Comparative efficacy and tolerability of antidepressants for major depression in children and adolescents: a network meta-analysis

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Supplementary appendix to the manuscript

Contents of Supplementary appendix

Appendix 1

Published protocol and changes made to the protocol

The protocol has been registered in PROSPERO (Registration No. CRD42015016023) and published in BMJ Open (Zhou X, et al. 2015;5(9):e007768 – available at http://bmjopen.bmj.com/content/5/9/e007768.full.pdf+html.

Open Access Protocol

BMJ Open

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

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ABSTRACT

Introduction: Depressive disorders are among the most common psychiatric disorders in children and adolescents, and have adverse effects on their psychosocial functioning. Questions concerning the efficacy and safety of antidepressant medications in the treatment of depression in children and adolescents, led us to integrate the direct and indirect evidence using network meta-analysis to create hierarchies of these drugs.

Methods and analysis: Seven databases with PubMed, EMBASE, the Cochrane Library, Web of Science, CINAHL, LiLACS and PsycINFO will be searched from 1966 to December 2013 (updated to May, 2015). There are no restrictions on language or type of publication. Randomised clinical trials assessing first-generation and newer-generation antidepressant medications against active comparator or placebo as acute treatment for depressive disorders in children and adolescents (under 18 years of age) will be included. The primary outcome for efficacy will be mean improvement in depressive symptoms, as measured by the mean change score of a depression rating scale from baseline to post-treatment. The tolerability of treatment will be defined as side effect discontinuation, as defined by the proportion of patients who discontinued treatment due to adverse events during the trial. We will also assess the secondary outcome for efficacy (response rate), acceptability (all-cause discontinuation) and suicide-related outcomes. We will perform the Bayesian network meta-analyses for all relative outcome measures. Subgroup analyses and sensitivity analyses will be conducted to assess the robustness of the findings.

Dissemination: The network meta-analysis will provide useful information on antidepressant treatment for child and adolescent depression. The results will be disseminated through peer-reviewed publication or conference presentations.

Trial registration number: PROSPERO CRD42015016023.

Strengths and limitations of this study

- This Bayesian network meta-analysis can integrate direct evidence with indirect evidence from multiple treatment comparisons to estimate the interrelations across all treatments.
- We will comprehensively assess the efficacy, tolerability, acceptability and suicide-related outcomes of first-generation and newer-generation antidepressant medications for depression in children and adolescents.
- Several subgroup and sensitivity analyses will address some clinically relevant questions.
- This method comprehensively synthesises data to provide a clinically useful summary that can guide treatment decisions and guideline development.

BACKGROUND

Depressive disorders in children and adolescents are a major public health problem, demonstrated by the disorders ranking as the third most important in the estimation of disease burden.[1] The prevalence of experiencing at least one episode of major depression before adulthood is estimated to be approximately 1–2% for children (6–12 years old), and 2–5% for adolescents (13–18 years old).[2]

The course of major depression in young people is often characterised by frequent recurrence, protracted episodes and comorbid psychiatric disorders.[3] The consequences of an untreated episode of major depression in young people are likely to be serious impairment in social functioning, for example, poor school achievement, or relational problems with family members and peers.[4] A report from the American Academy of Child and Adolescent Psychiatry (AACAP) suggested that depression is responsible for over 500 000 suicide attempts by children and adolescents a year, with most of this group diagnosed with treatable forms of mental illness.[5 6] Thus, early recognition, diagnosis and treatment of depression in children and adolescents is an important strategy for curbing the rising rate of youth suicide, seen in many developed and advanced developing nations.[7]

Since the late 1960s, first-generation antidepressants, for example, tricyclic antidepressant (TCA) drugs, have been used to treat depressive symptoms in young patients.[8] In the US, the use of antidepressant medication in children and adolescents grew 3–10-fold between 1987 and 1996.[9] The efficacy of TCAs has been investigated in 13 randomised placebo-controlled trials,[10] which showed marginal evidence to support the use of TCAs in the treatment of depression in only adolescents. However, methodological deficiencies in these trials, including small sample sizes and diagnostic heterogeneity, restrict statistical inference and generalisability of the findings. At the same time, cardiovascular effects and overdose-related mortality associated with TCA use have greatly limited their utility in clinical practice.[11 12] Nevertheless, the TCA nortriptyline is still approved by the Food and Drug Administration (FDA) for the treatment of depression in adolescents and adults.[13]

In recent decades, newer-generation antidepressants, including second-generation antidepressants (eg, selective serotonin reuptake inhibitors (SSRIs)) and third-generation antidepressants (eg, serotonin–norepinephrine reuptake inhibitors (SNRIs)), have been widely used for the treatment of depression in children and adolescents.[14] The frequency of prescription of SSRIs and SNRIs in children and adolescents has progressively increased.[15] In European countries, there has been a doubling of SSRI use over a 4-year period.[16] However, only fluoxetine was approved by the US FDA for treating depression in children and adolescents in January 2003.[17] In the same year, concerns about the increased risk of suicide and suicide attempts with SSRIs were first raised.[18] In September 2004, the FDA cautioned practitioners in the use of antidepressant medications in children and adolescents.[19] Similar warnings were issued by other health regulatory agencies.[20–22] Thus, concerns about this issue have refocused attention on the question of how effective antidepressant medications are in treating youth depression.

Nonetheless, currently, no published meta-analysis has combined direct and indirect evidence for the use of antidepressant medications on children and adolescents, though it is an important study to perform, given the conflicting results regarding the efficacy and tolerability of various antidepressant medications in this age group, and lack of head-to-head trials of such drugs.[23–25] For these reasons, we will employ a network meta-analysis—a methodological approach that allows the simultaneous comparison of multiple psychotherapeutic interventions within a single analysis, while preserving randomisation.[26] This approach will be used to integrate direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator) from multiple treatment comparisons to estimate the interrelations across all treatments.[27] We have previously compared the efficacy and acceptability of psychotherapies for depression in children and adolescents,[28] and the augmentation agents for treatment-resistant depression in adults[29] in this way. The aim of the network meta-analysis of randomised controlled trials (RCTs) is to systematically reanalyse the efficacy, tolerability, acceptability and suicide risk of both first-generation and newer-generation antidepressant medications against active comparator or control conditions, in the treatment of child and adolescent depression.

METHODS

Criteria for included studies

Types of studies

Any prospective RCTs, including cross-over design and cluster randomised trials, will be included. However, quasi-randomised trials (eg, those allocating using alternate days of the week) will be excluded. Trials with sample sizes smaller than 10 will be excluded in this review.

Types of participants

Children and adolescents (aged from 6 to 18 years when they initially enrolled in the trials) with a primary diagnosis of current major depressive disorder according to standardised diagnostic interviews, for example, the Diagnostic and Statistical Manual of Mental Disorders (DSM)[30–32] or the International Classification of Diseases (ICD),[33 34] will be included. Where a trial contains a portion of participants who are over 18 years of age, we will contact the trial authors in order to obtain data for only those participants within our age range. We will exclude trials focusing on child or adolescent bipolar disorder, but will include trials involving patients with comorbid general psychiatric disorders, such as attention deficit hyperactivity disorder, anxiety disorder and substance-related disorder. Also, we will not exclude trials in which participants have a diagnosis of psychotic depression; these participants will be considered within a separate subgroup analysis. However we will exclude trials in which participants have a diagnosis of treatment-resistant depression, because these patients tend to have a different treatment response compared with patients with non-resistant depression.

Types of interventions

RCTs comparing any first-generation and newer-generation antidepressant drug against active comparator or placebo for treatment of depression in children and adolescents will be included. Trials comparing the same type of antidepressant but at different therapeutic dose (fixed or flexible dose) and different treatment duration will be considered as the same node in the network analysis. We will exclude trials involving combination therapy (ie, combination of antidepressant medications, combination of antidepressant medication with psychotherapy, or other non-psychotherapeutic interventions); however, trials will be considered as eligible if the concomitant psychotherapy is not predefined in the study.

Types of outcome measures

The acute phase will be defined as from 4 to 16 weeks, and if a trial presents data beyond 16 weeks or for more than one time period within our predefined acute phase periods, we will take the 8-week or close to 8-week time point.[35] We will exclude trials with treatment duration of <4 weeks. 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. This 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 Hetrick[14] *et al* study) (table 1). The Children's Depression Rating Scale Revised (CDRS-R)[36] is adapted for children and adolescents from the Hamilton Depression Rating Scale (HAMD),[37] a tool validated and commonly used in adult populations.[38] Both the CDRS-R and HAMD have good reliability and validity.[38] The Beck Depression Inventory (BDI)[39] and the Children's Depression Inventory (CDI)[40] are the most commonly used among depression symptom severity self-rated scales and are ranked second highest in the hierarchy.

1. Overall efficacy

   The primary outcome for efficacy will be mean improvement in depressive symptoms, as measured by the mean change score of depression rating scales (self-rated or assessor-rated) from baseline to end point.

   The secondary outcome for efficacy will be response in depressive symptoms, as estimated by the proportion of patients who achieved a decrease of a certain percentage (eg, a reduction of 50% or more) in depression rating score.[41] When 'response' is not reported, we will use 'remission', if available. Remission will be defined as the proportion of patients who achieved a depression rating score below the published threshold (eg, CDRS-R≤28).[41]

2. Overall tolerability

The tolerability of treatment will be defined as side effect discontinuation in this review, as defined by the proportion of patients who discontinued treatment due to adverse events during the study.

3. Overall acceptability

The acceptability of treatment will be defined as all-cause discontinuation, as measured by the proportion of patients who discontinued treatment (during the delivery of the intervention) up to the post-intervention time point.

4. Suicide-related outcomes

Suicide-related dichotomous and continuous outcomes will be measured. If data are available, we will extract the number of participants with suicide-related events (combined suicidal ideation and suicidal behaviour) during the acute treatment, as measured on a standardised, validated and reliable rating scale, or reported cases of suicidality.[42] In addition, we will also collect data on suicidal ideation as a continuous outcome where a standardised, validated and reliable rating scale, such as the Suicidal Ideation Questionnaire-Junior High School version (SIQ-JR),[43] has been used.

Table 1 Hierarchy of depression symptom severity measurement scales

Hierarchy	Depression symptom severity measurement scales	Abbreviation
1	Children's Depression Rating Scale	CDRS
2	Hamilton Depression Rating Scale	HAMD
3	Montgomery Asberg Depression Rating Scale	MADRS
4	Beck Depression Inventory	BDI
5	Children's Depression Inventory	CDI
6	Schedule for Affective Disorders and Schizophrenia for School Aged Children	K-SADS
7	Mood and Feeling Questionnaire	MFQ
8	Reynolds Adolescent Depression Scale	RADS
9	Bellevue Index of Depression	BID
10	Child Depression Scale	CDS
11	Centre for Epidemiologic Studies Depression Scale	CESD
12	Child Assessment Schedule	CAS
13	Child Behaviour Checklist—Depression	CBCL-D

Data sources and search strategy

Seven electronic databases (PubMed, EMBASE, the Cochrane Library, Web of Science, CINAHL, LiLACS and PsycINFO) will be searched from 1966 to December 2013 (updated to May, 2015), with Medical Subject Headings (MeSH) and text words: 'depress*' or 'dysthymi*' or 'mood disorder*' or 'affective disorder*' and 'selective serotonin reuptake inhibitor*' or 'SSRIs' or

'serotonin norepinephrine reuptake inhibitor*' or 'SNRIs' or 'noradrenergic and specific serotonergic antidepressants' or 'NaSSA' or 'citalopram' or 'fluoxetine' or 'paroxetine' or 'sertraline' or 'escitalopram[' or 'fluvoxamine' or 'venlafaxine' or 'duloxetine' or 'milnacipran' or 'reboxetine' or 'bupropion' or 'mirtazapine' or 'tricyclic' or 'amersergide' or 'amineptine' or 'amitriptyline' or 'amoxapine' or 'butriptyline' or 'chlorpoxiten' or 'clomipramine' or 'clorimipramine' or 'demexiptiline' or 'desipramine' or 'dibenzipin' or 'dothiepin' or 'doxepin' or 'imipramine' or 'lofepramine' or 'melitracen' or 'metapramine' or 'nortriptyline' or 'noxiptiline' or 'opipramol' or 'protriptyline' or 'quinupramine' or 'tianeptine' or 'trimipramine' 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*'. Also, ClinicalTrials.gov, WHO's trial portal, and US FDA reports will be reviewed. There are no restrictions on language or type of publication. Additional studies will be searched in the reference lists of all identified publications including relevant meta-analyses and systematic reviews. All relevant authors and principal manufacturers will be contacted to supplement incomplete reports of the original papers or to provide new data for unpublished trials.

Study selection

Two reviewers (BQ and YL) will independently scan citations at the title/abstract level identified from the search strategies and then obtain potentially relevant studies in full text, and determine whether to include them by the same eligibility criteria. Besides, the references of relevant reviews and included trials will also be checked by the two reviewers. The reasons for exclusion of trials will be reported in the characteristics of excluded studies tables. Any disagreements will be resolved by a third review author (XZ).

