adolescents (13–18 years old), with a peak incidence around puberty.[1,2] The course of depressive disorder in young people is often characterised by protracted episodes, frequent recurrence, and comorbid psychiatric disorders.[3] Compared with adults, the identification and diagnosis of depressive disorder in children and adolescents may be more often missed by clinicians[4] 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),[5] and are significantly increased risk for suicide behaviors and ideation.[6] For example, a report from the American Academy of Child and Adolescent Psychiatry (AACAP) suggested that depressive disorder is responsible for over 500,000 suicide attempts by children and adolescents a year.[7]

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, CBT and IPT seem to be the best available psychotherapies for depression in children and adolescents.[8,9] Multiple pharmacological therapies have also been studied for the treatment of depressive disorder in children and adolescents.[10-12] The controversy about the use of antidepressants in this age group, due the potentially increased risk of suicidality, has not been fully resolved.[13] Recently, the findings of our previous studies showed most antidepressants do not seem to offer a clear benefit for children and adolescents, and fluoxetine is probably the best option to consider when a pharmacological treatment is indicated.[10]

Several clinical practice guidelines recommend that in children and adolescents, psychotherapy should be considered as the first-line intervention for the management of depressive disorder, while pharmacological treatments are often reserved for more severe illness or when psychotherapy does not work or is not available.[14,15] Nevertheless, the evidence-base for psychotherapy to be more effective and safer than antidepressants in the treatment of child and adolescent depressive disorder is not well established. A large, non-industry funded trial reported superior efficacy for fluoxetine compared to CBT in adolescents with

major depression.[16] Literature supports the notion that psychotherapy has its own side-effects.[17] However, unlike with antidepressants, they are rarely measured systematically, making the comparison of safety and tolerability harder.[18] Moreover, data from the adult studies showed that combination antidepressants and psychotherapy is superior to either intervention alone.[19,20] Recently, a Cochrane conventional meta-analysis, on the basis of the very limited evidence, reported that the effectiveness of psychological interventions, antidepressant medication and a combination of these interventions for treating depressive disorders in children and adolescents cannot be established.[21]

Network meta-analysis has the advantage that all interventions that have been tested in randomised controlled trials (RCTs) can be simultaneously compared, without requiring direct within-study treatment vs. treatment comparisons. Thus effects of the different treatments can be estimated relative to each other as well as to a common reference condition (e.g., pill placebo or psychological controls).[22] Network meta-analysis thus overcomes some of the limitations of traditional meta-analysis, in which conclusions are largely restricted to comparisons between treatments that have been directly compared in RCTs.[23] In our two previous network meta-analyses the comparative efficacy and acceptability of psychotherapies and antidepressants for depressive disorder in children and adolescents have been separately investigated[8,10] The aim of 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 randomised controlled trials (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 utilise 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 based on standardised diagnostic criteria (e.g., the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases).[24-29] 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 heterogeneity could violate the transitivity assumption in NMA (i.e. one can compare indirectly intervention B and C via intervention A).[30] 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 (e.g., anxiety 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 ten 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, e.g., behavioral therapy, cognitive-behavioral therapy, 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 always is pill placebo, and these for psychological control conditions will include waiting-list (WL), treatment as usual (TAU), psychological placebo or attention placebo, as well as 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 week. 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 present data for more than one time point within our pre-defined 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- or assessor-rated), e.g., Children's Depression Rating Scale (CDRS-R)[31] and Hamilton Depression Rating Scale (HAMD)[32] 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 (e.g., less than 28 for CDRS-R),[33] 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 behavior 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).[34] For the antidepressants trials, the data on suicidality mainly referred to the Columbia re-analysis data reported in the FDA report.[35] 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, e.g., Children's Global Assessment Scale (CGAS)[36] and Global Assessment of Functioning Scale (GAF),[37] or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[38] When data are reported on more than one measure, we will first chose 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[39], 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 network meta-analyses.[8,10] 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 viathe International Clinical Trials Registry Platform (ICTRP) in WHO. We will also check relevant reports on the US Food and Drug Administration (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, 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 (e.g., 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 (e.g., first listed author, publication year, title, publication type, publication journal, country, and sponsor), patient characteristics (e.g., 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 (e.g., 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 Hand book for Systematic Reviews of Interventions.[40] 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 (e.g., 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

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum power.[23] First, we will perform pairwise meta-analyses of direct evidence using the random-effects model with STATA version 14.0. Second, we will also perform a random-effects network meta-analysis (NMA) within a Bayesian framework using Markov chain Monte Carlo in WinBUGS version 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 odds ratio (OR). In the presence of minimally informative priors, Credible Intervals (CrIs) can be interpreted similarly to confidence intervals (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, confidence intervals or

standard errors are reported in articles, SD will be calculated from their values.[41] 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.[41]

In the analysis of network meta-analysis, 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.[42] 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.[43]

Measures for transitivity assumption

We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; and whether the distributions of clinical and methodological variables that can act as effect modifiers across treatment comparison are balanced across comparisons. The clinical features, which have been demonstrated to date to moderate efficacy of antidepressants and psychotherapy in children and adolescents include bipolarity,[44] psychotic features,[45] subthreshold depression.[46] 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 network meta-analysis 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-squared statistic[47] and its 95% confidence interval 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 (τ^2) estimated from the NMA models. We will also estimate a total I-squared value and predictive intervals for heterogeneity in the network.[48]

Measures for inconsistency

NMA assumes that there is consistency in the network (i.e. direct and indirect evidence are in agreement). However, the assumption of consistency can be violated either in the entire network or in certain parts (i.e. loops of evidence) of the network.[49] Therefore, consistency needs to be checked. We will evaluate the presence of local inconsistency and global inconsistency in STATA version 14.0 and will be duplicated in R software.[50]

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.[51] 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 network meta-analysis.[52]

Subgroup analyses and sensitivity analyses

Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (i) age of participants (children vs. adolescents); (ii) sex ratio; (iii) the severity of depressive symptoms at baseline; and (iv) the treatment duration. 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, and trials where high risk of bias rating have been assessed 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 (e.g., sample size of trials[53]), 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.[54] 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 network meta-analysis 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.

Contributors PX, AC, and XZ conceived the study and drafted the protocol. PX, AC and XZ wrote the first draft of the manuscript. PC, SEH, JRW, CDG, TAF, JB, DC, SL, AVR assisted in protocol design and revision. XZ, YZ, and LY participated in the search strategy development. CDG, and JP participated in the design of data synthesis and analysis. All the authors have approved the publication of the protocol.

Funding This work is supported by the National Basic Research Program of China (973 Program) (Grant No. 2009CB918300). The funders had no role in the protocol design; the writing of the protocol; or the decision to submit the protocol for publication.

Competing interests AC reports personal fees from Accord Healthcare as an expert witness for a patent issue about quetiapine extended release. SEH is an Editor of the Cochrane Common Mental Disorders Group, an author of the Cochrane systematic review of newer generation antidepressants for depression in children and adolescents, and an author (senior) on the Cochrane review of psychological, pharmacological and their combination for child/adoles depression. DC reports grants and personal fees from Shire; personal fees from Eli Lilly, Janssen Cilag, Novartis, Sandoz, Oxford University Press; and grants from European Union FP7, outside of the submitted work. Eli Lilly has provided drugs for a clinical trial led by SL as the principal investigator. AVR reports personal fees from Bristol Myers Squibb, Pfizer, Sunovion; grants from Pfizer, Grand Challenges Canada, Canadian Institute of Health Research, and AstraZeneca, outside of the submitted work. TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui Chemicals and Takeda Science Foundation. He has received royalties from

Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Tanabe-Mitsubishi. XZ, YZ, PC, JRW, JP, CDG, TAF, JB, and LY declare no competing interests.

Acknowledgments Andrea Cipriani is supported by the National Institute for Health Research Oxford Cognitive Health Clinical Research Facility. We thank Philip Hazell from Discipline of Psychiatry, Sydney Medical School, Concord West, NSW, Australia, David Cohen from Department of Child and Adolescent Psychiatry, Hôpital Pitié–Salpétrière, Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Paris, France, and Craig Whittington from Doctor Evidence, Santa Monica, CA, USA, for their valuable advice.

Provenance and peer review Not commissioned; externally peer-reviewed.

References

1. Costello EJ, Mustillo S, Erkanli A, et al. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry* 2003;60:837-44.
2. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2005;62:593-602.
3. Thapar A, Collishaw S, Pine DS, et al. Depression in adolescence. *Lancet* 2012;379:1056-67.
4. Philip H. Depression in children may go unnoticed and untreated. *BMJ* 2002;325:229-30.
5. Puig-Antich J, Lukens E, Davies M, et al. Psychosocial functioning in prepubertal major depressive disorders. II. Interpersonal relationships after sustained recovery from affective episode. *Arch Gen Psychiatry* 1985;42:511-17.
6. Gould MS, King R, Greenwald S, et al. Psychopathology associated with suicidal ideation and attempts among children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1998;37:915-23.
7. Centers for Disease Control and Prevention (CDC). Suicide trends among youths and young adults aged 10-24 years-United States, 1990-2004. *Morb Mortal Wkly Rep* 2007;56:905-8.
8. Zhou X, Hetrick SE, Cuijpers P, et al. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: A systematic review and network meta-analysis. *World Psychiatry* 2015;14:207-22.
9. Weisz JR, McCarty CA, Valeri SM. Effects of Psychotherapy for Depression in Children and Adolescents: A Meta-Analysis. *Psychol Bull* 2006;132:132-49.
10. Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016;388:881-90.
11. Hetrick SE, McKenzie JE, Cox GR, et al. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev* 2012;11:CD004851.
12. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst Rev* 2013;6:CD002317.

13. U.S. Food and Drug Administration (FDA). Suicidality in children and adolescents being treated with antidepressant medications. www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm161679.htm (accessed 20 Jan 2017).

14. National Collaborating Centre for Mental Health (UK). Depression in Children and Young People: Identification and management in primary, community and secondary care. British Psychological Society, 2005; Available from www.ncbi.nlm.nih.gov/books/NBK56425/. (accessed 20 Jan 2017).

15. McDermott B, Baigent M, Chanen A, et al. Clinical practice guidelines: Depression in adolescents and young adults. Melbourne: beyondblue: the national depression initiative, 2011.https://www.bspg.com.au/dam/bsg/product?client=BEYONDBLUE&prodid=BL/0890&type=file (accessed 20 Jan 2017).

16. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; 292(7): 807-20.