Data extraction and risk of bias assessment

Two independent reviewers (YL, BQ) will independently extract the key trial parameters using a standardised data abstraction form and assess the risk of bias. The standardised data extraction forms will include the trial characteristics (eg, first listed author, publication year, journal, country, institution and sponsor), patient characteristics (eg, diagnostic criteria for depression, the type of patients, the number of patients, level of depressive symptoms, comorbidities, the age of patients and the gender of patients), intervention details (eg, antidepressant type, dose of antidepressant and the duration of treatment) and outcome measures (efficacy, tolerability, acceptability and suicide-related outcome). The risk of bias in trials will be assessed by the Cochrane risk of bias tool.[42] Trials attracting a rating of high risk of bias in one or more domains will be considered as 'high risk', low risk of bias in all domains as 'low risk' and one or more unclear risk of bias in each domain as 'unclear risk'.[42] Any disagreements will be resolved by a third review author (XZ). In addition, we will calculate the inter-rater reliability of the two raters.

Data synthesis and analysis

We will perform Bayesian network meta-analysis to compare the relative outcomes of different antidepressant medications and placebo with each other from the median of the posterior distribution.[26 27] The pooled estimates of standardised mean difference (SMD) with 95% credible intervals (CrIs) will be calculated for the continuous outcomes; and ORs with 95% CrIs will be calculated for the categorical outcomes. The SMD is that the difference in means (MD) of change scores between the two groups divided by the pooled SD of the measurements, with a negative SMD value, indicates greater symptomatic relief. In the presence of minimally informative priors, CrIs can be interpreted similarly to CIs, and at conventional levels of statistical significance a two sided $p<0.05$ can be assumed if 95% CrIs do not include 0. If means and SDs are not provided, we will calculate them from the p value or other statistical indices as described elsewhere.[44 45] Results from intention-to-treat analysis (ITT) or modified ITT will be preferred over results from completer analyses, while we will also consider the data set for the means and SDs that are presented in the literature.

The pooled estimates will be obtained using the Markov Chains Monte Carlo method. Two Markov chains will be run simultaneously with different arbitrarily chosen initial values. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic will be assessed.[46] Convergence will be found to be adequate after running 50 000 samples for both chains. These samples will be then discarded as 'burn-in', and posterior summaries will be based on 100 000 subsequent simulations. The node splitting method will be used to calculate the inconsistency of the model, which separates evidence on a particular comparison into direct and indirect evidence.[47] Probability values will be summarised and reported as surface under the cumulative ranking curve (SUCRA) and rankograms, a simple transformation of the mean rank used to provide a hierarchy of the treatments and accounts for both the location and the variance of all relative treatment effects.[48] Network meta-analysis will be performed using the WinBUGS software package (V.1.4.3, MRC Biostatistics Unit, Cambridge, UK) with random-effects models for multiarm trials. The other analyses will be performed and presented by the Stata V.11.0 and R 2.11.1 software packages.

Subgroup analyses

The antidepressant medications will be coded according to clinical characteristics, risk of bias and sample size. We will conduct the subgroup analyses of data in primary outcome for efficacy. We will perform the following subgroup analyses by using the meta-regression model, and calculate Somer's D (a correlation

coefficient for a dichotomous and an ordinal variable):[49] (1) sex ratio (male-to-female ratio >1 vs male-to-female ratio <1); (2) age group; (3) treatment duration; (4) severity of depressive symptom (mild-to-moderate vs moderate-to-severe); (5) comorbid general psychiatric disorders (with vs without comorbidity); (6) risk of bias ('high risk' literature vs 'unclear and low risk' literature); (7) sample size; (8) company sponsor (with vs without sponsor); and (9) the type of trials (published literature vs unpublished literature). When there is the limitation of a small number of comparisons for some potential modifiers in carrying out subgroup analyses on these variables, we will perform the sensitivity analyses by omitting specific trials from the overall analysis.

Other analyses

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

Ethics and dissemination

This network meta-analysis does not need ethical approval, as data used here are not individual or private. The analysis will be published in a peer-reviewed journal. The results will provide a general overview, and evidence of efficacy and safety of antidepressant medications for depression in children and adolescents. The results will also have implications for clinical practice and further research.

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Contributors XZ and BQ conceived the study and drafted the protocol. XZ and PX wrote the first draft of the manuscript. KDM, CW and DC assisted in protocol design and revision. YL and YZ participated in the search strategy development. CDG and BQ participated in the design of data synthesis and analysis. All the authors have approved the publication of the protocol.

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Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Here below some changes and clarifications to the published protocol:

1. In order to obtain more comprehensive data, we added to search several additional international trial registers, including Australian New Zealand Clinical Trials Registry (ANZCTR), Chinese Clinical Trial Register (ChiCTR), UMIN Clinical Trials Registry (UMIN-CTR) in Japan, the International Standard Randomised Controlled Trial Number (ISRCTN) in UN, Netherlands Trial Register. We also added to hand-search key journals, and conference proceedings.

2. Outcomes measures
The primary outcomes were efficacy (measured as the mean overall change in total scores from baseline to endpoint on standardised depressive rating scales) and tolerability (measured as the proportion of patients who discontinued treatment due to any adverse events). Secondary outcomes included response rate, measured as the proportion of patients whose total score on the depression rating scales reduced by at least 50% from baseline to endpoint, or who scored much improved or very much improved on the clinical global impression (CGI); and when 'response' was not reported, we used 'remission'), and all-cause discontinuation (measured as the proportion of patients who discontinued treatment for any reason). We also examined suicide-related outcome, measured as the reported cases of definitive and suicidal behavior or suicidal ideation during the acute of treatment. The definition of suicide-related outcome was based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA).

3. We added our intention to perform meta-analysis of pairwise comparisons for all outcomes, and assessment of the heterogeneity and publication bias of pairwise comparisons for all outcomes.

4. We added the assessment of the quality of evidence of network estimates for primary outcomes by using the GRADE framework, which characterizes the quality of a body of evidence on the basis of the study limitations, imprecision, inconsistency, indirectness, and publication bias.

5. We had planned to conduct subgroup analyses, sensitivity analyses and meta-regressions, while we have adjusted some analyses according to the number of trials. We changed the subgroups analysis with the type of trials (published trials vs unpublished trials) as the sensitivity analysis for primary outcomes by omitting the unpublished trials. We added to perform a sensitivity network meta-analysis for response rate outcome by omitting the trials where only data on 'remission', but not on 'response' was reported. Due to the limit~~at~~ed number of trials in subgroups, we did not perform subgroup analyses by using the meta-regression model, and calculate Somer's D (a correlation coefficient for a dichotomous and an ordinal variable). Thus, we performed network subgroup analyses in Winbugs 1.4.3 with Markov Chains Monte Carlo method.

APPENDIX 2

Search strategy and results

Number of citations by each database and trial register searched*

Databases and Trial registers:	Citations
Databases:	
PubMmed	364
Cochrane	1556
Web of Science	1743
Embase	638
CINAHL	172
PsychInfo	1277
LILACS	44
Total (databases)	**5794**
Trial registers:	
Australian (ANZCTR)	108
China (ChiCTR)	12
USA (CelinicalTtrials.gov)	214
Japan (UMIN-CTR)	56
Netherlands (Trial Register)	14
UN (ISRCTN)	110
World Health Organization (ICTRP)	1003
USA Food and Drug Administration (FDA)	992
Total (trial registers)	**2509**

***Explicit search strategy:** title/abstract = (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 SSRI or citalopram or fluoxetine or paroxetine or sertraline or escitalopram or fluvoxamine or serotonin norepinephrine reuptake inhibitor* or SNRI or venlafaxine or duloxetine or milnacipran or reboxetine or bupropion or noradrenergic and specific serotonergic antidepressants or NaSSA or mirtazapine or TCA or tricyclic or amersergide or amineptine or amitriptyline or amoxapine or butriptyline or chlorpoxiten or clomipramine or clorimipramine or demexiptiline or desipramine or dibenzipin or dothiepin or doxepin or imipramine or lofepramine or melitracen or metapramine or nortriptyline or noxiptiline or opipramol or protriptyline or quinupramine or tianeptine or trimipramine)
MeSH search strategy: MeSH = ("depressive disorder" or "dysthymic disorder" or "mood disorders" or "affective disorders") AND (child or adolescent or minors or pediatrics or "young adult") AND (citalopram or fluoxetine or paroxetine or sertraline or fluvoxamine or venlafaxine or duloxetine or milnacipran or reboxetine or bupropion or mirtazapine or tricyclic or amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or demexiptiline or desipramine or dothiepin or doxepin or imipramine or lofepramine or metapramine or nortriptyline or opipramol or protriptyline or quinupramine or tianeptine or trimipramine)

Other sources: Relevant principal manufacturers (e.g., GlaxoSmithKline, Lilly, Organon, Forest Pharmaceuticals, Bristol-Myers Squibb) were contacted. Some key journals and conference proceedings, including *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*, were hand-searched. Additional relevant studies were obtained by scanning relevant systematic reviews, meta-analyses, and reviews as well as reference lists of eligible trials.

APPENDIX 3

Hierarchy of depressive scales

Hierarchy of depression symptom severity measurement scales

Hierarchy	Depressive 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	CES-D
12	Child Assessment Schedule	CAS
13	Child Behavior Checklist-Depression	CBCL-D

Note: where different depression symptom severity rating scales were used, for the purpose of pooling results, we chose the single best available outcome measure according to a hierarchy based on psychometric properties and appropriateness for use with children and adolescents.

APPENDIX 4

Network meta-analysis model

NMA model description

1. Random Effects Model for Continuous Data in WinBUGS

y=a table of the arm-means, sd=a table of the arm sd, n=a table of the arm sample size, t=a table with the names (numbers) of treatments, na=a vector with the number of arms in each study, ref=a number specifying which is the reference treatment

```
model{
for(i in 1:ns){
w[i,1] <- 0
delta[i,t[i,1]]<-0
u[i] ~ dnorm(0,.0001)

for (k in 1:na[i])    {
se[i,t[i,k]]<- sd[i,t[i,k]]/sqrt(n[i,t[i,k]])
var[i,t[i,k]]<- se[i,t[i,k]]*se[i,t[i,k]]
prec[i,t[i,k]]<- 1/var[i,t[i,k]]

#normal likelihood
y[i,t[i,k]] ~ dnorm(phi[i,t[i,k]],prec[i,t[i,k]])
phi[i,t[i,k]]<- (u[i]+delta[i,t[i,k]])*pooled.sd[i]

#calculate the pooled SD
nom1[i,k]<- n[i,t[i,k]]*sd[i,t[i,k]]*sd[i,t[i,k]]    #nominator for the pooled sd
      }

ss[i]<- sum(n[i,1:nt])-nt+na[i]    #total sample size in a study
nom[i]<- sum(nom1[i,1:na[i]])    #nominator for the pooled sd
pooled.sd[i]<- sqrt(nom[i]/(ss[i]-na[i]))    #pooled sd

for (k in 2:na[i]) {
delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])    # trial-specific SMD distributions
md[i,t[i,k]]<- d[t[i,k]]-d[t[i,1]]+sw[i,k]    # mean of SMD distributions
taud[i,t[i,k]]<- tau*2*(k-1)/k    #precision of SMD distributions
w[i,k] <- (delta[i,t[i,k]]-d[t[i,k]]+d[t[i,1]])    #adjustment, multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) }    # cumulative adjustment for multi-arm trials
      }

d[ref]<-0
for (k in 2:nt) {d[k] ~ dnorm(0,.0001) }
SD~dunif(0,1)    #vague prior for random effects standard deviation
tau<-1/pow(SD,2)
```

```
# Collection of results#
# pairwise SMDs
# for all comparisons
for (c in 1:(nt-1)) { for (k in (c+1):nt) { SMD[c,k] <- d[c] - d[k] }    #to have negative values
      }

#Fit of the Model#
for(i in 1:ns) {
for(k in 1:na[i]) {
Darm[i,k]<-(y[i,t[i,k]]-phi[i,t[i,k]])*(y[i,t[i,k]]-phi[i,t[i,k]])/var[i,t[i,k]]
      }
D[i]<- sum(Darm[i,1:na[i]])
      }
D.bar<- sum(D[])
}
```

2. Random Effects Model for Dichotomous Data in WinBUGS

r= a table of the number of events, n=a table of the arm sample size, t=a table with the names (numbers) of treatments, na=a vector with the number of arms in each study, ref=a number specifying which is the reference treatment

```
model {
for(i in 1:ns) {
w[i,1]<- 0
delta[i,t[i,1]]<- 0

#Binomial Likelihood#
for (k in 1:na[i]) {
r[i,t[i,k]] ~ dbin(p[i,t[i,k]],n[i,t[i,k]])
      }
#Parameterization of the model#
logit(p[i,t[i,1]])<- mu[i]
for (k in 2:na[i]) {
logit(p[i,t[i,k]])<- mu[i] + delta[i,t[i,k]]
delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
taud[i,t[i,k]]<- tau *2*(k-1)/k
md[i,t[i,k]]<-d[t[i,k]] - d[t[i,1]]    + sw[i,k]
w[i,k]<- (delta[i,t[i,k]]    - d[t[i,k]] + d[t[i,1]])
sw[i,k]<- sum(w[i,1:k-1])/(k-1)
      }
      }

#Priors#
sd ~ dnorm(0,1)I(0,1)
```

```
tau<- 1/pow(sd,2)

for(k in 1:(ref-1)) {
d[k] ~ dnorm(0,.0001)
      }
for(k in (ref+1):nt) {
d[k] ~ dnorm(0,.0001)
      }
for(i in 1:ns) {
mu[i] ~ dnorm(0,.0001)
      }

# Collection of results#
#Estimated & Predicted Odds Ratios#
d[ref]<- 0
for(i in 1:(nt-1)) {
for (j in (i+1):nt) {
OR[i,j]<- exp(d[i] - d[j])
LOR[i,j]<- d[i] - d[j]
      }
      }

#Fit of the Model#

for(i in 1:ns) {
for (k in 1:na[i]) {
Darm[i,k]<- -2*( r[i,t[i,k]] *log(n[i,t[i,k]]*p[i,t[i,k]]/ r[i,t[i,k]])+(n[i,t[i,k]] -
      r[i,t[i,k]])*log((n[i,t[i,k]]-n[i,t[i,k]]* p[i,t[i,k]])/(n[i,t[i,k]]- r[i,t[i,k]])))
      }
D[i]<- sum(Darm[i,1:na[i]])
      }
D.bar<- sum(D[])
}
```

APPENDIX 5

Categorisation of depressive symptom severity with cut-off scores

Categorisation of depressive symptoms severity with cut-off scores

No.	Depressive rating scales	Abbreviation	Cut-off scores		
			Mild	Moderate	Severe
1	Children's Depression Rating Scale-Revised	CDRS-R	29-40	≥ 40	
2	Hamilton Rating Scale for Depression-17/21 item	HAMD-17/21	7-17	18-23	≥ 24
3	Montgomery–Asberg Depression Rating Scale	MADRS	15-24	25-30	≥ 31
4	Children Depression Inventory	CDI	< 20	20-36	≥ 36
5	Beck Depression Inventory	BDI	10-20	21-30	≥ 31
6	The Clinical Global Impression – Severity scale	CGI-S	3	4-5	≥ 6

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APPENDIX 6

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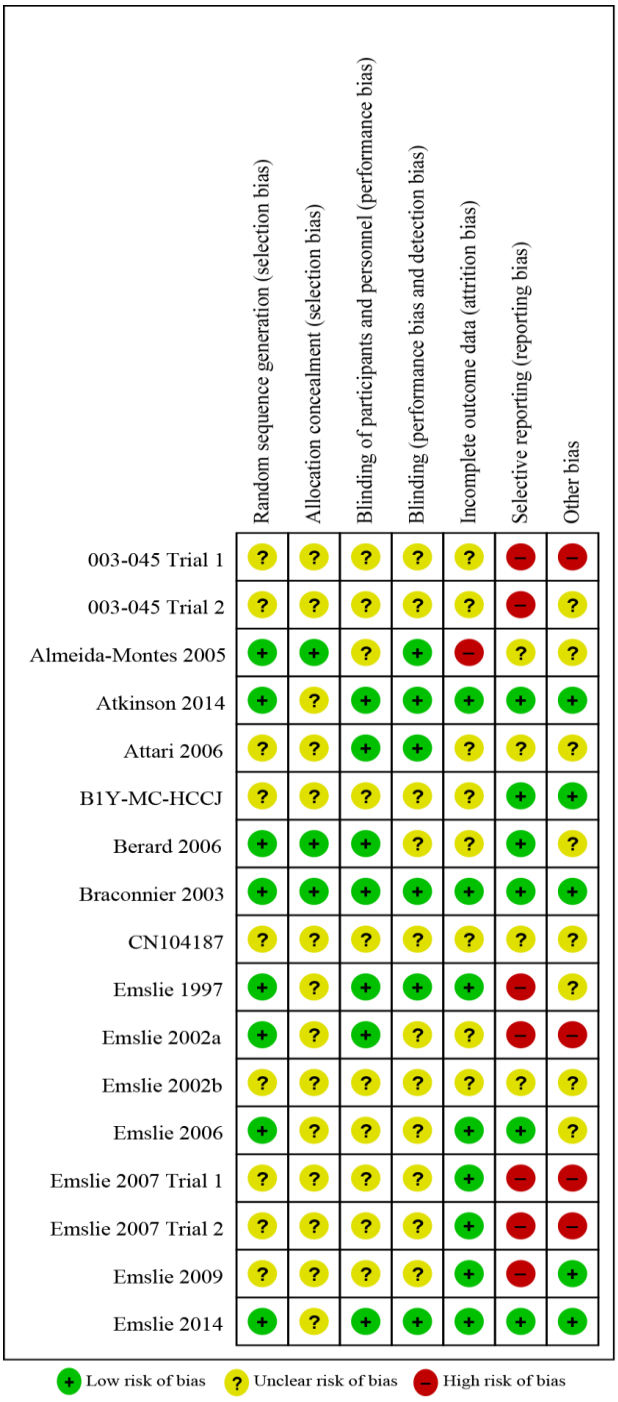
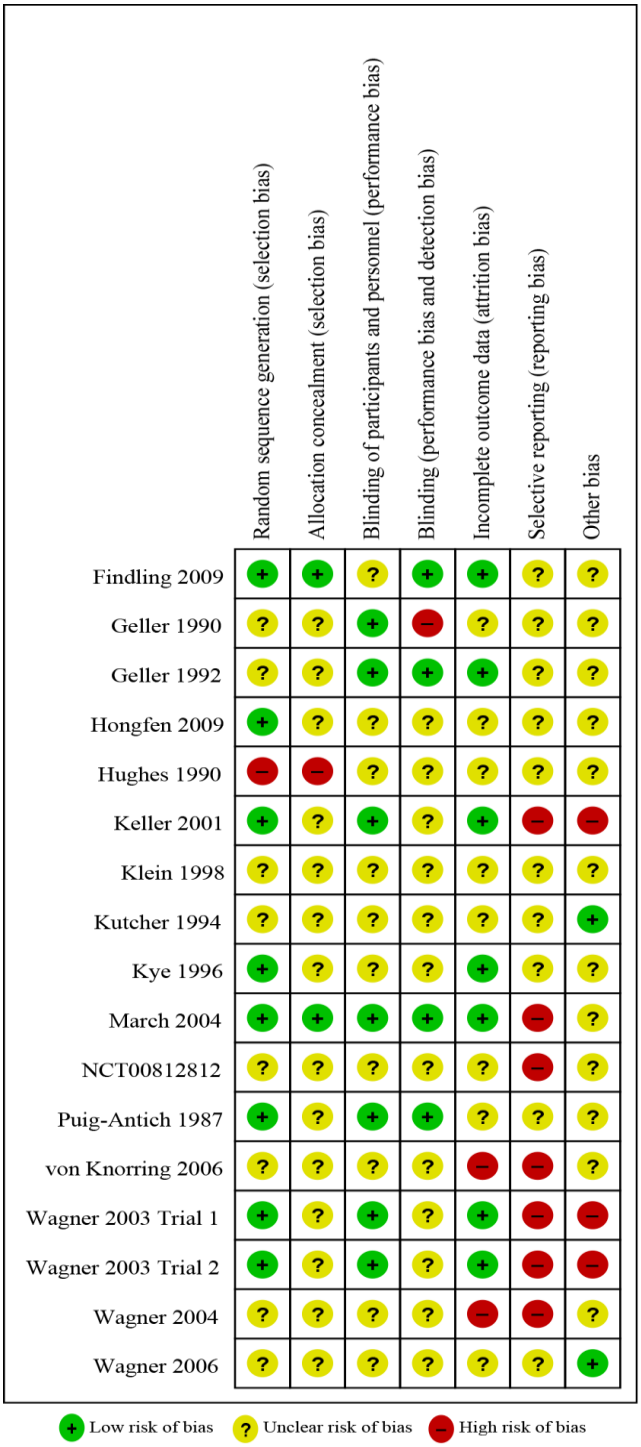
APPENDIX 7

Risk of bias assessment

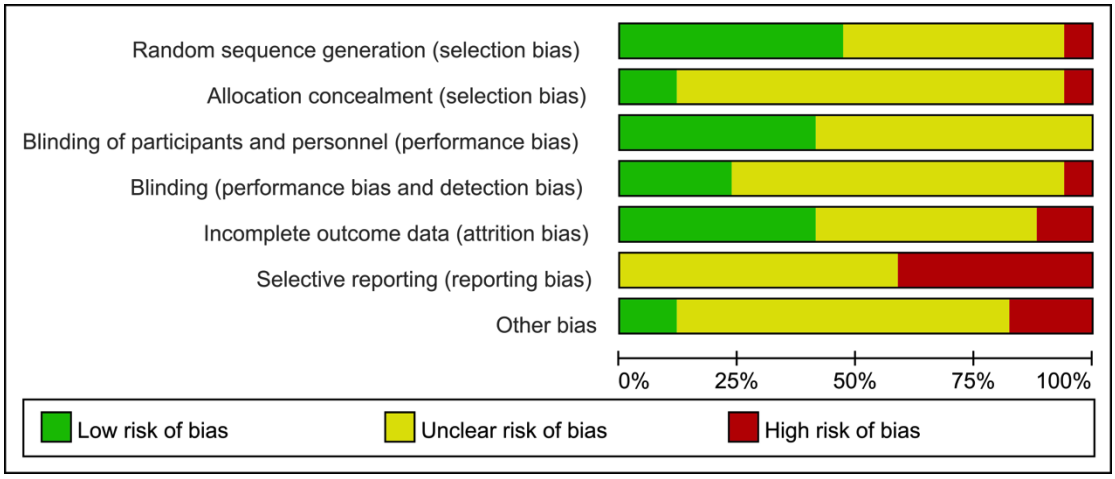
We used the Cochrane Collaboration's tool for assessing risk of bias. A trial that received a rating of "high risk of bias" in 2 or more entries was rated as a high risk trial; a rating of "low risk of bias"in 5 of 7 entries and "high risk of bias" in at most one entry was rated as a low risk trial; and the remaining were rated as moderate risk trials.

Risk of bias graph: it is a plot of the distribution of judgments (Yes, No, Unclear) across studies for each risk of bias entry




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding (performance bias and detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Findling 2009
Geller 1990
Geller 1992
Hongfen 2009
Hughes 1990
Keller 2001
Klein 1998
Kutcher 1994
Kye 1996
March 2004
NCT00812812
Puig-Antich 1987
von Knorring 2006
Wagner 2003 Trial 1
Wagner 2003 Trial 2
Wagner 2004
Wagner 2006
Low risk of bias
Unclear risk of bias
High risk of bias

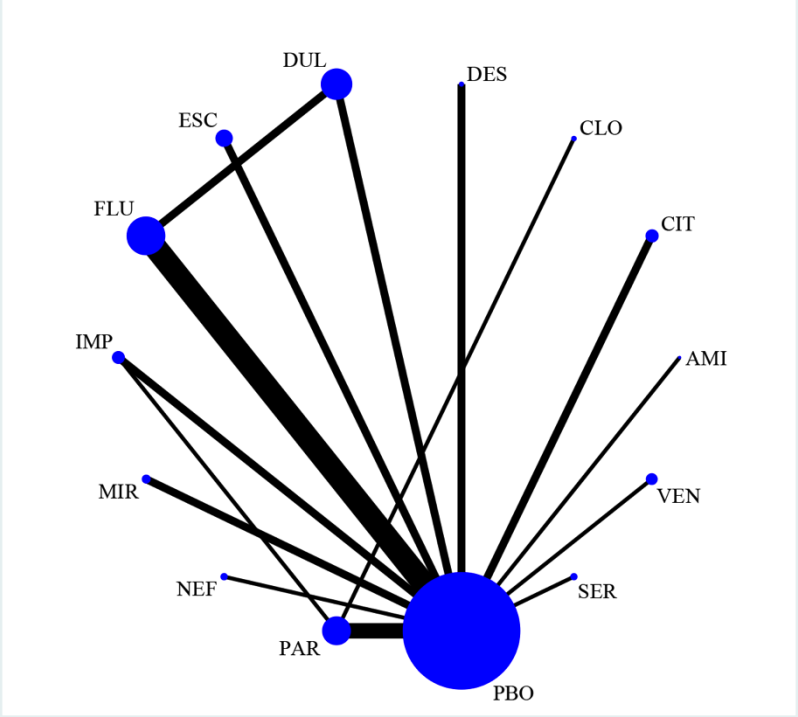
Risk of bias summary: it is a summary table of review authors' judgments for each risk of bias entriy for each study



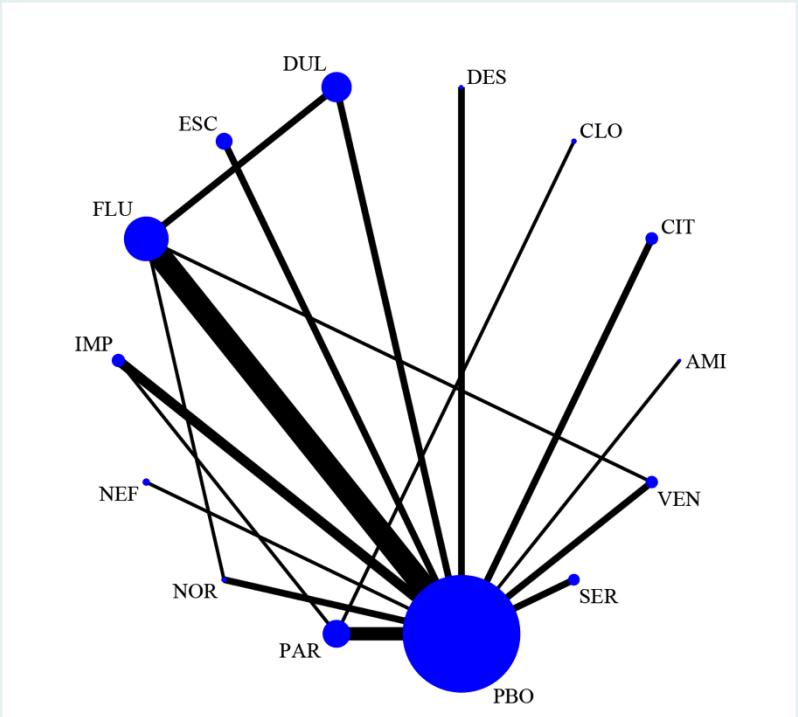
We found the overall quality of studies to be moderate, although most of the studies did not report the details about the method of random sequence generation and allocation concealment.