17. Nutt DJ, Sharpe M. Uncritical positive regard? Issues in the efficacy and safety of psychotherapy. *J Psychopharmacol* 2008; 22(1): 3-6.

18. Linden M, Schermuly-Haupt ML. Definition, assessment and rate of psychotherapy side effects. *World Psychiatry* 2014; 13(3): 306-9.

19. Pampallona S, Bollini P, Tibaldi G, et al. Combined pharmacotherapy and psychological treatment for depression: A systematic review. *Arch Gen Psychiatry.* 2004;61(7):714-9.

20. de Maat SM, Dekker J, Schoevers RA, et al. Relative efficacy of psychotherapy and combined therapy in the treatment of depression: A meta-analysis. *Eur Psychiatry* 2007;22(1):1-8.

21. Cox GR, Callahan P, Churchill R, et al. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst Rev* 2012;11:CD008324.

22. Mavridis D, Giannatsi M, Cipriani A, et al. A primer on network meta-analysis with emphasis on mental health. Evid Based Ment Health. 2015 May;18(2):40-6.

23. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105-24.

24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1980.

25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th Edition. Washington, DC: American Psychiatric Association, 1994.

27. World Health Organization (WHO).*The ninth revision of the international classification of diseases and related health problems (ICD-9)*. Geneva: World Health Organization, 1978.

28. World Health Organization (WHO).*The tenth revision of the international classification of diseases and related health problems (ICD-10)*. Geneva: World Health Organization, 1992.

29. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980-8.

30. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Meth* 2012; 3:80-97.

31. Poznanski EO, Mokros HB. Children's depression rating scale, revised (CDRS-R): manual. *Western Psychological Services*, 1996.

32. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.

33. Riedel M, Moller HJ, Obermeier M, et al. Response and remission criteria in major depression—a validation of current practice. *J Psychiatr Res* 2010;44:1063-8.

34. Posner K, Oquendo MA, Gould M, et al. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164:1035-43.

35. Hammad TA. Review and evaluation of clinical data. Washington, DC, US Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10- tab08-hammads-review.pdf (accessed 20 Jan 2017).

36. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry* 1983;40:1228-3l.

37. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33:766-71.

38. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull* 1993;29:321-326.

39. Zhou X, Qin B, Whittington C, et al. Comparative efficacy and tolerability of first-generation and newer-generation antidepressant medications for depressive disorders in children and adolescents: study protocol for a systematic review and network meta-analysis. *BMJ Open* 2015;5:e007768.

40. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions version 5.1. 0* [updated March 2011]. The Cochrane Collaboration, 2011. http://handbook.cochrane.org/ (accessed 20 Jan 2017).

41. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7-10.

42. Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998;7:434-45.

43. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64:163-71.

44. Liu HY, Potter MP, Woodworth KY, et al. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2011;50:749-62.

45. Sullivan SA, Lewis G, Gunnell D, et al. The longitudinal association between psychotic experiences, depression and suicidal behaviour in a population sample of adolescents. *Soc Psychiatry Psychiatr Epidemiol*. 2015;50:1809-17.

46. Wesselhoeft R, Sørensen MJ, Heiervang ER, et al. Subthreshold depression in children and adolescents - a systematic review. *J Affect Disord*. 2013; 151:7-22.

47. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

48. Jackson D, Barrett JK, Rice S, et al. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine* 2014; 33:3639-54.

49. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013; 33:641-656.

50. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012; 3:98-110.

51. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991-6.

52. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment met-aanalysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163-71.

53. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012;3:161-76.

54. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682.

TABLES

Table 1 Description of Psychotherapeutic interventions and control conditions

Interventions	Abbreviation	Description
Psychotherapeutic Intervention:		
Behavioral therapy	BT	BT uses some kind of behavioral training and psychoeducation. BT programs provide parents and youths information about MDD and interventions; teach youths to monitor their mood, thoughts and behaviors; proposed pleasant activity scheduling and behavioral activation.
Cognitive-behavioral therapy	CBT	CBT is a combination of BT and CT. Additional CBT skill-building techniques are used in many programs by teaching relaxation techniques to cope with environmental stressors, providing social skills and resolution training, and teaching general problem-solving.
Cognitive therapy	CT	CT uses some kind of cognitive restructuring training. CT programs ask youths to examine their automatic thoughts and core schemas and to assess the accuracy and affective consequences of their views. They aim to teach youths to engage in "rational" thinking about themselves, the world and their possibilities for the future.
Family therapy	FT	FT works with families to nurture change and development. FT tends to view change in terms of the systems of interaction between family members. In the case of youth with MDD, FT aims at helping the family to answer the child's needs for completing age-appropriate developmental tasks to relieve depression.
Interpersonal therapy	IPT	IPT aim at educating patients as to how their depression and the quality of interpersonal relationships affect one another and at addressing interpersonal problems that may be contributing to the depression (e.g. grief, disputes, role transitions, social deficits). Compared to its adult version, IPT in youths is shorter, involves parents, and adds a liaison role for the therapist between schools and families.
Play therapy	PT	PT used techniques to engage participants in recreational activities to help them cope with their problems and fears.
Problem-solving therapy	PST	PST focus on the problems participants are currently facing and on helping them find solutions to those problems.
Psychodynamic therapy	DYN	DYN proposed patients to help understand the origin and nature of long standing problems by investigating both conscious and non-conscious thoughts and emotional feelings. DYN uses free associations and interpretation of dreams (or drawing in children), and addresses how personal history and experience may alter the patient/therapist transference. In youth MDD, a particular interest is given to psychological trauma, early

		parent/child relationships, narcissistic organization and experiences of loss.
Supportive therapy	SUP	SUP is an unstructured therapy without specific psychological techniques that it helped people to ventilate their experiences and emotions and offering empathy. These therapies are commonly described in the literature as either counseling or supportive therapy.
Control conditions:		
No-treatment	NT	NT is a control condition in which the participants receive no active treatment during the study and in which they do not expect to receive such after the study is over.
Psychological placebo	PBO	PBO is a control condition that was regarded as inactive by the researchers but was to be the participants.
Treatment-as-usual	TAU	TAU is not considered to be structured psychotherapy but may have some treatment effects.
Waitlist	WL	WL is a control condition in which the participants receive no active treatment during the study but are forewarned that they can receive one after the study period is over.

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 Behavior Checklist-Depression	CBCL-D

Figure 1. Possible interventions eligible for the ideal network plot

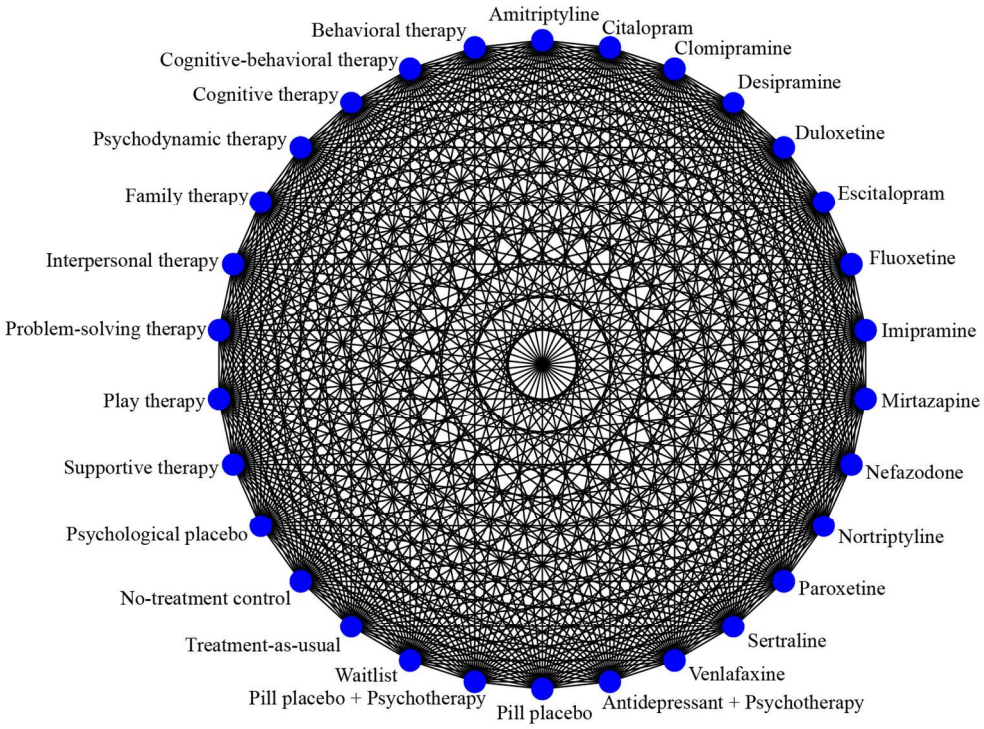

Figure 1. Possible interventions eligible for the ideal network plot

139x102mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis	1
Update	1b	None	
Registration	2	PROSPERO CRD42015020841	4
Authors:			
Contact	3a	Xinyu Zhou, Yuqing Zhang, Juncai Pu, Lining Yang, Peng Xie (Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University, Chongqing, China) Andrea Cipriani (Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK) Pim Cuijpers (Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, The Netherlands) Sarah E. Hetrick (Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health, University of Melbourne, Melbourne, Australia) John R. Weisz (Department of Psychology, Harvard University, Cambridge, MA, USA) Cinzia Del Giovane (Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy) Toshiaki A. Furukawa (Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan) Jürgen Barth (Institute of Complementary and Integrative Medicine, University Hospital and University of Zurich, Zurich, Switzerland) David Coghill (Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, Australia) Stefan Leucht (Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany) Arun V Ravindran (Department of Psychiatry, University of Toronto, Toronto, ON, Canada) Corresponding author :Peng Xie, Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuzhong District, Chongqing 400016, China; E-mail: xiepeng973@126.com	1-2
Contributions	3b	PX, AC, and XZ conceived the study and drafted the protocol. PX, AC and XZ wrote the first draft of the manuscript. PC, SEH, JRW, CDG, TAF, JB, DC, AVR assisted in protocol design and revision. XZ, YZ, and LY participated in the search strategy	17

		development. CDG, and JP participated in the design of data synthesis and analysis. All the authors have approved the publication of the protocol.	
Amendments	4	None	
Support:			
Sources	5a	ational Basic Research Program of China (973 Program) (Grant No. 2009CB918300)	
Sponsor	5b	This work is supported by the National Basic Research Program of China (973 Program) (Grant No. 2009CB918300).	
Role of sponsor or funder	5c	The funders had no role in the protocol design; the writing of the protocol; or the decision to submit the protocol for publication.	
INTRODUCTION			
Rationale	6	Depressive disorder in children and adolescents is a major public health problem. The course of depressive disorder in young people is often characterised by protracted episodes, frequent recurrence, and comorbid psychiatric disorders. Several clinical practice guidelines recommend that in children and adolescents, psychotherapy should be considered as the first-line intervention for the management of depressive disorder, while pharmacological treatments are often reserved for more severe illness or when psychotherapy does not work or is not available. Nevertheless, the evidence-base for psychotherapy to be more effective and safer than antidepressants in the treatment of child and adolescent depressive disorder is not well established. In our two previous network meta-analyses the comparative efficacy and acceptability of psychotherapies and antidepressants for depressive disorder in children and adolescents have been separately investigated	6
Objectives	7	The aim of 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.	7
METHODS			
Eligibility criteria	8	**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 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 heterogeneity could violate the transitivity assumption in NMA (i.e. 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 (e.g., anxiety 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 ten patients will be excluded.	7-10