APPENDIX 8

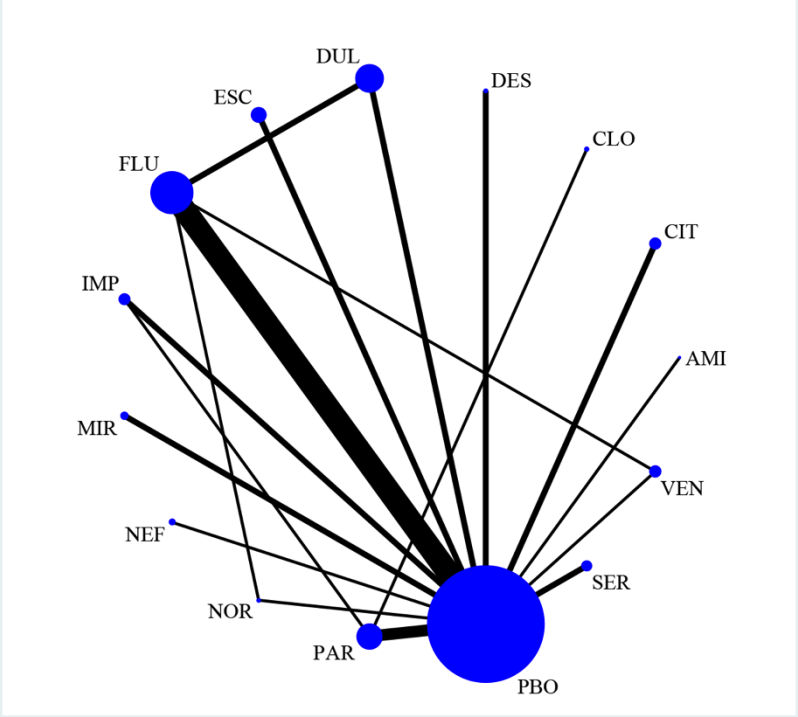
Network plot for each outcome



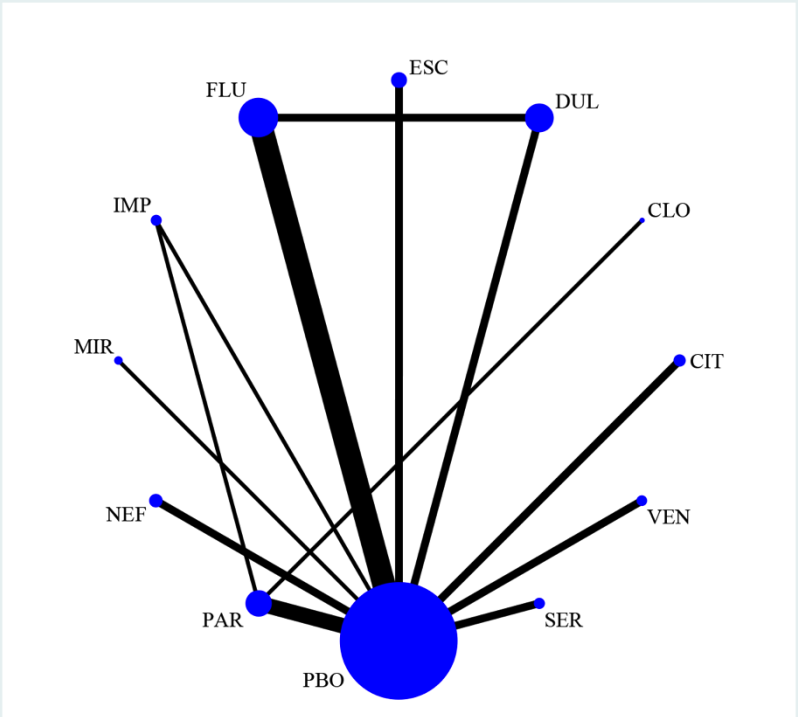
Network of eligible comparisons for discontinuation due to adverse events (tolerability)



Network of eligible comparisons for response rate.



Network of eligible comparisons for all-cause discontinuation (acceptability)



Network of eligible comparisons for suicidal behavior or ideation (suicide-related outcome)

APPENDIX 9

Results from pairwise meta-analysis for each outcome: numbers, estimates and heterogeneity

a. Summary numbers of studies and patients from pair-wise meta-analysis of direct comparisons

	Mean overall change in symptoms (N / n)*	Discontinuation due to adverse events (N / n)	Response rate (N / n)	All-cause discontinuation (N / n)	Suicidal behavior or ideation (N / n)
Amitriptyline vs.					
Placebo	1 / 31	1 / 31	1 / 31	1 / 31	NA
Citalopram vs.					
Placebo	2 / 361	2 / 422	2 / 407	2 / 422	2 / 422
Clomipramine vs.					
Paroxetine	1 / 121	1 / 121	1 / 121	1 / 121	1 / 121
Desipramine vs.					
Placebo	2 / 78	2 / 105	2 / 78	2 / 105	NA
Duloxetine vs.					
Fluoxetine	2 / 557	2 / 575	2 / 557	2 / 575	2 / 575

Placebo	2 / 552	2 / 566	2 / 552	2 / 566	2 / 566
Escitalopram vs.					
Placebo	2 / 572	2 / 584	2 / 572	2 / 584	2 / 584
Fluoxetine vs.					
Nortriptyline	1 / 40	NA	1 / 40	1 / 40	NA
Placebo	8 / 1066	6 / 848	7 / 1022	6 / 849	6 / 1035
Venlafaxine	1 / 59	NA	1 / 59	1 / 60	NA
Imipramine vs.					
Paroxetine	1 / 184	1 / 188	1 / 184	1 / 188	1 / 188
Placebo	2 / 219	2 / 224	3 / 246	2 / 224	1 / 182
Mirtazapine vs.					
Placebo	2 / 250	2 / 259	NA	2 / 259	2 / 259
Nefazodone vs.					
Placebo	2 / 468	1 / 195	1 / 195	1 / 195	2 / 479

Nortriptyline vs.					
Placebo	2 / 81	NA	2 / 81	1 / 60	NA
Paroxetine vs.					
Placebo	4 / 702	4 / 728	4 / 702	4 / 728	4 / 728
Sertraline vs.					
Placebo	2 / 364	2 / 376	2 / 364	2 / 376	2 / 376
Venlafaxine vs.					
Placebo	2 / 334	2 / 367	2 / 328	2 / 367	2 / 367

* N= number of studies; n= number of patients;
NA= not available.

b. Summary estimates from pair-wise meta-analysis of direct comparisons*

	Mean overall change in symptoms SMD (95% CI)	Discontinuation due to adverse events OR (95% CI)	Response rate OR (95% CI)	All-cause discontinuation OR (95% CI)	Suicidal behavior or ideation OR (95% CI)
Amitriptyline vs.					
Placebo	0·09 (-0·63 to 0·80)	0·71 (0·04 to 12·43)	0·47 (0·08 to 2·94)	1·67 (0·33 to 8·42)	NA
Citalopram vs.					
Placebo	-0·18 (-0·51 to 0·15)	1·32 (0·64 to 2·72)	1·05 (0·71 to 1·56)	0·99 (0·65 to 1·51)	1·39 (0·48 to 4·01)
Clomipramine vs.					
Paroxetine	**0·49 (0·13 to 0·85)**	1·01 (0·43 to 2·38)	0·50 (0·24 to 1·04)	1·52 (0·72 to 3·20)	0·82 (0·29 to 2·38)
Desipramine vs.					
Placebo	-0·44 (-1·50 to 0·62)	2·52 (0·10 to 65·72)	1·76 (0·70 to 4·42)	2·38 (0·80 to 7·02)	NA
Duloxetine vs.					
Fluoxetine	-0·10 (-0·27 to 0·07)	3·17 (0·61 to 16·57)	1·34 (0·93 to 1·91)	1·15 (0·78 to 1·68)	0·92 (0·56 to 1·51)

Placebo	-0·12 (-0·32 to 0·09)	**2·75 (1·18 to 6·44)**	1·39 (0·97 to 1·99)	1·31 (0·71 to 2·40)	0·90 (0·55 to 1·48)
Escitalopram vs.					
Placebo	**-0·17 (-0·34 to -0·01)**	1·90 (0·44 to 8·28)	**1·58 (1·13 to 2·20)**	1·47 (0·96 to 2·24)	0·99 (0·47 to 2·08)
Fluoxetine vs.					
Nortriptyline	**-4·33 (-5·48 to -3·17)**	NA	**9·00 (1·64 to 49·45)**	0·44 (0·07 to 2·76)	NA
Placebo	**-0·26 (-0·50 to -0·03)**	1·09 (0·44 to 2·72)	**1·69 (1·11 to 2·58)**	0·87 (0·54 to 1·40)	1·12 (0·72 to 1·73)
Venlafaxine	0·00 (-0·51 to 0·51)	NA	0·81 (0·27 to 2·43)	1·00 (0·06 to 16·76)	NA
Imipramine vs.					
Paroxetine	0·27 (-0·02 to 0·56)	**4·31 (1·91 to 9·71)**	0·57 (0·32 to 1·04)	1·72 (0·93 to 3·17)	0·48 (0·09 to 2·68)
Placebo	0·00 (-0·27 to 0·26)	**6·23 (2·45 to 15·88)**	1·03 (0·62 to 1·70)	2·74 (0·78to 9·57)	1·85 (0·17 to 20·76)
Mirtazapine vs.					
Placebo	-0·23 (-0·52 to 0·05)	1·51 (0·39 to 5·88)	NA	0·91 (0·48 to 1·74)	1·58 (0·06 to 39·29)
Nefazodone vs.					
Placebo	-0·14 (-0·40 to 0·13)	1·98 (0·35 to 11·06)	**2·25 (1·27 to 3·99)**	0·55 (0·30 to 1·00)	NA

Nortriptyline vs.					
Placebo	-0·11 (-0·55 to 0·34)	NA	1·11 (0·19 to 6·59)	0·62 (0·16 to 2·45)	NA
Paroxetine vs.					
Placebo	-0·10 (-0·26 to 0·05)	1·68 (0·91 to 3·09)	1·33 (0·98 to 1·80)	1·28 (0·91 to 1·79)	1·44 (0·44 to 4·74)
Sertraline vs.					
Placebo	**-0·23 (-0·44 to -0·03)**	**3·60 (1·30 to 9·96)**	**1·52 (1·00 to 2·31)**	1·52 (0·48 to 4·82)	1·92 (0·33 to 11·06)
Venlafaxine vs.					
Placebo	-0·14 (-0·36 to 0·07)	**3·86 (1·40 to 10·63)**	1·08 (0·69 to 1·67)	1·26 (0·80 to 1·97)	**9·11 (1·14 to 73·00)**

Significant results are bolded and underscored. SMD=standardized mean difference, OR=odds ratio, CI=confidence interval, NA= not available.

*DerSimonian R, Laird N. Metaanalysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–87.

c. Heterogeneity test result, I^2 and heterogeneity estimate

Mean overall change in symptoms (efficacy)

	No. of studies	P-value	I^2	τ^2
Citalopram vs Placebo*	2	0·11019	60·7%	0·0345
Desipramine vs Placebo*	2	0·02325	80·8%	0·4720
Duloxetine vs Placebo	2	0·23889	27·9%	0·0062
Duloxetine vs Fluoxetine	2	0·62657	0·0%	0·0000
Escitalopram vs Placebo	2	0·6070	0·0%	0·0000
Fluoxetine vs Placebo*	8	0·0031	67·4%	0·0679
Imipramine vs Placebo	2	0·6430	0·0%	0·0000
Mirtazapine vs Placebo	2	0·2810	14·0%	0·0058
Nefazodone vs Placebo	2	0·16596	47·9%	0·0170
Nortriptyline vs Placebo	2	0·3214	0·0%	0·0000
Paroxetine vs Placebo	4	0·39273	0·0%	0·0000
Sertraline vs Placebo	2	0·7951	0·0%	0·0000
Venlafaxine vs Placebo	2	0·9094	0·0%	0·0000

* The comparisons between citalopram and placebo, between desipramine and placebo, and between fluoxetine and placebo had higher I^2 values than the other comparisons.

Discontinuation due to adverse events (tolerability)

	No. of studies	P-value	I^2	τ^2
Citalopram vs Placebo	2	0·4895	0·0%	0·0000
Desipramine vs Placebo*	2	0·0463	74·8%	4·1445
Duloxetine vs Placebo	2	0·98576	0·0%	0·0000
Duloxetine vs Fluoxetine*	2	0·1311	56·1%	0·8710
Escitalopram vs Placebo	2	0·3594	0·0%	0·0000
Fluoxetine vs Placebo	5	0·2413	27·0%	0·2926
Mirtazapine vs Placebo	2	0·4774	0·0%	0·0000
Paroxetine vs Placebo	4	0·40384	0·0%	0·0000

* The comparisons between desipramine and placebo, duloxetine and fluoxetine had higher I^2 values than the other comparisons.

Respnse rate

	No. of studies	P-value	I^2	τ^2
Citalopram vs Placebo	2	0·8360	0·0%	0·0000
Desipramine vs Placebo	2	0·80192	0·0%	0·0000
Duloxetine vs Placebo	2	0·6381	0·0%	0·0000
Duloxetine vs Fluoxetine	2	0·6504	0·0%	0·0000
Escitalopram vs Placebo	2	0·9054	0·0%	0·0000
Fluoxetine vs Placebo*	7	0·039540	54·7%	0·1585
Imipramine vs Placebo	3	0·6500	0·0%	0·0000
Nortriptyline vs Placebo	2	0·1710	46·6%	0·8253
Paroxetine vs Placebo	4	0·39586	0·0%	0·0000
Venlafaxine vs Placebo	2	0·789990	0·0%	0·0000

* The comparison between fluoxetine and placebo had a higher I^2 value than the other comparisons.

All-cause discontinuation

	No. of studies	P-value	I^2	τ^2
Citalopram vs Placebo	2	0·6071	0·0%	0·0000
Desipramine vs Placebo	2	0·2480	25·1%	0·1567
Duloxetine vs Placebo*	2	0·13798	54·6%	0·1074
Duloxetine vs Fluoxetine	2	0·8322	0·0%	0·0000
Escitalopram vs Placebo	2	0·68384	0·0%	0·0000
Fluoxetine vs Placebo*	8	0·022215	57·4%	0·2378
Imipramine vs Placeb	2	0·25293	23·5%	0·3740
Mirtazapine vs Placebo	2	0·5374	0·0%	0·0000
Paroxetine vs Placebo	4	0·77859	0·0%	0·0000
Sertraline vs Placebo*	2	0·02798	79·3%	0·5501

* The comparisons between duloxetine and placebo, between fluoxetine and placebo, sertraline and placebo had higher I^2 values than the other comparisons.

Suicidal behavior or ideation

	No. of studies	P-value	I^2	τ^2
Citalopram vs Placebo	2	0·3090	3·4%	0·0325
Duloxetine vs Placebo	2	0·91889	0·0%	0·0000
Duloxetine vs Fluoxetine	2	0·829530	0·0%	0·0000
Escitalopram vs Placebo	2	0·4711	0·0%	0·0000
Fluoxetine vs Placebo	6	0·5271	0·0%	0·0000
Paroxetine vs Placebo	4	0·31273	15·8%	0·2427
Sertraline vs Placebo	2	0·29475	8·9%	0·1630
Venlafaxine vs Placebo	2	0·87899	0·0%	0·0000

Appendix 10

The results of network meta-analysis for secondary outcomes

NEF	0·42 (0·16 to 1·47)	0·58 (0·23 to 1·81)	**0·16 (0·05 to 0·89)**	0·31 (0·12 to 1·16)	0·42 (0·11 to 1·15)	0·47 (0·14 to 1·16)	0·55 (0·13 to 1·58)	0·45 (0·17 to 1·69)	0·49 (0·21 to 1·40)	**0·16 (0·06 to 0·67)**	0·20 (0·06 to 1·16)	0·78 (0·12 to 2·64)	0·17 (0·04 to 2·29)	0·48 (0·17 to 2·10)
1·14 (0·52 to 3·13)	**DUL**	1·41 (0·75 to 2·42)	0·36 (0·13 to 1·47)	0·83 (0·31 to 1·86)	0·79 (0·28 to 1·84)	0·89 (0·38 to 1·80)	1·03 (0·34 to 2·55)	0·99 (0·46 to 2·71)	1·06 (0·63 to 2·03)	0·47 (0·14 to 1·09)	0·43 (0·15 to 1·96)	1·48 (0·31 to 4·43)	0·36 (0·08 to 4·08)	1·38 (0·44 to 3·37)
1·20 (0·57 to 3·02)	1·07 (0·65 to 1·65)	**FLU**	0·27 (0·10 to 1·01)	0·51 (0·26 to 1·22)	0·57 (0·23 to 1·23)	0·64 (0·32 to 1·17)	0·74 (0·28 to 1·69)	0·75 (0·38 to 1·79)	0·80 (0·56 to 1·24)	**0·34 (0·12 to 0·73)**	0·33 (0·12 to 1·35)	1·06 (0·25 to 2·97)	0·28 (0·06 to 2·88)	0·99 (0·35 to 2·25)
1·01 (0·36 to 4·42)	0·84 (0·33 to 2·96)	0·82 (0·34 to 2·72)	**DES**	2·12 (0·50 to 6·09)	2·02 (0·45 to 5·96)	2·27 (0·58 to 6·29)	2·64 (0·55 to 8·07)	2·04 (0·72 to 8·94)	2·20 (0·89 to 7·57)	1·20 (0·24 to 3·62)	0·89 (0·26 to 5·99)	3·84 (0·52 to 14·21)	0·75 (0·16 to 11·56)	3·53 (0·72 to 10·86)
1·28 (0·58 to 3·61)	1·20 (0·57 to 2·22)	1·04 (0·60 to 1·97)	1·35 (0·37 to 3·44)	**ESC**	1·07 (0·36 to 2·55)	1·20 (0·47 to 2·53)	1·40 (0·43 to 3·51)	1·30 (0·57 to 3·75)	1·40 (0·76 to 2·88)	0·63 (0·18 to 1·52)	0·57 (0·19 to 2·68)	2·01 (0·39 to 6·27)	0·48 (0·11 to 5·57)	1·86 (0·55 to 4·65)
1·69 (0·54 to 4·10)	1·27 (0·52 to 2·62)	1·21 (0·54 to 2·36)	1·43 (0·36 to 3·93)	1·13 (0·45 to 2·36)	**SER**	1·05 (0·47 to 2·82)	1·50 (0·43 to 3·82)	1·37 (0·57 to 4·13)	1·47 (0·75 to 3·23)	0·50 (0·18 to 1·69)	0·60 (0·19 to 2·94)	1·27 (0·40 to 6·73)	0·50 (0·11 to 5·99)	1·45 (0·56 to 5·08)
1·87 (0·72 to 4·03)	1·41 (0·73 to 2·46)	1·34 (0·78 to 2·16)	1·58 (0·46 to 3·92)	1·25 (0·63 to 2·22)	1·06 (0·53 to 2·49)	**PAR**	1·25 (0·43 to 2·98)	1·21 (0·58 to 3·12)	1·30 (0·81 to 2·29)	0·46 (0·21 to 1·10)	0·57 (0·23 to 1·83)	1·13 (0·38 to 5·48)	0·45 (0·10 to 4·91)	1·29 (0·55 to 3·89)
2·11 (0·74 to 4·76)	1·58 (0·75 to 2·90)	1·50 (0·80 to 2·53)	1·77 (0·49 to 4·56)	1·41 (0·64 to 2·66)	1·39 (0·54 to 2·91)	1·17 (0·57 to 2·12)	**VEN**	1·04 (0·41 to 3·44)	1·12 (0·53 to 2·75)	0·38 (0·13 to 1·37)	0·45 (0·14 to 2·38)	0·97 (0·29 to 5·62)	0·38 (0·08 to 4·83)	1·11 (0·41 to 4·18)
1·91 (0·84 to 5·47)	1·59 (0·82 to 3·43)	1·55 (0·87 to 3·05)	1·45 (0·55 to 5·25)	1·40 (0·71 to 3·10)	1·32 (0·61 to 3·38)	1·19 (0·64 to 2·46)	1·06 (0·54 to 2·42)	**CIT**	0·96 (0·52 to 1·98)	0·43 (0·12 to 1·04)	0·62 (0·13 to 1·85)	1·38 (0·26 to 4·24)	0·33 (0·07 to 3·81)	1·28 (0·37 to 3·21)
2·10 (1·06 to 4·89)	**1·74 (1·12 to 2·84)**	**1·70 (1·25 to 2·39)**	1·59 (0·67 to 4·84)	1·53 (0·96 to 2·58)	1·44 (0·79 to 2·97)	1·30 (0·89 to 1·99)	1·16 (0·72 to 2·03)	1·02 (0·62 to 1·82)	**PBO**	**0·41 (0·15 to 0·82)**	0·58 (0·15 to 1·52)	1·29 (0·31 to 3·66)	0·85 (0·08 to 3·36)	1·19 (0·47 to 2·48)
2·32 (1·01 to 6·88)	2·21 (0·99 to 4·34)	**2·11 (1·03 to 3·88)**	2·49 (0·65 to 6·60)	1·96 (0·85 to 3·90)	1·60 (0·74 to 4·27)	1·46 (0·83 to 2·90)	1·28 (0·64 to 3·05)	1·32 (0·56 to 2·71)	1·21 (0·65 to 2·07)	**IMP**	1·04 (0·36 to 5·06)	3·79 (0·66 to 12·71)	0·85 (0·19 to 10·97)	3·50 (0·93 to 9·78)
2·79 (1·00 to 11·90)	2·31 (0·92 to 7·98)	2·26 (0·94 to 7·36)	2·11 (0·65 to 10·93)	2·04 (0·80 to 7·14)	1·92 (0·72 to 7·54)	1·81 (0·84 to 4·94)	1·54 (0·61 to 5·54)	1·87 (0·52 to 4·90)	1·71 (0·57 to 4·04)	1·12 (0·45 to 3·86)	**CLO**	3·17 (0·40 to 11·77)	0·59 (0·12 to 9·74)	2·92 (0·54 to 9·29)
4·26 (1·05 to 12·19)	3·19 (1·00 to 8·04)	**3·02 (1·04 to 7·22)**	3·60 (0·72 to 11·44)	2·85 (0·85 to 7·33)	1·98 (0·76 to 7·68)	1·79 (0·75 to 5·94)	1·60 (0·65 to 5·62)	1·92 (0·57 to 5·04)	1·74 (0·61 to 4·12)	1·58 (0·44 to 4·10)	1·32 (0·26 to 4·15)	**NOR**	0·27 (0·06 to 4·69)	0·77 (0·23 to 4·57)
3·13 (0·69 to 57·34)	2·61 (0·60 to 40·78)	2·55 (0·60 to 38·55)	2·38 (0·51 to 49·12)	2·30 (0·53 to 36·34)	2·16 (0·48 to 36·70)	1·95 (0·45 to 30·28)	1·74 (0·40 to 27·69)	1·52 (0·35 to 24·78)	4·56 (0·36 to 21·90)	1·24 (0·28 to 20·45)	0·87 (0·19 to 17·76)	0·87 (0·19 to 15·93)	**AMI**	3·46 (0·27 to 15·83)
…	…	…	…	…	…	…	…	…	…	…	…	…	…	**MIR**

Treatment Response rate (OR with 95% CrI) All-cause discontinuation (OR with 95% CrI)

Drugs are reported in order of ranking of response rate. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining treatment and the row-defining treatment. For both the response rate and all-cause discontinuation, an OR value higher than 1 favors the column-defining treatment. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. Significant results are bolded and underscored. AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, CrI=credibility interval, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, OR=odds ratio, PAR=paroxetine, PBO=placebo, SER=sertraline, VEN=venlafaxine

APPENDIX 11

Assessment of inconsistency results for each outcome: global, local and from the node-splitting model

a. Evaluation of the global inconsistency

For evaluating the global inconsistency, we present the mean posterior deviance (D), the number of data points and the Deviance Information Criterion (DIC) of the NMA model. The mean posterior deviance should approximate the number of data points for models with good fit to the data. The DIC is a Bayesian model evaluation criterion that measures model fit adjusted with complexity of the model; smaller DIC values correspond to more preferable models.