Types of studies

Any randomised controlled trials (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 utilise 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 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, e.g., behavioral therapy, cognitive-behavioral therapy, cognitive therapy, family therapy, interpersonal therapy, play therapy, problem-solving therapy, psychodynamic therapy, and supportive therapy. Also, we will include the combination of both psychological interventions and pharmacological interventions. For the pharmacological interventions, the control condition always is pill placebo, and these for psychological control conditions will include waiting-list (WL), treatment as usual (TAU), psychological placebo or attention placebo, as well as 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 week. 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 present data for more than one time point within our pre-defined 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.

Types of outcome measures

Primary outcomes

(1) Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self- or assessor-rated), e.g., 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 (e.g., 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 behavior 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 re-analysis data reported in the 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, e.g., Children's Global Assessment Scale (CGAS) and Global Assessment of Functioning Scale (GAF), or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). When data are reported on more than one measure, we will first chose data from the CGAS, then the GAF, and finally the Q-LES-Q and others.	
Information sources	9	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 network meta-analyses.8,10 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. We will also search ClinicalTrials.gov in USA and other international trial registers viathe International Clinical Trials Registry Platform (ICTRP) in WHO. We will also check relevant reports on the US Food and Drug Administration (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, 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 (e.g., 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.	11-12
Search strategy	10	(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).	11
Study records:			

Data management	11a	Literature search results will be imported to Endnote and the duplicates will be removed during the study selection process. We will screening citations based on the inclusion and exclusion criteria.	12
Selection process	11b	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.	12
Data collection process	11c	Two independent reviewers (XZ and YZ) will extract the data from each included trial using standardised data extraction forms. 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.	12-13
Data items	12	Study characteristics (e.g., first listed author, publication year, title, publication type, publication journal, country, and sponsor), patient characteristics (e.g., 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 (e.g., 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).	12
Outcomes and prioritization	13	Primary outcomes (1) Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self- or assessor-rated), e.g., 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 (e.g., 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 behavior 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 re-analysis data reported in the 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, e.g., Children's Global Assessment Scale (CGAS) and Global Assessment of Functioning Scale (GAF), or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). When data are reported on more than one measure, we will first chose	10-11

		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). 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.	
Risk of bias in individual studies	14	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 Hand book 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 (e.g., 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.	13
Data synthesis	15a	We will perform Bayesian network meta-analysis to compare the relative outcomes of different antidepressant medications, psychotherapies or their combination from the median of the posterior distribution.	13
	15b	Network meta-analysis 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 version 14.0. Second, we will also perform a random-effects network meta-analysis (NMA) within a Bayesian framework using Markov chain Monte Carlo in WinBUGS version 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 odds ratio (OR). In the presence of minimally informative priors, Credible Intervals (CrIs) can be interpreted similarly to confidence intervals (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, confidence intervals or standard errors 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 network meta-analysis, 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.	13-14
	15c	Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (i) age of participants (children vs. adolescents); (ii) sex ratio; (iii) the severity of depressive symptoms at baseline; and (iv) the treatment duration. If possible, we will do some extra subgroup analyses according to the results of heterogeneity and inconsistency. In the	15-16

		sensitivity analysis, trials where missing data have been imputed will be excluded, and trials where high risk of bias rating have been assessed 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 (e.g., sample size of trials53), as continuous measure in meta-regression analyses.	
	15d	A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies.	15
Meta-bias(es)	16	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 network meta-analysis.	15
Confidence in cumulative evidence	17	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.	16

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016608.R1
Article Type:	Protocol
Date Submitted by the Author:	11-May-2017
Complete List of Authors:	Zhou, Xinyu; The First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Cipriani, Andrea; University of Oxford, Department of Psychiatry; Warneford Hospital, Oxford Health NHS Foundation Trust Zhang, Yuqing; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology Cuijpers, Pim; Vrije Universiteit Amsterdam, Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute Hetrick, Sarah; University of Melbourne, Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health Weisz, John; Harvard University, Department of Psychology Pu, Juncai; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology Del Giovane, Cinzia; University of Modena and Reggio Emilia, Clinical and Diagnostic Medicine and Public Health Furukawa, Toshi; Kyoto University, Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health Barth, Jürgen; University Hospital and University of Zurich, Institute of Complementary and Integrative Medicine Coghill, David; University of Melbourne, Departments of Paediatrics and Psychiatry Leucht, Stefan; Technische Universität München, Department of Psychiatry and Psychotherapy Yang, Lining; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology Ravindran, Arun ; University of Toronto, Department of Psychiatry Xie, Peng; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology; Chongqing Medical University, Institute of Neuroscience and the Collaborative Innovation Center for Brain Science
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health, Pharmacology and therapeutics, Evidence based practice
Keywords:	Depression & mood disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY, antidepressant, psychotherapy, network meta-analysis, systematic review

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

Xinyu Zhou,[1] Andrea Cipriani,[2,3] Yuqing Zhang,[4] Pim Cuijpers,[5] Sarah E. Hetrick,[6] John R. Weisz,[7] Juncai Pu,[4] Cinzia Del Giovane,[8] Toshiaki A. Furukawa,[9] Jürgen Barth,[10] David Coghill,[11] Stefan Leucht,[12] Lining Yang,[4] Arun V Ravindran,[13] Peng Xie[4]

[1] Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

[2] Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

[3] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

[4] Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China;

Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University, Chongqing, China

[5] Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, The Netherlands

[6] Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health, University of Melbourne, Melbourne, Australia

[7] Department of Psychology, Harvard University, Cambridge, MA, USA

[8] Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy

[9] Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan

[10] Institute for Complementary and Integrative Medicine, UniversityHospital and University of Zurich,

Zurich, Switzerland

[11] Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, Australia

[12] Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany

[13] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Direct correspondence to:

Prof. Peng Xie, Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuzhong District, Chongqing 400016, China; E-mail: xiepeng973@126.com

Xinyu Zhou and Andrea Cipriani contributed equally to this work.

Keywords: depression, child, adolescent, antidepressant, psychotherapy, network meta-analysis, systematic review

Word count: 3509.

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, PsycINFO, CINAHL, LiLACS) will be searched from date of inception. We will also search ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and check relevant reports on the US FDA 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 behavior 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 network meta-

analysis 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

Strengths and limitations of this study

1. The network meta-analysis can integrate direct evidence with indirect evidence from multiple treatment comparisons and multiple control approaches to estimate the interrelations across all treatments, which can guide treatment decisions and guideline development.

2. For the first time the efficacy, acceptability, tolerability, and suicide-related outcomes of pharmacological and psychological interventions, alone or in combination for depressive disorder in children and adolescents will be comprehensively assessed in a network meta-analysis.

3. We will employ validated local and global methods to evaluate consistency and we will explore whether treatment effects are robust in network subgroup analyses and sensitivity analyses. The quality of evidence for network estimates of the primary outcomes will be assessed 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.

Background

Depressive disorder in children and adolescents is a major public health problem, affecting 1% to 2% of children (6–12 years old) and 2% to 5% of adolescents (13–18 years old), with a peak incidence around puberty.[1,2] The course of depressive disorder in children and adolescents is often characterised by protracted episodes, frequent recurrence, and comorbid psychiatric disorders.[3] Compared with adults, the identification and diagnosis of depressive disorder in children and adolescents may be more often missed by clinicians[4] 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),[5] and are significantly increased risk for suicide behaviors and ideation.[6] 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.[7]

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 behavior therapy (CBT) and interpersonal psychotherapy (IPT) seem to be the best available psychotherapies for depression in children and adolescents.[8,9] Multiple pharmacological therapies have also been studied for the treatment of depressive disorder in children and adolescents.[10-12] The controversy about the use of antidepressants in this age group, due the potentially increased risk of suicidality, has not been fully resolved.[13] Recently, the findings of our previous studies showed most antidepressants do not seem to offer a clear benefit for children and adolescents, and fluoxetine is probably the best option to consider when a pharmacological treatment is indicated.[10]

Several clinical practice guidelines recommend that in children and adolescents, psychotherapy should be considered as the first-line intervention for the management of depressive disorder, while pharmacological treatments are often reserved for more severe illness or when psychotherapy does not work or is not available.[14,15] Nevertheless, the evidence-base for psychotherapy to be more effective and safer than antidepressants in the treatment of child and adolescent depressive disorder is not well established. A large,

non-industry funded trial reported superior efficacy for fluoxetine compared to CBT in adolescents with major depression.[16] Previous research supports the notion that psychotherapy has its own side-effects, such as dependency on the therapist, and leading to distress for the patients' family.[17] However, unlike with antidepressants, they are rarely measured systematically, making the comparison of safety and tolerability harder.[18] Moreover, data from the adult studies showed that combination antidepressants and psychotherapy is superior to either intervention alone.[19,20] Recently, a Cochrane conventional meta-analysis, on the basis of the very limited evidence, reported that the effectiveness of psychological interventions, antidepressant medication and a combination of these interventions for treating depressive disorders in children and adolescents cannot be established.[21]