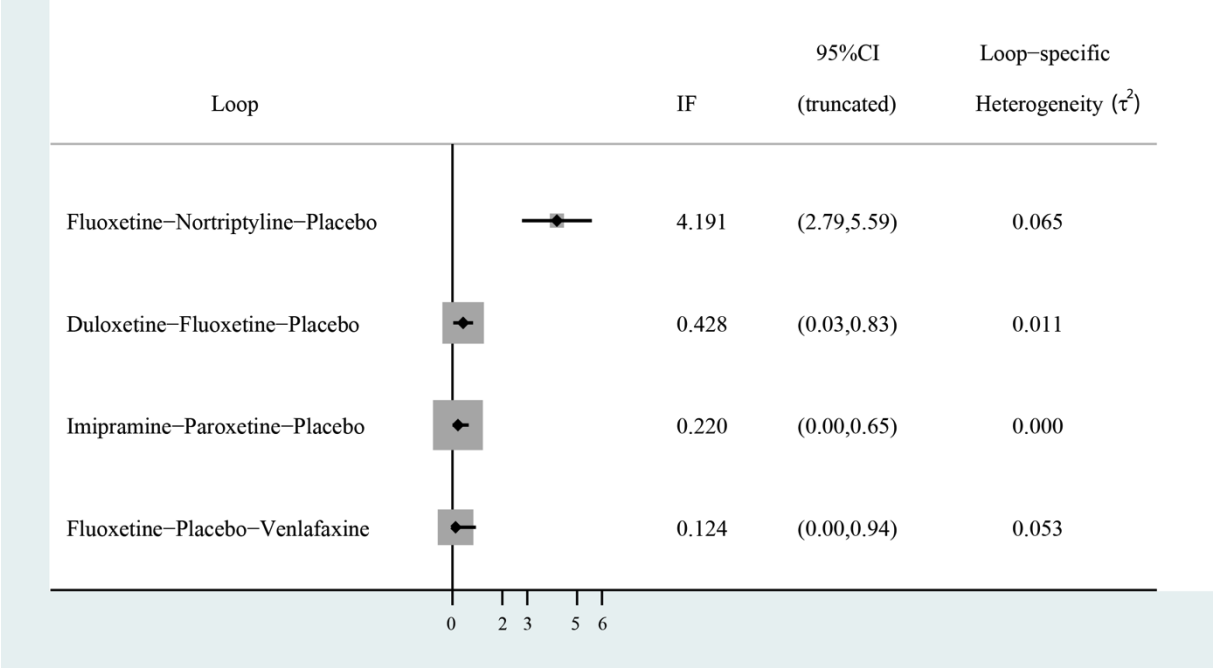
Model assumption	D	# of data points	DIC
Mean overall change in symptoms [Test of global inconsistency: ~~P~~p<0·0001~~=0.0000~~]			
Consistency	71·32	69	292·203
Inconsistency	71·91	69	284·414
Discontinuation due to adverse events [Test of global inconsistency: P = 0.8432]			
Consistency	54·89	51	250·470
Inconsistency	54·60	51	250·372
Response rate [Test of global inconsistency: P = 0.0023]			
Consistency	61·57	61	373·605
Inconsistency	59·99	61	373·219
All-cause discontinuation [Test of global inconsistency: P = 0.5202]			
Consistency	66·11	63	377·201
Inconsistency	67·53	63	380·468
Suicidal behavior or ideation [Test of global inconsistency: P = 0.4394]			
Consistency	41·23	41	197·952
Inconsistency	41·22	41	197·707

b. Evaluation of the local inconsistency

Tests of local inconsistency revealed that the percentages for inconsistent loops were to be expected according to empirical data with the methods of Veroniki et al (Int J Epidemiol 2013; 42:332-45).

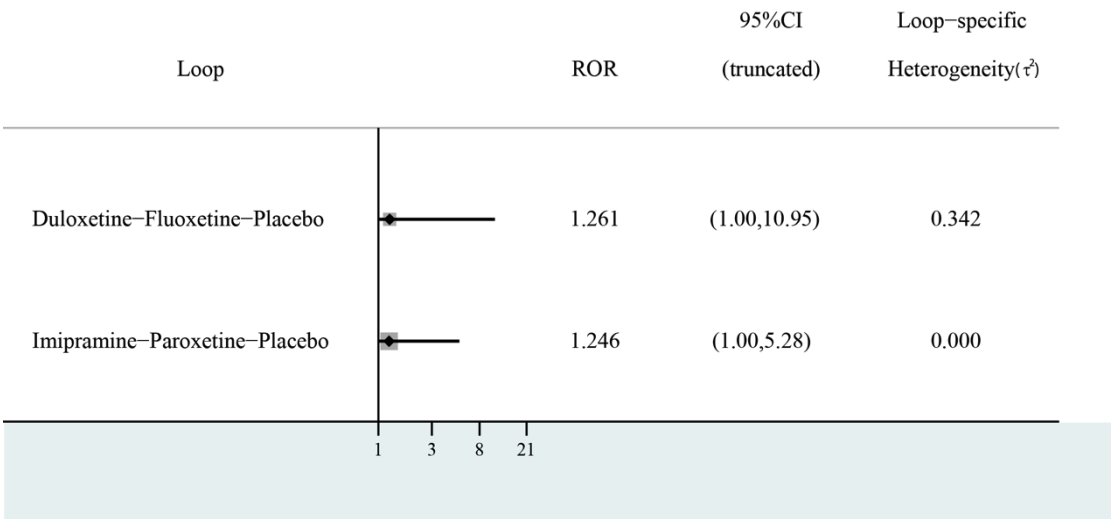
Mean overall change in symptoms

Loop	IF	z-value	P-value	95%CI	τ^2
FLU-NOR-PBO	4·191	5·868	<0·0001	(2·79,5·59)	0·065
DUL-FLU-PBO	0·428	2·116	0·0343	(0·03,0·83)	0·011
IMP-PAR-PBO	0·220	0·999	0·31778	(0·00,0·65)	0·000
FLU-PBO-VEN	0·124	0·298	0·7653	(0·00,0·94)	0·053



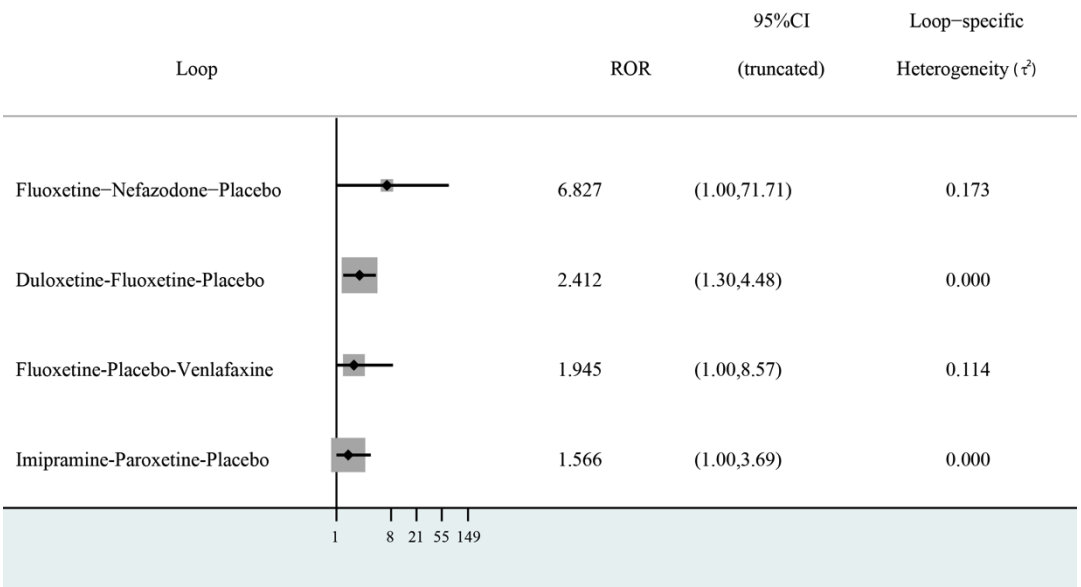
Discontinuation due to adverse events

Loop	RoR	z-value	P-value	95%CI	τ^2
DUL-FLU-PBO	1·261	0·210	0·83374	(1·00,10·95)	0·342
IMP-PAR-PBO	1·246	0·298	0·7655	(1·00,5·28)	0·000



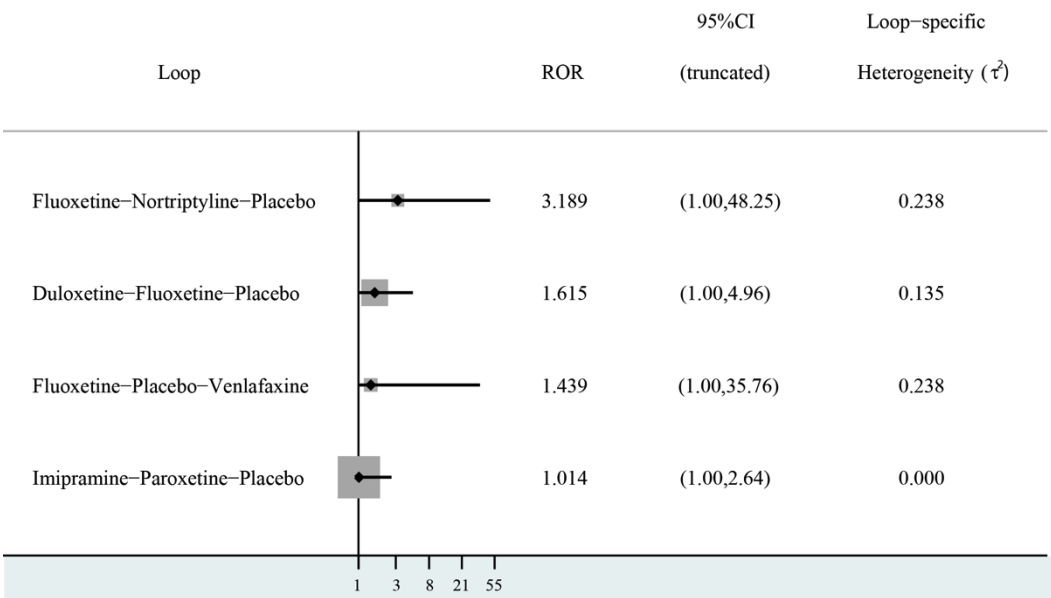
Response rate

Loop	RoR	z-value	P-value	95%CI	τ^2
FLU-NEF-PBO	6·827	1·601	0·1094	(1·00,71·71)	0·173
DUL-FLU-PBO	2·412	2·785	0·0053	(1·30,4·48)	0·000
FLU-PBO-VEN	1·945	0·880	0·3791	(1·00,8·57)	0·114
IMP-PAR-PBO	1·566	1·026	0·30475	(1·00,3·69)	0·000



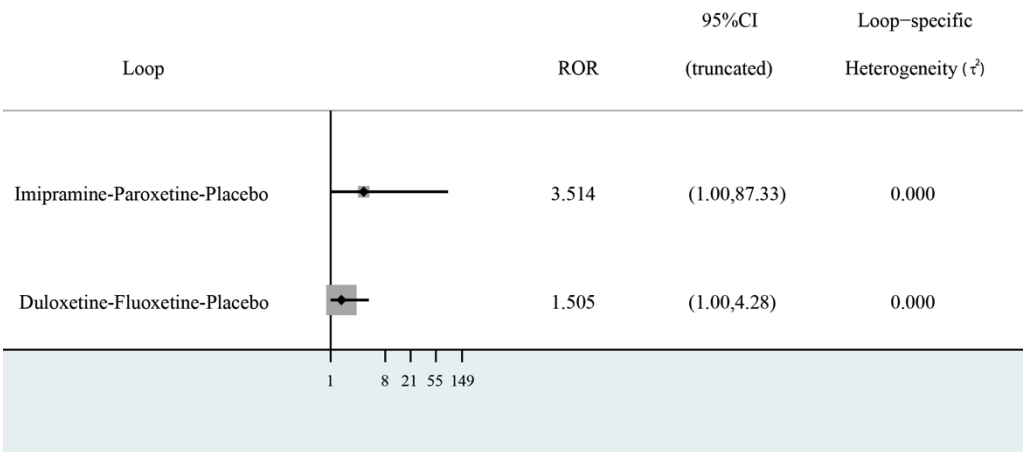
All-cause discontinuation

Loop	RoR	z-value	P-value	95%CI	τ^2
FLU-NOR-PBO	3·189	0·837	0·40273	(1·00,48·25)	0·238
DUL-FLU-PBO	1·615	0·836	0·4030	(1·00,4·96)	0·135
FLU-PBO-VEN	1·439	0·222	0·8242	(1·00,35·76)	0·238
IMP-PAR-PBO	1·014	0·028	0·97768	(1·00,2·64)	0·000



Suicidal behavior or ideation

Loop	RoR	z-value	P-value	95%CI	τ^2
IMP-PAR-PBO	3·514	0·767	0·4432	(1·00,87·33)	0·000
DUL-FLU-PBO	1·505	0·768	0·44253	(1·00,4·28)	0·000



c. Evaluation of the inconsistency by node-splitting model

Tests of inconsistency by node-splitting method fitted the node-splitting model of Dias et al (Stat Med 2010; 29:932-44). The results reported the estimated direct and indirect treatment effects and their difference; the P-value for the difference is the test of consistency.