Network meta-analysis has the advantage that all interventions that have been tested in randomised controlled trials (RCTs) can be simultaneously compared, without requiring direct within-study treatment vs. treatment comparisons. Thus effects of the different treatments can be estimated relative to each other as well as to a common reference condition (e.g., pill placebo or psychological controls).[22] Network meta-analysis thus overcomes some of the limitations of traditional meta-analysis, in which conclusions are largely restricted to comparisons between treatments that have been directly compared in RCTs.[23] In our two previous network meta-analyses the comparative efficacy and acceptability of psychotherapies and antidepressants for depressive disorder in children and adolescents have been separately investigated[8,10] The aim of 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 randomised controlled trials (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 utilise 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).[24-29] 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 heterogeneity could violate the transitivity assumption in NMA (i.e. one can compare indirectly intervention B and C via intervention A).[30] 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 (e.g., 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 ten 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, e.g., behavioral therapy, cognitive-behavioral therapy, 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, whilst 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 week. 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.[31] If a study present data for more than one time point within our pre-defined 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- or assessor-rated), e.g., Children's Depression Rating Scale (CDRS-R)[32] and Hamilton Depression Rating Scale (HAMD)[33] 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 (e.g., less than 28 for CDRS-R),[34] 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 behavior 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).[35] For the antidepressants trials, the data on suicidality mainly referred to the Columbia re-analysis data reported in the FDA report.[36] 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, e.g., Children's Global Assessment Scale (CGAS)[37] and Global Assessment of Functioning Scale (GAF),[38] or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[39] When data are reported on more than one measure, we will first chose 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[40], 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 network meta-analyses.[8,10] 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 viathe International Clinical Trials Registry Platform (ICTRP) in WHO. We will also check relevant reports on the US Food and Drug Administration (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, 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 (e.g., 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 (e.g., first listed author, publication year, title, publication type, publication journal, country, and sponsor), patient characteristics (e.g., 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 (e.g., 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 Hand book for Systematic Reviews of Interventions.[41] 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 (e.g., 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

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum power.[23] First, we will perform pairwise meta-analyses of direct evidence using the random-effects model with STATA version 14.0. Second, we will also perform a random-effects network meta-analysis (NMA) within a Bayesian framework using Markov chain Monte Carlo in WinBUGS version 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 odds ratio (OR). In the presence of minimally informative priors, Credible Intervals (CrIs) can be interpreted similarly to confidence intervals (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, confidence intervals or standard errors are reported in articles, SD will be calculated from their values.[42] 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.[42]

In the analysis of network meta-analysis, 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.[43] 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.[44]

Measures for transitivity assumption

We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; and whether the distributions of clinical and methodological variables that can act as effect modifiers across treatment comparison are balanced across comparisons. The clinical features, which have been demonstrated to date to moderate efficacy of antidepressants and psychotherapy in children and adolescents include bipolarity,[45] psychotic features,[46] subthreshold depression.[47] 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 network meta-analysis 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-squared statistic[48] and its 95% confidence interval 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 (τ^2) estimated from the NMA models. We will also estimate a total I-squared value and predictive intervals for heterogeneity in the network.[49]

Measures for inconsistency

NMA assumes that there is consistency in the network (i.e. direct and indirect evidence are in agreement). However, the assumption of consistency can be violated either in the entire network or in certain parts (i.e. loops of evidence) of the network.[50] Therefore, consistency needs to be checked. We will evaluate the presence of local inconsistency and global inconsistency in STATA version 14.0 and will be duplicated in R software.[51]

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.[52] 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 network meta-analysis.[53]

Subgroup analyses and sensitivity analyses

Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (i) age of participants (children vs. adolescents); (ii) sex ratio; (iii) the severity of depressive symptoms at baseline; (iv) the treatment duration; (v) the dosing schedule (fixed or flexible doses). 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 (e.g., sample size of trials[54]), 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.[55] 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 network meta-analysis 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.

Contributors PX, AC, and XZ conceived the study and drafted the protocol. PX, AC and XZ wrote the first draft of the manuscript. PC, SEH, JRW, CDG, TAF, JB, DC, SL, AVR assisted in protocol design and revision. XZ, YZ, and LY participated in the search strategy development. CDG, and JP participated in the design of data synthesis and analysis. All the authors have approved the publication of the protocol.

Funding This work is supported by the National Basic Research Program of China (973 Program) (Grant No. 2009CB918300). The funders had no role in the protocol design; the writing of the protocol; or the decision to submit the protocol for publication.

Competing interests AC reports personal fees from Accord Healthcare as an expert witness for a patent issue about quetiapine extended release. SEH is an Editor of the Cochrane Common Mental Disorders Group, an author of the Cochrane systematic review of newer generation antidepressants for depression in children and adolescents, and an author (senior) on the Cochrane review of psychological, pharmacological and their combination for child/adoles depression. DC reports grants and personal fees from Shire; personal fees from Eli Lilly, Janssen Cilag, Novartis, Sandoz, Oxford University Press; and grants from European Union FP7, outside of the submitted work. Eli Lilly has provided drugs for a clinical trial led by SL as the principal investigator. AVR reports personal fees from Bristol Myers Squibb, Pfizer, Sunovion; grants from Pfizer, Grand Challenges Canada, Canadian Institute of Health Research, and AstraZeneca, outside of the submitted work. TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui Chemicals and Takeda Science Foundation. He has received royalties from

Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Tanabe-Mitsubishi. XZ, YZ, PC, JRW, JP, CDG, TAF, JB, and LY declare no competing interests.

Acknowledgments Andrea Cipriani is supported by the National Institute for Health Research Oxford Cognitive Health Clinical Research Facility. We thank Philip Hazell from Discipline of Psychiatry, Sydney Medical School, Concord West, NSW, Australia, David Cohen from Department of Child and Adolescent Psychiatry, Hôpital Pitié–Salpétrière, Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Paris, France, and Craig Whittington from Doctor Evidence, Santa Monica, CA, USA, for their valuable advice.

Provenance and peer review Not commissioned; externally peer-reviewed.

References

1. Costello EJ, Mustillo S, Erkanli A, *et al*. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry* 2003;60:837-44.
2. Kessler RC, Berglund P, Demler O, *et al*. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:593-602.
3. Thapar A, Collishaw S, Pine DS, *et al*. Depression in adolescence. *Lancet* 2012;379:1056-67.
4. Hazell P. Depression in children. *BMJ* 2002;325:229-30.
5. Puig-Antich J, Lukens E, Davies M, *et al*. Psychosocial functioning in prepubertal major depressive disorders. II. Interpersonal relationships after sustained recovery from affective episode. *Arch Gen Psychiatry* 1985;42:511-7.
6. Gould MS, King R, Greenwald S, *et al*. Psychopathology associated with suicidal ideation and attempts among children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1998;37:915-23.
7. Centers for Disease Control and Prevention (CDC). Suicide trends among youths and young adults aged 10-24 years-United States, 1990-2004. *Morb Mortal Wkly Rep* 2007;56:905-8.
8. Zhou X, Hetrick SE, Cuijpers P, *et al*. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry* 2015;14:207-22.9. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull* 2006;132:132-49.
10. Cipriani A, Zhou X, Del Giovane C, *et al*. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016;388:881-90.
11. Hetrick SE, McKenzie JE, Cox GR, *et al*. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev* 2012;11:CD004851.
12. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst Rev* 2013;6:CD002317.
13. U.S. Food and Drug Administration (FDA). Suicidality in children and adolescents being treated with antidepressant medications.

www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm161679.htm (accessed 20 Jan 2017).

14. National Collaborating Centre for Mental Health (UK). Depression in Children and Young People: Identification and management in primary, community and secondary care. British Psychological Society, 2005; Available from www.ncbi.nlm.nih.gov/books/NBK56425/. (accessed 20 Jan 2017).
15. McDermott B, Baigent M, Chanen A, *et al*. Clinical practice guidelines: Depression in adolescents and young adults. Melbourne: beyondblue: the national depression initiative, 2011.https://www.bspg.com.au/dam/bsg/product?client=BEYONDBLUE&prodid=BL/0890&type=file (accessed 20 Jan 2017).
16. March J, Silva S, Petrycki S, *et al*. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; 292: 807-20.
17. Nutt DJ, Sharpe M. Uncritical positive regard? Issues in the efficacy and safety of psychotherapy. *J Psychopharmacol* 2008; 22: 3-6.
18. Linden M, Schermuly-Haupt ML. Definition, assessment and rate of psychotherapy side effects. *World Psychiatry* 2014; 13: 306-9.
19. Pampallona S, Bollini P, Tibaldi G, *et al*. Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Arch Gen Psychiatry.* 2004;61:714-9.
20. de Maat SM, Dekker J, Schoevers RA, *et al*. Relative efficacy of psychotherapy and combined therapy in the treatment of depression: a meta-analysis. *Eur Psychiatry* 2007;22:1-8.
21. Cox GR, Callahan P, Churchill R, *et al*. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst Rev* 2012;11:CD008324.
22. Mavridis D, Giannatsi M, Cipriani A, *et al*. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health* 2015;18:40-6.

23. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105-24.

24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1980.

25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th Edition. Washington, DC: American Psychiatric Association, 1994.

27. World Health Organization (WHO).*The ninth revision of the international classification of diseases and related health problems (ICD-9)*. Geneva: World Health Organization, 1978.

28. World Health Organization (WHO).*The tenth revision of the international classification of diseases and related health problems (ICD-10)*. Geneva: World Health Organization, 1992.

29. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980-8.

30. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Meth* 2012; 3:80-97.

31. Birmaher B, Brent D, AACAP Work Group on Quality Issues, *et al*. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 2007;46:1503-26.

32. Poznanski EO, Mokros HB. *Children's depression rating scale, revised (CDRS-R): manual*. Los Angeles: Western Psychological Services, 1996.

33. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.

34. Riedel M, Moller HJ, Obermeier M, *et al*. Response and remission criteria in major depression—a validation of current practice. *J Psychiatr Res* 2010;44:1063-8.

35. Posner K, Oquendo MA, Gould M, *et al*. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164:1035-43.

36. Hammad TA. Review and evaluation of clinical data. Washington, DC, US Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10- tab08-hammads-review.pdf (accessed 20 Jan 2017).

37. Shaffer D, Gould MS, Brasic J, *et al*. A children's global assessment scale (CGAS). *Arch Gen Psychiatry* 1983;40:1228-3l.

38. Endicott J, Spitzer RL, Fleiss JL, *et al*. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33:766-71.

39. Endicott J, Nee J, Harrison W, *et al*. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull* 1993;29:321-6.

40. Zhou X, Qin B, Whittington C, *et al*. Comparative efficacy and tolerability of first-generation and newer-generation antidepressant medications for depressive disorders in children and adolescents: study protocol for a systematic review and network meta-analysis. *BMJ Open* 2015;5:e007768.

41. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions version 5.1. 0* [updated March 2011]. The Cochrane Collaboration, 2011. http://handbook.cochrane.org/ (accessed 20 Jan 2017).

42. Furukawa TA, Barbui C, Cipriani A, *et al*. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7-10.

43. Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998;7:434-45.

44. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64:163-71.

45. Liu HY, Potter MP, Woodworth KY, *et al*. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2011;50:749-62.

46. Sullivan SA, Lewis G, Gunnell D, *et al*. The longitudinal association between psychotic experiences, depression and suicidal behaviour in a population sample of adolescents. *Soc Psychiatry Psychiatr Epidemiol* 2015;50:1809-17.

47. Wesselhoeft R, Sørensen MJ, Heiervang ER, *et al*. Subthreshold depression in children and adolescents - a systematic review. *J Affect Disord* 2013; 151:7-22.

48. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

49. Jackson D, Barrett JK, Rice S, *et al*. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Stat Med* 2014; 33:3639-54.

50. Dias S, Welton NJ, Sutton AJ, *et al*. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013; 33:641-56.

51. Higgins JP, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012; 3:98-110.

52. Peters JL, Sutton AJ, Jones DR, *et al*. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991-6.

53. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment met-aanalysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163-71.

54. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012;3:161-76.

55. Salanti G, Del Giovane C, Chaimani A, *et al*. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682.

TABLES

Table 1 Description of Psychotherapeutic interventions and control conditions

Interventions	Abbreviation	Description
Psychotherapeutic Intervention:		
Behavioral therapy	BT	BT uses some kind of behavioral training and psychoeducation. BT programs provide parents and youths information about MDD and interventions; teach youths to monitor their mood, thoughts and behaviors; proposed pleasant activity scheduling and behavioral activation.
Cognitive-behavioral therapy	CBT	CBT is a combination of BT and CT. Additional CBT skill-building techniques are used in many programs by teaching relaxation techniques to cope with environmental stressors, providing social skills and resolution training, and teaching general problem-solving.
Cognitive therapy	CT	CT uses some kind of cognitive restructuring training. CT programs ask youths to examine their automatic thoughts and core schemas and to assess the accuracy and affective consequences of their views. They aim to teach youths to engage in "rational" thinking about themselves, the world and their possibilities for the future.
Family therapy	FT	FT works with families to nurture change and development. FT tends to view change in terms of the systems of interaction between family members. In the case of youth with MDD, FT aims at helping the family to answer the child's needs for completing age-appropriate developmental tasks to relieve depression.
Interpersonal therapy	IPT	IPT aim at educating patients as to how their depression and the quality of interpersonal relationships affect one another and at addressing interpersonal problems that may be contributing to the depression (e.g. grief, disputes, role transitions, social deficits). Compared to its adult version, IPT in youths is shorter, involves parents, and adds a liaison role for the therapist between schools and families.
Play therapy	PT	PT used techniques to engage participants in recreational activities to help them cope with their problems and fears.
Problem-solving therapy	PST	PST focus on the problems participants are currently facing and on helping them find solutions to those problems.
Psychodynamic therapy	DYN	DYN proposed patients to help understand the origin and nature of long standing problems by investigating both conscious and non-conscious thoughts and emotional feelings. DYN uses free associations and interpretation of dreams (or drawing in children), and addresses how personal history and experience may alter the patient/therapist transference. In youth MDD, a particular interest is given to psychological trauma, early

		parent/child relationships, narcissistic organization and experiences of loss.
Supportive therapy	SUP	SUP is an unstructured therapy without specific psychological techniques that it helped people to ventilate their experiences and emotions and offering empathy. These therapies are commonly described in the literature as either counseling or supportive therapy.
Control conditions:		
No-treatment	NT	NT is a control condition in which the participants receive no active treatment during the study and in which they do not expect to receive such after the study is over.
Psychological placebo	PBO	PBO is a control condition that was regarded as inactive by the researchers but was to be the participants.
Treatment-as-usual	TAU	TAU is not considered to be structured psychotherapy but may have some treatment effects.
Waitlist	WL	WL is a control condition in which the participants receive no active treatment during the study but are forewarned that they can receive one after the study period is over.

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 Behavior Checklist-Depression	CBCL-D

Figure 1. Possible interventions eligible for the ideal network plot

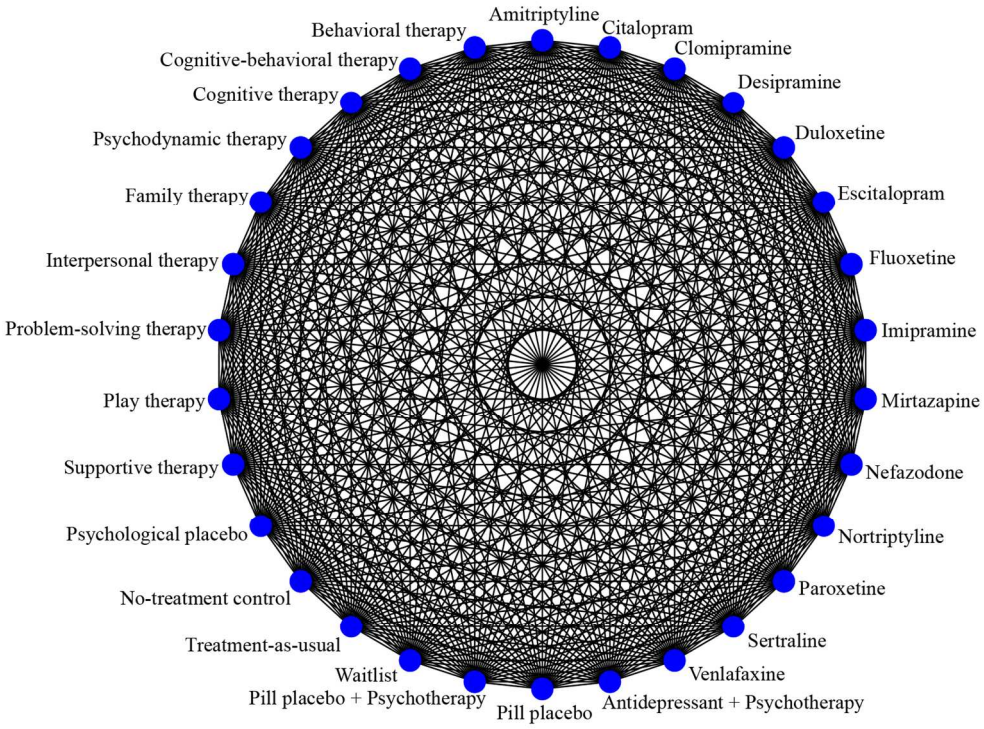

Figure 1. Possible interventions eligible for the ideal network plot

139x102mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis	1
Update	1b	None	
Registration	2	PROSPERO CRD42015020841	4
Authors:			
Contact	3a	Xinyu Zhou, Yuqing Zhang, Juncai Pu, Lining Yang, Peng Xie (Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University, Chongqing, China) Andrea Cipriani (Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK) Pim Cuijpers (Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, The Netherlands) Sarah E. Hetrick (Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health, University of Melbourne, Melbourne, Australia) John R. Weisz (Department of Psychology, Harvard University, Cambridge, MA, USA) Cinzia Del Giovane (Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy) Toshiaki A. Furukawa (Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan) Jürgen Barth (Institute of Complementary and Integrative Medicine, University Hospital and University of Zurich, Zurich, Switzerland) David Coghill (Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, Australia) Stefan Leucht (Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany) Arun V Ravindran (Department of Psychiatry, University of Toronto, Toronto, ON, Canada) Corresponding author :Peng Xie, Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuzhong District, Chongqing 400016, China; E-mail: xiepeng973@126.com	1-2
Contributions	3b	PX, AC, and XZ conceived the study and drafted the protocol. PX, AC and XZ wrote the first draft of the manuscript. PC, SEH, JRW, CDG, TAF, JB, DC, AVR assisted in protocol design and revision. XZ, YZ, and LY participated in the search strategy	17

		development. CDG, and JP participated in the design of data synthesis and analysis. All the authors have approved the publication of the protocol.	
Amendments	4	None	
Support:			
Sources	5a	ational Basic Research Program of China (973 Program) (Grant No. 2009CB918300)	
Sponsor	5b	This work is supported by the National Basic Research Program of China (973 Program) (Grant No. 2009CB918300).	
Role of sponsor or funder	5c	The funders had no role in the protocol design; the writing of the protocol; or the decision to submit the protocol for publication.	
INTRODUCTION			
Rationale	6	Depressive disorder in children and adolescents is a major public health problem. The course of depressive disorder in young people is often characterised by protracted episodes, frequent recurrence, and comorbid psychiatric disorders. Several clinical practice guidelines recommend that in children and adolescents, psychotherapy should be considered as the first-line intervention for the management of depressive disorder, while pharmacological treatments are often reserved for more severe illness or when psychotherapy does not work or is not available. Nevertheless, the evidence-base for psychotherapy to be more effective and safer than antidepressants in the treatment of child and adolescent depressive disorder is not well established. In our two previous network meta-analyses the comparative efficacy and acceptability of psychotherapies and antidepressants for depressive disorder in children and adolescents have been separately investigated	6
Objectives	7	The aim of 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.	7
METHODS			
Eligibility criteria	8	**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 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 heterogeneity could violate the transitivity assumption in NMA (i.e. 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 (e.g., anxiety 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 ten patients will be excluded.	7-10

Types of studies

Any randomised controlled trials (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 utilise 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 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, e.g., behavioral therapy, cognitive-behavioral therapy, cognitive therapy, family therapy, interpersonal therapy, play therapy, problem-solving therapy, psychodynamic therapy, and supportive therapy. Also, we will include the combination of both psychological interventions and pharmacological interventions. For the pharmacological interventions, the control condition always is pill placebo, and these for psychological control conditions will include waiting-list (WL), treatment as usual (TAU), psychological placebo or attention placebo, as well as 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 week. 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 present data for more than one time point within our pre-defined 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.