Mean overall change in symptoms

Comparisons	Direct		Indirect		Difference			τ^2
	SMD	SE	SMD	SE	SMD	SE	P-value	
Placebo vs Amitriptyline	…	…	…	…	…	…	…	…
Placebo vs Citalopram	…	…	…	…	…	…	…	…
Paroxetine vs Clomipramine	-0·49	0·33	-0·31	63·38	-0·18	63·38	0·99788	0·2756
Placebo vs Desipramine	…	…	…	…	…	…	…	…
Fluoxetine vs Duloxetine	0·10	0·11	-0·86	0·26	0·97	0·29	0·0010	0·0878
Placebo vs Duloxetine	0·12	0·11	1·08	0·26	-0·97	0·29	0·0010	0·0878
Placebo vs Escitalopram	…	…	…	…	…	…	…	…
Nortriptyline vs Fluoxetine	4·22	0·62	0·15	0·26	4·07	0·67	<0·0001	0·1450
Placebo vs Fluoxetine	0·26	0·14	1·40	0·48	-1·14	0·50	0·02091	0·3296
Venlafaxine vs Fluoxetine	-0·00	0·40	0·25	0·28	-0·25	0·49	0·6192	0·3088
Paroxetine vs Imipramine	-0·27	0·33	0·04	0·44	-0·31	0·56	0·5884	0·2999
Placebo vs Imipramine	0·03	0·27	-0·32	0·73	0·36	0·78	0·65566	0·3098
Placebo vs Mirtazapine	…	…	…	…	…	…	…	…
Placebo vs Nefazodone	…	…	…	…	…	…	…	…
Placebo vs Nortriptyline	0·11	0·25	-3·96	0·62	4·07	0·67	<0·0001	0·1450
Placebo vs Paroxetine	0·13	0·17	0·57	1·07	-0·44	1·08	0·69172	0·3022
Placebo vs Sertraline	…	…	…	…	…	…	…	…
Placebo vs Venlafaxine	0·14	0·24	0·39	0·43	-0·25	0·49	0·6192	0·3088

Discontinuation due to adverse events

Comparisons	Direct		Indirect		Difference			τ^2
	LogOR	SE	LogOR	SE	LogOR	SE	P-value	
Placebo vs Amitriptyline	…	…	…	…	…	…	…	…
Placebo vs Citalopram	…	…	…	…	…	…	…	…
Paroxetine vs Clomipramine	-0·01	0·44	0·99	151·89	-1·00	151·89	0·99485	0·0000
Placebo vs Desipramine	…	…	…	…	…	…	…	…
Fluoxetine vs Duloxetine	-0·83	0·44	-1·22	1·30	0·39	1·46	0·789890	0·0000
Placebo vs Duloxetine	-0·99	0·43	-0·60	1·31	-0·39	1·46	0·789890	0·0000
Placebo vs Escitalopram	…	…	…	…	…	…	…	…
Placebo vs Fluoxetine	…	…	…	…	…	…	…	…
Paroxetine vs Imipramine	-1·48	0·43	-0·65	1·16	-0·83	1·28	0·5172	0·1284
Placebo vs Imipramine	-1·73	0·50	-2·33	1·19	0·60	1·39	0·6662	0·1628

Placebo vs Mirtazapine	…	…	…	…	…	…	…	…
Placebo vs Nefazodone	…	…	…	…	…	…	…	…
Placebo vs Paroxetine	-0·52	0·31	3·12	4·10	-3·64	4·12	0·37657	0·0000
Placebo vs Sertraline	…	…	…	…	…	…	…	…
Placebo vs Venlafaxine	…	…	…	…	…	…	…	…

Response rate

Comparisons	Direct		Indirect		Difference			τ^2
	LogOR	SE	LogOR	SE	LogOR	SE	P-value	
Placebo vs Amitriptyline	…	…	…	…	…	…	…	…
Placebo vs Citalopram	…	…	…	…	…	…	…	…
Paroxetine vs Clomipramine	0·69	0·42	0·58	127·73	0·11	127·73	0·9993	0·1907
Placebo vs Desipramine	…	…	…	…	…	…	…	…
Fluoxetine vs Duloxetine	-0·30	0·18	1·38	0·48	-1·68	0·52	0·0012	0·0000
Placebo vs Duloxetine	-0·33	0·18	-2·01	0·48	1·68	0·52	0·0012	0·0000
Placebo vs Escitalopram	…	…	…	…	…	…	…	…
Nortriptyline vs Fluoxetine	-2·20	0·89	-0·18	0·63	-2·02	1·09	0·0633	0·1733
Placebo vs Fluoxetine	-0·52	0·16	-0·56	0·56	0·04	0·58	0·9455	0·2028
Venlafaxine vs Fluoxetine	0·21	0·59	-0·49	0·31	0·70	0·67	0·29566	0·1946
Paroxetine e vs Imipramin	0·55	0·36	0·15	0·51	0·40	0·63	0·52182	0·1877
Placebo vs Imipramine	-0·00	0·29	0·98	0·74	-0·98	0·80	0·21677	0·1653
Placebo vs Nefazodone	…	…	…	…	…	…	…	…
Placebo vs Nortriptyline	-0·31	0·61	1·71	0·90	-2·02	1·09	0·0633	0·1733
Placebo vs Paroxetine	-0·30	0·19	0·31	1·23	-0·61	1·24	0·6243	0·2000
Placebo vs Sertraline	…	…	…	…	…	…	…	…
Placebo vs Venlafaxine	-0·07	0·26	-0·77	0·61	0·70	0·67	0·29566	0·1946

All-cause discontinuation

Comparisons	Direct		Indirect		Difference			τ^2
	LogOR	SE	LogOR	SE	LogOR	SE	P-value	
Placebo vs Amitriptyline	…	…	…	…	…	…	…	…
Placebo vs Citalopram	…	…	…	…	…	…	…	…
Paroxetine vs Clomipramine	-0·42	0·47	0·54	131·44	-0·96	131·44	0·9942	0·2771
Placebo vs Desipramine	…	…	…	…	…	…	…	…
Fluoxetine vs Duloxetine	-0·13	0·24	-1·26	0·61	1·13	0·67	0·09081	0·1885
Placebo vs Duloxetine	-0·24	0·25	0·89	0·61	-1·13	0·67	0·09081	0·1885
Placebo vs Escitalopram	…	…	…	…	…	…	…	…
Nortriptyline vs Fluoxetine	0·81	0·97	-0·30	0·78	1·11	1·25	0·37495	0·2830
Placebo vs Fluoxetine	0·19	0·19	0·69	0·96	-0·49	0·97	0·61384	0·2848
Venlafaxine vs Fluoxetine	0·00	1·47	0·45	0·41	-0·45	1·52	0·7692	0·2814
Paroxetine vs Imipramine	-0·54	0·44	-0·85	0·88	0·32	0·99	0·74975	0·3088
Placebo vs Imipramine	-0·88	0·44	-0·89	0·96	0·01	1·07	0·9932	0·3095

Placebo vs Mirtazapine	…	…	…	…	…	…	…	…
Placebo e vs Nefazodon	…	…	…	…	…	…	…	…
Placebo vs Nortriptyline	0·49	0·76	-0·62	0·99	1·11	1·25	0·37495	0·2830
Placebo vs Paroxetine	-0·25	0·23	-3·72	3·18	3·47	3·19	0·27697	0·2761
Placebo vs Sertraline	…	…	…	…	…	…	…	…
Placebo vs Venlafaxine	-0·23	0·36	0·22	1·48	-0·45	1·52	0·7692	0·2814

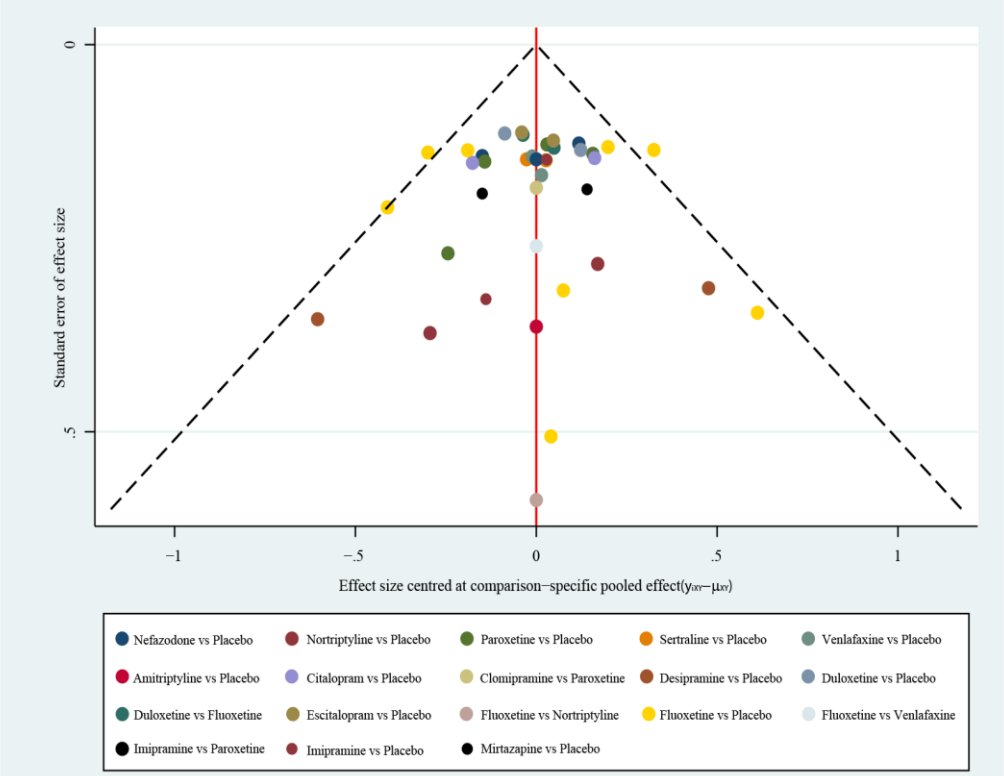
Suicidal behavior or ideation

Comparisons	Direct		Indirect		Difference			τ^2
	LogOR	SE	LogOR	SE	LogOR	SE	P-value	
Placebo vs Citalopram	…	…	…	…	…	…	…	…
Paroxetine vs Clomipramine	0·19	0·54	0·80	186·66	-0·60	186·66	0·9974	0·0000
Fluoxetine vs Duloxetine	0·08	0·25	0·88	0·91	-0·80	0·96	0·4040	0·0000
Placebo vs Duloxetine	0·99	0·25	-0·70	0·91	0·80	0·96	0·4040	0·0000
Placebo vs Escitalopram	…	…	…	…	…	…	…	…
Placebo vs Fluoxetine	…	…	…	…	…	…	…	…
Paroxetine vs Imipramine	0·74	0·88	-1·78	2·53	2·51	2·58	0·3301	0·0000
Placebo vs Imipramine	-0·61	1·23	1·90	2·03	-2·51	2·58	0·3301	0·0000
Placebo vs Mirtazapine	…	…	…	…	…	…	…	…
Placebo vs Nefazodone	…	…	…	…	…	…	…	…
Placebo vs Paroxetine	-0·39	0·55	-0·09	93·36	-0·30	93·36	0·9974	0·0000
Placebo vs Sertraline	…	…	…	…	…	…	…	…
Placebo vs Venlafaxine	…	…	…	…	…	…	…	…