Types of outcome measures

Primary outcomes

(1) Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self- or assessor-rated), e.g., 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 (e.g., 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 behavior 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 re-analysis data reported in the 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, e.g., Children's Global Assessment Scale (CGAS) and Global Assessment of Functioning Scale (GAF), or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). When data are reported on more than one measure, we will first chose data from the CGAS, then the GAF, and finally the Q-LES-Q and others.	
Information sources	9	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 network meta-analyses.8,10 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. We will also search ClinicalTrials.gov in USA and other international trial registers viathe International Clinical Trials Registry Platform (ICTRP) in WHO. We will also check relevant reports on the US Food and Drug Administration (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, 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 (e.g., 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.	11-12
Search strategy	10	(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).	11
Study records:			

Data management	11a	Literature search results will be imported to Endnote and the duplicates will be removed during the study selection process. We will screening citations based on the inclusion and exclusion criteria.	12
Selection process	11b	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.	12
Data collection process	11c	Two independent reviewers (XZ and YZ) will extract the data from each included trial using standardised data extraction forms. 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.	12-13
Data items	12	Study characteristics (e.g., first listed author, publication year, title, publication type, publication journal, country, and sponsor), patient characteristics (e.g., 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 (e.g., 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).	12
Outcomes and prioritization	13	Primary outcomes (1) Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self- or assessor-rated), e.g., 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 (e.g., 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 behavior 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 re-analysis data reported in the 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, e.g., Children's Global Assessment Scale (CGAS) and Global Assessment of Functioning Scale (GAF), or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). When data are reported on more than one measure, we will first chose	10-11

		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). 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.	
Risk of bias in individual studies	14	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 Hand book 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 (e.g., 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.	13
Data synthesis	15a	We will perform Bayesian network meta-analysis to compare the relative outcomes of different antidepressant medications, psychotherapies or their combination from the median of the posterior distribution.	13
	15b	Network meta-analysis 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 version 14.0. Second, we will also perform a random-effects network meta-analysis (NMA) within a Bayesian framework using Markov chain Monte Carlo in WinBUGS version 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 odds ratio (OR). In the presence of minimally informative priors, Credible Intervals (CrIs) can be interpreted similarly to confidence intervals (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, confidence intervals or standard errors 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 network meta-analysis, 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.	13-14
	15c	Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (i) age of participants (children vs. adolescents); (ii) sex ratio; (iii) the severity of depressive symptoms at baseline; and (iv) the treatment duration. If possible, we will do some extra subgroup analyses according to the results of heterogeneity and inconsistency. In the	15-16

		sensitivity analysis, trials where missing data have been imputed will be excluded, and trials where high risk of bias rating have been assessed 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 (e.g., sample size of trials53), as continuous measure in meta-regression analyses.	
	15d	A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies.	15
Meta-bias(es)	16	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 network meta-analysis.	15
Confidence in cumulative evidence	17	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.	16

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016608.R2
Article Type:	Protocol
Date Submitted by the Author:	30-May-2017
Complete List of Authors:	Zhou, Xinyu; The First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry Cipriani, Andrea; University of Oxford, Department of Psychiatry; Warneford Hospital, Oxford Health NHS Foundation Trust Zhang, Yuqing; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology Cuijpers, Pim; Vrije Universiteit Amsterdam, Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute Hetrick, Sarah; University of Melbourne, Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health Weisz, John; Harvard University, Department of Psychology Pu, Juncai; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology Del Giovane, Cinzia; University of Modena and Reggio Emilia, Clinical and Diagnostic Medicine and Public Health Furukawa, Toshi; Kyoto University, Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health Barth, Jürgen; University Hospital and University of Zurich, Institute of Complementary and Integrative Medicine Coghill, David; University of Melbourne, Departments of Paediatrics and Psychiatry Leucht, Stefan; Technische Universität München, Department of Psychiatry and Psychotherapy Yang, Lining; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology Ravindran, Arun ; University of Toronto, Department of Psychiatry Xie, Peng; The First Affiliated Hospital of Chongqing Medical University, Department of Neurology; Chongqing Medical University, Institute of Neuroscience and the Collaborative Innovation Center for Brain Science
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health, Pharmacology and therapeutics, Evidence based practice
Keywords:	Depression & mood disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY, antidepressant, psychotherapy, network meta-analysis, systematic review

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

Xinyu Zhou,[1] Andrea Cipriani,[2,3] Yuqing Zhang,[4] Pim Cuijpers,[5] Sarah E. Hetrick,[6] John R. Weisz,[7] Juncai Pu,[4] Cinzia Del Giovane,[8] Toshiaki A. Furukawa,[9] Jürgen Barth,[10] David Coghill,[11] Stefan Leucht,[12] Lining Yang,[4] Arun V Ravindran,[13] Peng Xie[4]

[1] Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

[2] Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

[3] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

[4] Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China;

Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University, Chongqing, China

[5] Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, The Netherlands

[6] Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health, University of Melbourne, Melbourne, Australia

[7] Department of Psychology, Harvard University, Cambridge, MA, USA

[8] Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy

[9] Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan

[10] Institute for Complementary and Integrative Medicine, UniversityHospital and University of Zurich,

Zurich, Switzerland

[11] Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, Australia

[12] Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany

[13] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Direct correspondence to:

Prof. Peng Xie, Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuzhong District, Chongqing 400016, China; E-mail: xiepeng973@126.com

Xinyu Zhou and Andrea Cipriani contributed equally to this work.

Keywords: depression, child, adolescent, antidepressant, psychotherapy, network meta-analysis, systematic review

Word count: 3509.

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, PsycINFO, CINAHL, LiLACS) will be searched from date of inception. We will also search ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and check relevant reports on the US FDA 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 behavior 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 network meta-

analysis 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

Strengths and limitations of this study

1. The network meta-analysis can integrate direct evidence with indirect evidence from multiple treatment comparisons and multiple control approaches to estimate the interrelations across all treatments, which can guide treatment decisions and guideline development.

2. For the first time the efficacy, acceptability, tolerability, and suicide-related outcomes of pharmacological and psychological interventions, alone or in combination for depressive disorder in children and adolescents will be comprehensively assessed in a network meta-analysis.

3. We will employ validated local and global methods to evaluate consistency and we will explore whether treatment effects are robust in network subgroup analyses and sensitivity analyses. The quality of evidence for network estimates of the primary outcomes will be assessed 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.

Background

Depressive disorder in children and adolescents is a major public health problem, affecting 1% to 2% of children (6–12 years old) and 2% to 5% of adolescents (13–18 years old), with a peak incidence around puberty.[1,2] The course of depressive disorder in children and adolescents is often characterised by protracted episodes, frequent recurrence, and comorbid psychiatric disorders.[3] Compared with adults, the identification and diagnosis of depressive disorder in children and adolescents may be more often missed by clinicians[4] 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),[5] and are significantly increased risk for suicide behaviors and ideation.[6] 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.[7]

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 behavior therapy (CBT) and interpersonal psychotherapy (IPT) seem to be the best available psychotherapies for depression in children and adolescents.[8,9] Multiple pharmacological therapies have also been studied for the treatment of depressive disorder in children and adolescents.[10-12] The controversy about the use of antidepressants in this age group, due the potentially increased risk of suicidality, has not been fully resolved.[13] Recently, the findings of our previous studies showed most antidepressants do not seem to offer a clear benefit for children and adolescents, and fluoxetine is probably the best option to consider when a pharmacological treatment is indicated.[10]

Several clinical practice guidelines recommend that in children and adolescents, psychotherapy should be considered as the first-line intervention for the management of depressive disorder, while pharmacological treatments are often reserved for more severe illness or when psychotherapy does not work or is not available.[14,15] Nevertheless, the evidence-base for psychotherapy to be more effective and safer than antidepressants in the treatment of child and adolescent depressive disorder is not well established. A large,

non-industry funded trial reported superior efficacy for fluoxetine compared to CBT in adolescents with major depression.[16] Previous research supports the notion that psychotherapy has its own side-effects, such as dependency on the therapist, and leading to distress for the patients' family.[17] However, unlike with antidepressants, they are rarely measured systematically, making the comparison of safety and tolerability harder.[18] Moreover, data from the adult studies showed that combination antidepressants and psychotherapy is superior to either intervention alone.[19,20] Recently, a Cochrane conventional meta-analysis, on the basis of the very limited evidence, reported that the effectiveness of psychological interventions, antidepressant medication and a combination of these interventions for treating depressive disorders in children and adolescents cannot be established.[21]

Network meta-analysis has the advantage that all interventions that have been tested in randomised controlled trials (RCTs) can be simultaneously compared, without requiring direct within-study treatment vs. treatment comparisons. Thus effects of the different treatments can be estimated relative to each other as well as to a common reference condition (e.g., pill placebo or psychological controls).[22] Network meta-analysis thus overcomes some of the limitations of traditional meta-analysis, in which conclusions are largely restricted to comparisons between treatments that have been directly compared in RCTs.[23] In our two previous network meta-analyses the comparative efficacy and acceptability of psychotherapies and antidepressants for depressive disorder in children and adolescents have been separately investigated[8,10] The aim of 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 randomised controlled trials (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 utilise 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).[24-29] 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 heterogeneity could violate the transitivity assumption in NMA (i.e. one can compare indirectly intervention B and C via intervention A).[30] 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 (e.g., 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 ten 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, e.g., behavioral therapy, cognitive-behavioral therapy, 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, whilst 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 week. 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.[31] If a study present data for more than one time point within our pre-defined 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- or assessor-rated), e.g., Children's Depression Rating Scale (CDRS-R)[32] and Hamilton Depression Rating Scale (HAMD)[33] 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 (e.g., less than 28 for CDRS-R),[34] 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 behavior 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).[35] For the antidepressants trials, the data on suicidality mainly referred to the Columbia re-analysis data reported in the FDA report.[36] 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, e.g., Children's Global Assessment Scale (CGAS)[37] and Global Assessment of Functioning Scale (GAF),[38] or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[39] When data are reported on more than one measure, we will first chose 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[40], 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 network meta-analyses.[8,10] 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 viathe International Clinical Trials Registry Platform (ICTRP) in WHO. We will also check relevant reports on the US Food and Drug Administration (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, 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 (e.g., 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 (e.g., first listed author, publication year, title, publication type, publication journal, country, and sponsor), patient characteristics (e.g., 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 (e.g., 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 Hand book for Systematic Reviews of Interventions.[41] 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 (e.g., 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

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum power.[23] First, we will perform pairwise meta-analyses of direct evidence using the random-effects model with STATA version 14.0. Second, we will also perform a random-effects network meta-analysis (NMA) within a Bayesian framework using Markov chain Monte Carlo in WinBUGS version 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 odds ratio (OR). In the presence of minimally informative priors, Credible Intervals (CrIs) can be interpreted similarly to confidence intervals (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, confidence intervals or standard errors are reported in articles, SD will be calculated from their values.[42] 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.[42]

In the analysis of network meta-analysis, 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.[43] 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.[44]

Measures for transitivity assumption

We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; and whether the distributions of clinical and methodological variables that can act as effect modifiers across treatment comparison are balanced across comparisons. The clinical features, which have been demonstrated to date to moderate efficacy of antidepressants and psychotherapy in children and adolescents include bipolarity,[45] psychotic features,[46] subthreshold depression.[47] 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 network meta-analysis 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-squared statistic[48] and its 95% confidence interval 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 (τ^2) estimated from the NMA models. We will also estimate a total I-squared value and predictive intervals for heterogeneity in the network.[49]

Measures for inconsistency

NMA assumes that there is consistency in the network (i.e. direct and indirect evidence are in agreement). However, the assumption of consistency can be violated either in the entire network or in certain parts (i.e. loops of evidence) of the network.[50] Therefore, consistency needs to be checked. We will evaluate the presence of local inconsistency and global inconsistency in STATA version 14.0 and will be duplicated in R software.[51]

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.[52] 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 network meta-analysis.[53]

Subgroup analyses and sensitivity analyses

Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (i) age of participants (children vs. adolescents); (ii) sex ratio; (iii) the severity of depressive symptoms at baseline; (iv) the treatment duration; (v) 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 (e.g., sample size of trials[54]), 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.[55] 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 network meta-analysis 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.

Contributors PX, AC, and XZ conceived the study and drafted the protocol. PX, AC and XZ wrote the first draft of the manuscript. PC, SEH, JRW, CDG, TAF, JB, DC, SL, AVR assisted in protocol design and revision. XZ, YZ, and LY participated in the search strategy development. CDG, and JP participated in the design of data synthesis and analysis. All the authors have approved the publication of the protocol.

Funding This work is supported by the National Basic Research Program of China (973 Program) (Grant No. 2009CB918300). The funders had no role in the protocol design; the writing of the protocol; or the decision to submit the protocol for publication.

Competing interests AC reports personal fees from Accord Healthcare as an expert witness for a patent issue about quetiapine extended release. SEH is an Editor of the Cochrane Common Mental Disorders Group, an author of the Cochrane systematic review of newer generation antidepressants for depression in children and adolescents, and an author (senior) on the Cochrane review of psychological, pharmacological and their combination for child/adoles depression. DC reports grants and personal fees from Shire; personal fees from Eli Lilly, Janssen Cilag, Novartis, Sandoz, Oxford University Press; and grants from European Union FP7, outside of the submitted work. Eli Lilly has provided drugs for a clinical trial led by SL as the principal investigator. AVR reports personal fees from Bristol Myers Squibb, Pfizer, Sunovion; grants from Pfizer, Grand Challenges Canada, Canadian Institute of Health Research, and AstraZeneca, outside of the submitted work. TAF has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui Chemicals and Takeda Science Foundation. He has received royalties from

Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Tanabe-Mitsubishi. XZ, YZ, PC, JRW, JP, CDG, TAF, JB, and LY declare no competing interests.

Acknowledgments Andrea Cipriani is supported by the National Institute for Health Research Oxford Cognitive Health Clinical Research Facility. We thank Philip Hazell from Discipline of Psychiatry, Sydney Medical School, Concord West, NSW, Australia, David Cohen from Department of Child and Adolescent Psychiatry, Hôpital Pitié–Salpétrière, Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Paris, France, and Craig Whittington from Doctor Evidence, Santa Monica, CA, USA, for their valuable advice.

Provenance and peer review Not commissioned; externally peer-reviewed.

References

1. Costello EJ, Mustillo S, Erkanli A, *et al*. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry* 2003;60:837-44.
2. Kessler RC, Berglund P, Demler O, *et al*. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:593-602.
3. Thapar A, Collishaw S, Pine DS, *et al*. Depression in adolescence. *Lancet* 2012;379:1056-67.
4. Hazell P. Depression in children. *BMJ* 2002;325:229-30.
5. Puig-Antich J, Lukens E, Davies M, *et al*. Psychosocial functioning in prepubertal major depressive disorders. II. Interpersonal relationships after sustained recovery from affective episode. *Arch Gen Psychiatry* 1985;42:511-7.
6. Gould MS, King R, Greenwald S, *et al*. Psychopathology associated with suicidal ideation and attempts among children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1998;37:915-23.
7. Centers for Disease Control and Prevention (CDC). Suicide trends among youths and young adults aged 10-24 years-United States, 1990-2004. *Morb Mortal Wkly Rep* 2007;56:905-8.
8. Zhou X, Hetrick SE, Cuijpers P, *et al*. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry* 2015;14:207-22.9.
9. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull* 2006;132:132-49.
10. Cipriani A, Zhou X, Del Giovane C, *et al*. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016;388:881-90.
11. Hetrick SE, McKenzie JE, Cox GR, *et al*. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev* 2012;11:CD004851.
12. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst Rev* 2013;6:CD002317.

13. U.S. Food and Drug Administration (FDA). Suicidality in children and adolescents being treated with antidepressant medications. www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm161679.htm (accessed 20 Jan 2017).

14. National Collaborating Centre for Mental Health (UK). Depression in Children and Young People: Identification and management in primary, community and secondary care. British Psychological Society, 2005; Available from www.ncbi.nlm.nih.gov/books/NBK56425/. (accessed 20 Jan 2017).

15. McDermott B, Baigent M, Chanen A, *et al*. Clinical practice guidelines: Depression in adolescents and young adults. Melbourne: beyondblue: the national depression initiative, 2011.https://www.bspg.com.au/dam/bsg/product?client=BEYONDBLUE&prodid=BL/0890&type=file (accessed 20 Jan 2017).

16. March J, Silva S, Petrycki S, *et al*. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; 292: 807-20.

17. Nutt DJ, Sharpe M. Uncritical positive regard? Issues in the efficacy and safety of psychotherapy. *J Psychopharmacol* 2008; 22: 3-6.

18. Linden M, Schermuly-Haupt ML. Definition, assessment and rate of psychotherapy side effects. *World Psychiatry* 2014; 13: 306-9.

19. Pampallona S, Bollini P, Tibaldi G, *et al*. Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Arch Gen Psychiatry*. 2004;61:714-9.

20. de Maat SM, Dekker J, Schoevers RA, *et al*. Relative efficacy of psychotherapy and combined therapy in the treatment of depression: a meta-analysis. *Eur Psychiatry* 2007;22:1-8.

21. Cox GR, Callahan P, Churchill R, *et al*. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst Rev* 2014;11:CD008324.

22. Mavridis D, Giannatsi M, Cipriani A, *et al*. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health* 2015;18:40-6.

23. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105-24.

24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1980.

25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th Edition. Washington, DC: American Psychiatric Association, 1994.

27. World Health Organization (WHO).*The ninth revision of the international classification of diseases and related health problems (ICD-9)*. Geneva: World Health Organization, 1978.

28. World Health Organization (WHO).*The tenth revision of the international classification of diseases and related health problems (ICD-10)*. Geneva: World Health Organization, 1992.

29. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980-8.

30. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Meth* 2012; 3:80-97.

31. Birmaher B, Brent D, AACAP Work Group on Quality Issues, *et al*. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 2007;46:1503-26.

32. Poznanski EO, Mokros HB. *Children's depression rating scale, revised (CDRS-R): manual*. Los Angeles: Western Psychological Services, 1996.

33. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.

34. Riedel M, Moller HJ, Obermeier M, *et al*. Response and remission criteria in major depression—a validation of current practice. *J Psychiatr Res* 2010;44:1063-8.

35. Posner K, Oquendo MA, Gould M, *et al*. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164:1035-43.

36. Hammad TA. Review and evaluation of clinical data. Washington, DC, US Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10- tab08-hammads-review.pdf (accessed 20 Jan 2017).

37. Shaffer D, Gould MS, Brasic J, *et al*. A children's global assessment scale (CGAS). *Arch Gen Psychiatry* 1983;40:1228-3l.

38. Endicott J, Spitzer RL, Fleiss JL, *et al*. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33:766-71.

39. Endicott J, Nee J, Harrison W, *et al*. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull* 1993;29:321-6.

40. Zhou X, Qin B, Whittington C, *et al*. Comparative efficacy and tolerability of first-generation and newer-generation antidepressant medications for depressive disorders in children and adolescents: study protocol for a systematic review and network meta-analysis. *BMJ Open* 2015;5:e007768.

41. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions version 5.1. 0* [updated March 2011]. The Cochrane Collaboration, 2011. http://handbook.cochrane.org/ (accessed 20 Jan 2017).

42. Furukawa TA, Barbui C, Cipriani A, *et al*. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7-10.

43. Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998;7:434-45.

44. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64:163-71.

45. Liu HY, Potter MP, Woodworth KY, *et al*. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2011;50:749-62.

46. Sullivan SA, Lewis G, Gunnell D, *et al*. The longitudinal association between psychotic experiences, depression and suicidal behaviour in a population sample of adolescents. *Soc Psychiatry Psychiatr Epidemiol* 2015;50:1809-17.

47. Wesselhoeft R, Sørensen MJ, Heiervang ER, *et al*. Subthreshold depression in children and adolescents - a systematic review. *J Affect Disord* 2013; 151:7-22.

48. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

49. Jackson D, Barrett JK, Rice S, *et al*. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Stat Med* 2014; 33:3639-54.

50. Dias S, Welton NJ, Sutton AJ, *et al*. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013; 33:641-56.

51. Higgins JP, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012; 3:98-110.

52. Peters JL, Sutton AJ, Jones DR, *et al*. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991-6.

53. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment met-aanalysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163-71.

54. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012;3:161-76.

55. Salanti G, Del Giovane C, Chaimani A, *et al*. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682.

TABLES

Table 1 Description of Psychotherapeutic interventions and control conditions

Interventions	Abbreviation	Description
Psychotherapeutic Intervention:		
Behavioral therapy	BT	BT uses some kind of behavioral training and psychoeducation. BT programs provide parents and youths information about MDD and interventions; teach youths to monitor their mood, thoughts and behaviors; proposed pleasant activity scheduling and behavioral activation.
Cognitive-behavioral therapy	CBT	CBT is a combination of BT and CT. Additional CBT skill-building techniques are used in many programs by teaching relaxation techniques to cope with environmental stressors, providing social skills and resolution training, and teaching general problem-solving.
Cognitive therapy	CT	CT uses some kind of cognitive restructuring training. CT programs ask youths to examine their automatic thoughts and core schemas and to assess the accuracy and affective consequences of their views. They aim to teach youths to engage in "rational" thinking about themselves, the world and their possibilities for the future.
Family therapy	FT	FT works with families to nurture change and development. FT tends to view change in terms of the systems of interaction between family members. In the case of youth with MDD, FT aims at helping the family to answer the child's needs for completing age-appropriate developmental tasks to relieve depression.
Interpersonal therapy	IPT	IPT aim at educating patients as to how their depression and the quality of interpersonal relationships affect one another and at addressing interpersonal problems that may be contributing to the depression (e.g. grief, disputes, role transitions, social deficits). Compared to its adult version, IPT in youths is shorter, involves parents, and adds a liaison role for the therapist between schools and families.
Play therapy	PT	PT used techniques to engage participants in recreational activities to help them cope with their problems and fears.
Problem-solving therapy	PST	PST focus on the problems participants are currently facing and on helping them find solutions to those problems.
Psychodynamic therapy	DYN	DYN proposed patients to help understand the origin and nature of long standing problems by investigating both conscious and non-conscious thoughts and emotional feelings. DYN uses free associations and interpretation of dreams (or drawing in children), and addresses how personal history and experience may alter the patient/therapist transference. In youth MDD, a particular interest is given to psychological trauma, early

		parent/child relationships, narcissistic organization and experiences of loss.
Supportive therapy	SUP	SUP is an unstructured therapy without specific psychological techniques that it helped people to ventilate their experiences and emotions and offering empathy. These therapies are commonly described in the literature as either counseling or supportive therapy.
Control conditions:		
No-treatment	NT	NT is a control condition in which the participants receive no active treatment during the study and in which they do not expect to receive such after the study is over.
Psychological placebo	PBO	PBO is a control condition that was regarded as inactive by the researchers but was to be the participants.
Treatment-as-usual	TAU	TAU is not considered to be structured psychotherapy but may have some treatment effects.
Waitlist	WL	WL is a control condition in which the participants receive no active treatment during the study but are forewarned that they can receive one after the study period is over.

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 Behavior Checklist-Depression	CBCL-D

Figure 1. Possible interventions eligible for the ideal network plot

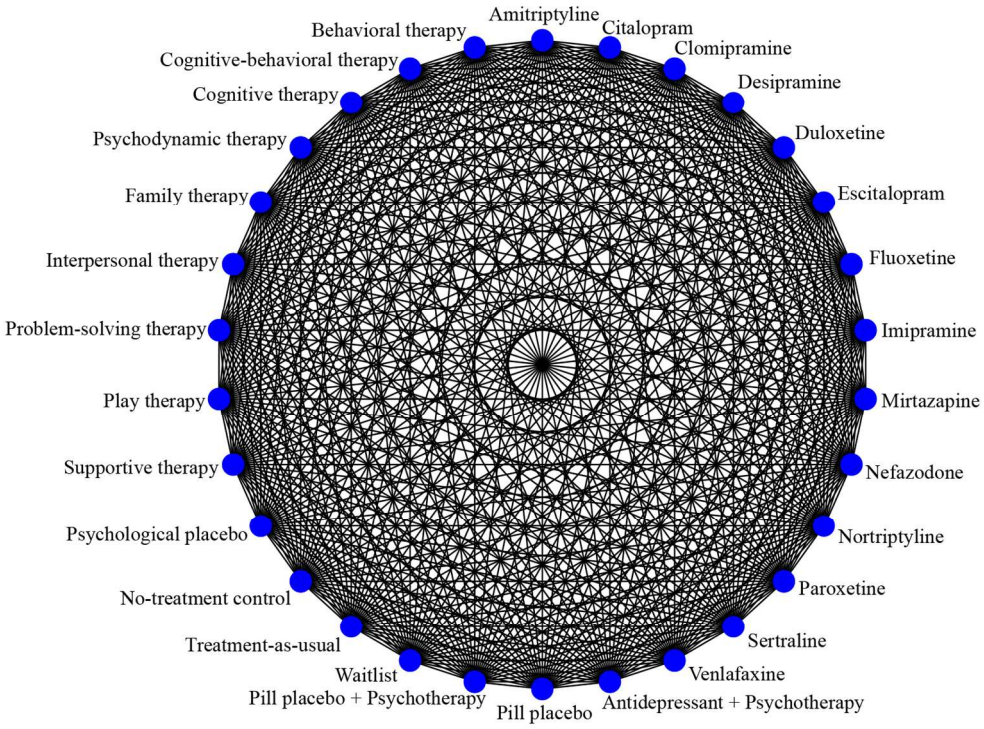

Figure 1. Possible interventions eligible for the ideal network plot

139x102mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis	1
Update	1b	None	
Registration	2	PROSPERO CRD42015020841	4
Authors:			
Contact	3a	Xinyu Zhou, Yuqing Zhang, Juncai Pu, Lining Yang, Peng Xie (Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University, Chongqing, China) Andrea Cipriani (Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK) Pim Cuijpers (Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, The Netherlands) Sarah E. Hetrick (Orygen, The National Centre of Excellence in Youth Mental Health, and the Centre of Youth Mental Health, University of Melbourne, Melbourne, Australia) John R. Weisz (Department of Psychology, Harvard University, Cambridge, MA, USA) Cinzia Del Giovane (Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy) Toshiaki A. Furukawa (Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan) Jürgen Barth (Institute of Complementary and Integrative Medicine, University Hospital and University of Zurich, Zurich, Switzerland) David Coghill (Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, Australia) Stefan Leucht (Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany) Arun V Ravindran (Department of Psychiatry, University of Toronto, Toronto, ON, Canada) Corresponding author :Peng Xie, Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuzhong District, Chongqing 400016, China; E-mail: xiepeng973@126.com	1-2
Contributions	3b	PX, AC, and XZ conceived the study and drafted the protocol. PX, AC and XZ wrote the first draft of the manuscript. PC, SEH, JRW, CDG, TAF, JB, DC, AVR assisted in protocol design and revision. XZ, YZ, and LY participated in the search strategy	17

		development. CDG, and JP participated in the design of data synthesis and analysis. All the authors have approved the publication of the protocol.	
Amendments	4	None	
Support:			
Sources	5a	ational Basic Research Program of China (973 Program) (Grant No. 2009CB918300)	
Sponsor	5b	This work is supported by the National Basic Research Program of China (973 Program) (Grant No. 2009CB918300).	
Role of sponsor or funder	5c	The funders had no role in the protocol design; the writing of the protocol; or the decision to submit the protocol for publication.	
INTRODUCTION			
Rationale	6	Depressive disorder in children and adolescents is a major public health problem. The course of depressive disorder in young people is often characterised by protracted episodes, frequent recurrence, and comorbid psychiatric disorders. Several clinical practice guidelines recommend that in children and adolescents, psychotherapy should be considered as the first-line intervention for the management of depressive disorder, while pharmacological treatments are often reserved for more severe illness or when psychotherapy does not work or is not available. Nevertheless, the evidence-base for psychotherapy to be more effective and safer than antidepressants in the treatment of child and adolescent depressive disorder is not well established. In our two previous network meta-analyses the comparative efficacy and acceptability of psychotherapies and antidepressants for depressive disorder in children and adolescents have been separately investigated	6
Objectives	7	The aim of 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.	7
METHODS			
Eligibility criteria	8	**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 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 heterogeneity could violate the transitivity assumption in NMA (i.e. 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 (e.g., anxiety 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 ten patients will be excluded.	7-10

Types of studies

Any randomised controlled trials (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 utilise 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 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, e.g., behavioral therapy, cognitive-behavioral therapy, cognitive therapy, family therapy, interpersonal therapy, play therapy, problem-solving therapy, psychodynamic therapy, and supportive therapy. Also, we will include the combination of both psychological interventions and pharmacological interventions. For the pharmacological interventions, the control condition always is pill placebo, and these for psychological control conditions will include waiting-list (WL), treatment as usual (TAU), psychological placebo or attention placebo, as well as 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 week. 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 present data for more than one time point within our pre-defined 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.

Types of outcome measures

Primary outcomes

(1) Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self- or assessor-rated), e.g., 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 (e.g., 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 behavior 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 re-analysis data reported in the 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, e.g., Children's Global Assessment Scale (CGAS) and Global Assessment of Functioning Scale (GAF), or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). When data are reported on more than one measure, we will first chose data from the CGAS, then the GAF, and finally the Q-LES-Q and others.	
Information sources	9	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 network meta-analyses.8,10 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. We will also search ClinicalTrials.gov in USA and other international trial registers viathe International Clinical Trials Registry Platform (ICTRP) in WHO. We will also check relevant reports on the US Food and Drug Administration (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, 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 (e.g., 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.	11-12
Search strategy	10	(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).	11
Study records:			

Data management	11a	Literature search results will be imported to Endnote and the duplicates will be removed during the study selection process. We will screening citations based on the inclusion and exclusion criteria.	12
Selection process	11b	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.	12
Data collection process	11c	Two independent reviewers (XZ and YZ) will extract the data from each included trial using standardised data extraction forms. 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.	12-13
Data items	12	Study characteristics (e.g., first listed author, publication year, title, publication type, publication journal, country, and sponsor), patient characteristics (e.g., 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 (e.g., 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).	12
Outcomes and prioritization	13	Primary outcomes (1) Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self- or assessor-rated), e.g., 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 (e.g., 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 behavior 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 re-analysis data reported in the 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, e.g., Children's Global Assessment Scale (CGAS) and Global Assessment of Functioning Scale (GAF), or quality of life scales, e.g., Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). When data are reported on more than one measure, we will first chose	10-11

		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). 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.	
Risk of bias in individual studies	14	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 Hand book 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 (e.g., 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.	13
Data synthesis	15a	We will perform Bayesian network meta-analysis to compare the relative outcomes of different antidepressant medications, psychotherapies or their combination from the median of the posterior distribution.	13
	15b	Network meta-analysis 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 version 14.0. Second, we will also perform a random-effects network meta-analysis (NMA) within a Bayesian framework using Markov chain Monte Carlo in WinBUGS version 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 odds ratio (OR). In the presence of minimally informative priors, Credible Intervals (CrIs) can be interpreted similarly to confidence intervals (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, confidence intervals or standard errors 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 network meta-analysis, 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.	13-14
	15c	Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (i) age of participants (children vs. adolescents); (ii) sex ratio; (iii) the severity of depressive symptoms at baseline; and (iv) the treatment duration. If possible, we will do some extra subgroup analyses according to the results of heterogeneity and inconsistency. In the	15-16

		sensitivity analysis, trials where missing data have been imputed will be excluded, and trials where high risk of bias rating have been assessed 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 (e.g., sample size of trials53), as continuous measure in meta-regression analyses.	
	15d	A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies.	15
Meta-bias(es)	16	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 network meta-analysis.	15
Confidence in cumulative evidence	17	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.	16

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.