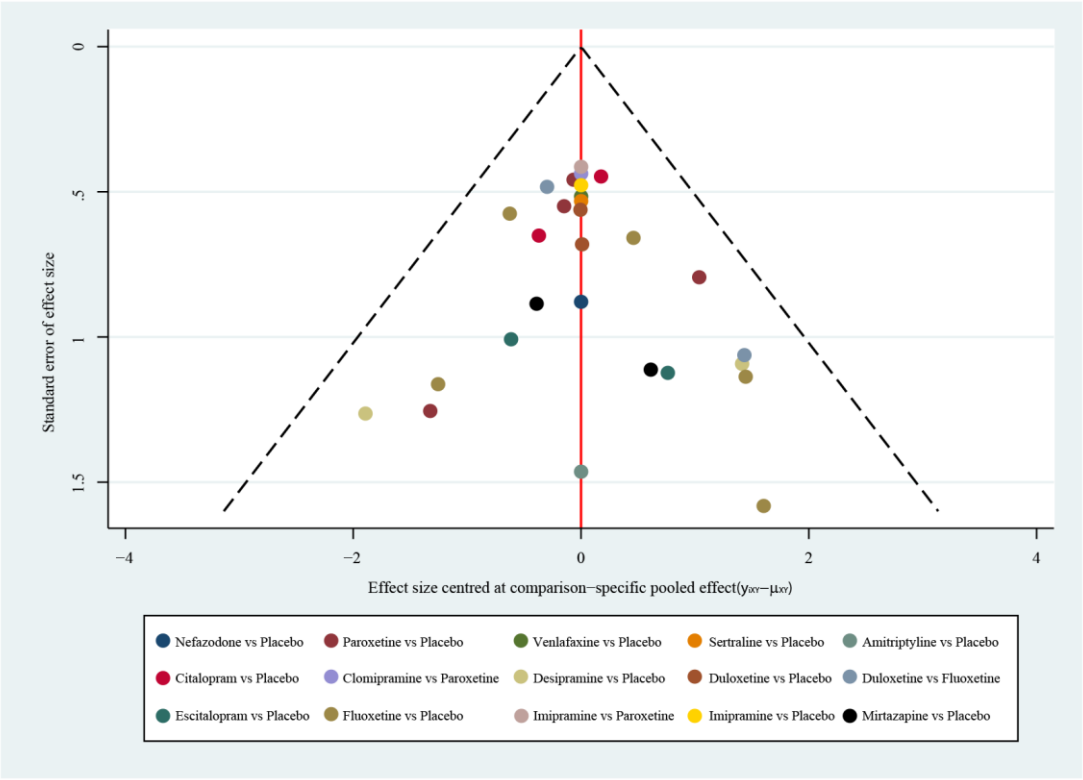
APPENDIX 12

Comparison-adjusted funnel plot for each outcome from the network meta-analysis

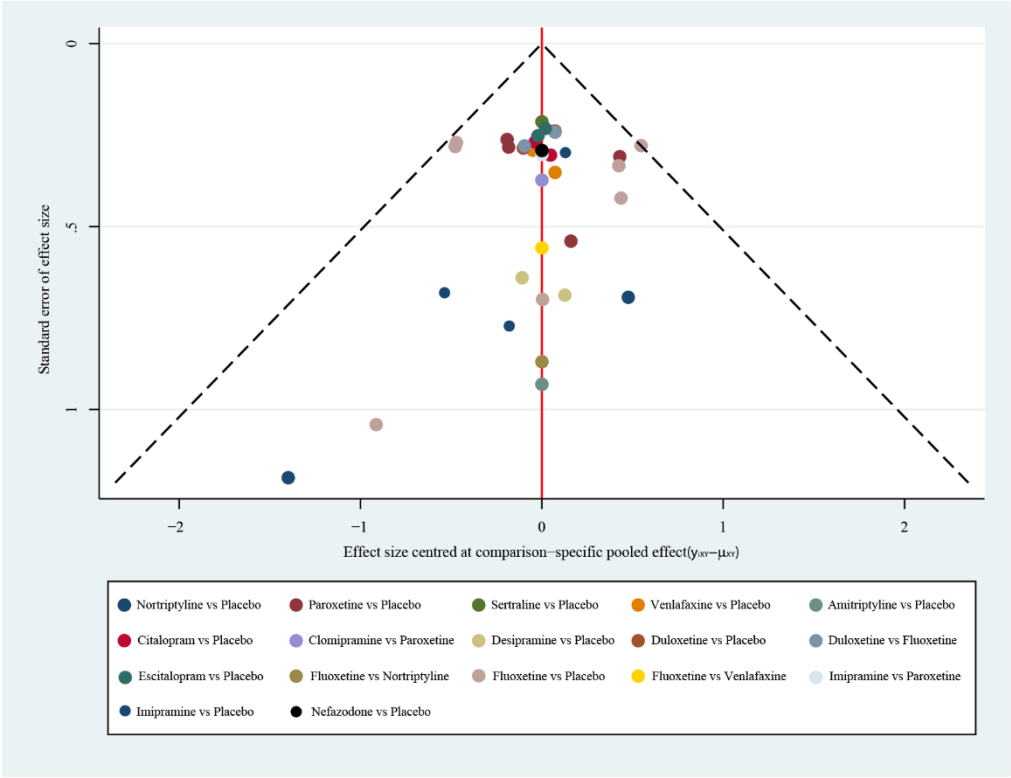
Comparison-adjusted funnel plot for mean overall change in symptoms in all comparisons



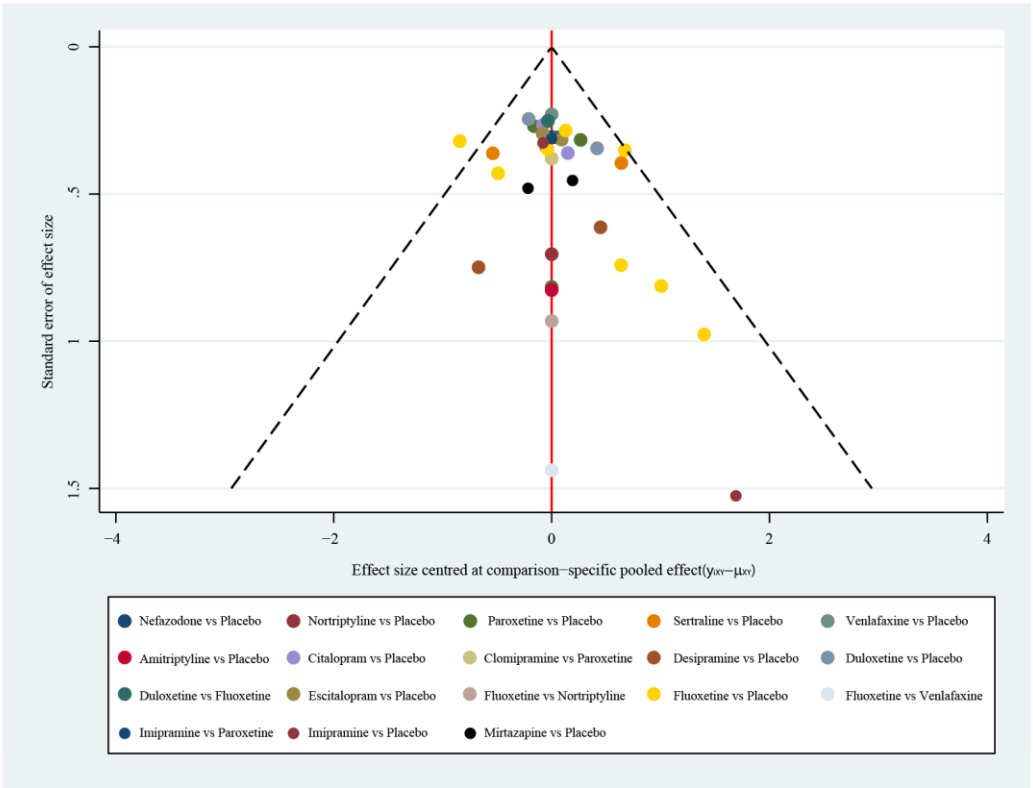
Comparison-adjusted funnel plot for discontinuation due to adverse events in all comparisons



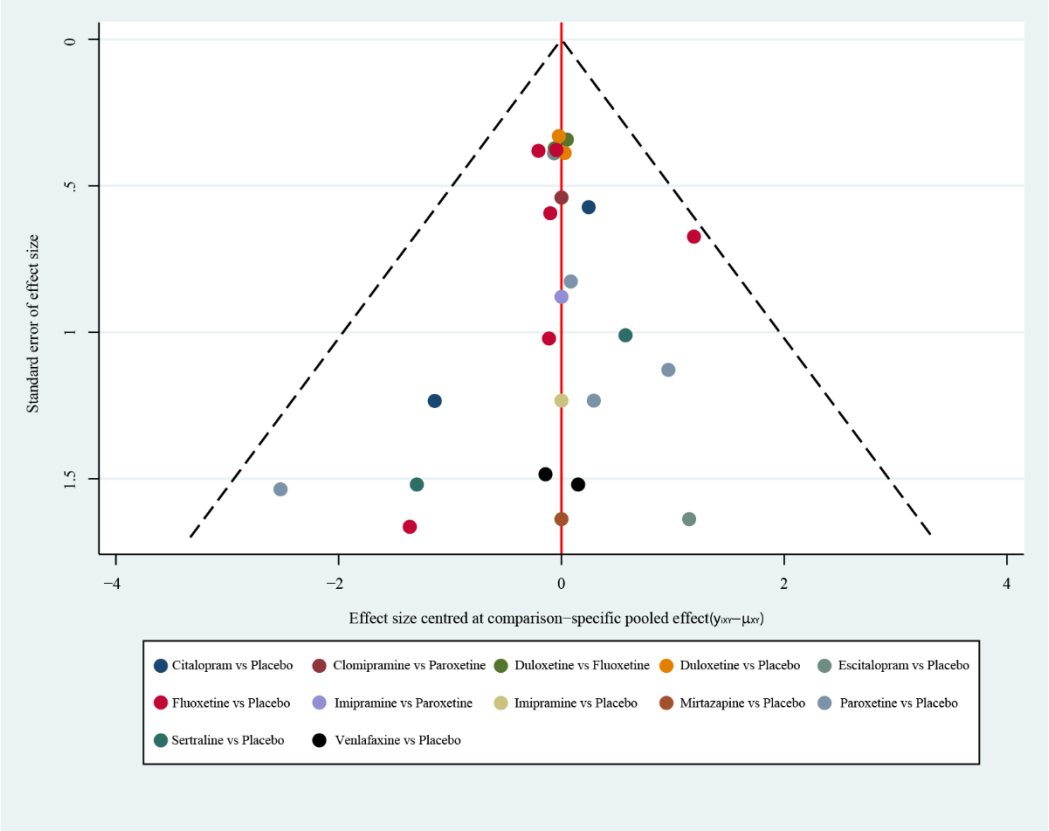
Comparison-adjusted funnel plot for response rate in all comparisons



Comparison-adjusted funnel plot for all-cause discontinuation in all comparisons



Comparison-adjusted funnel plot for suicidal behavior or ideation in all comparisons



Appendix 13

Treatment ranking and SUCRA plot for each outcome

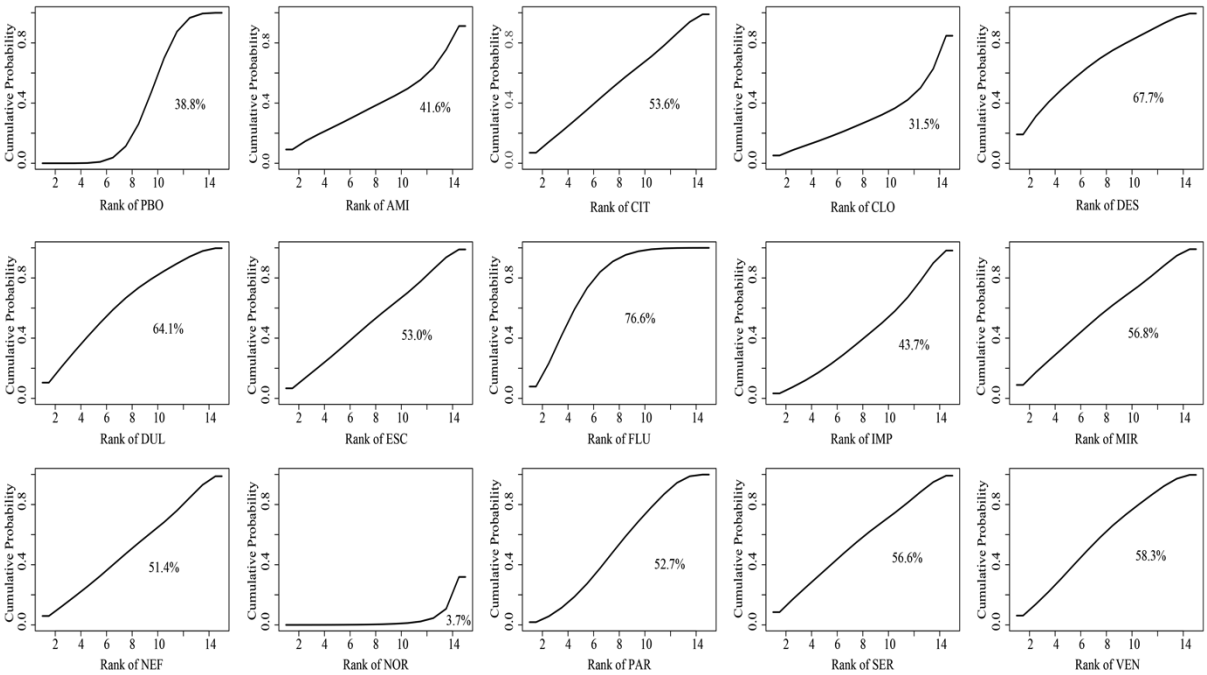
Mean overall change in symptoms

Treatment ranking:

Drugs	Abbreviation	SUCRA (%)
Fluoxetine	FLU	76·6%
Desipramine	DES	67·7%
Duloxetine	DUL	64·1%
Venlafaxine	VEN	58·3%
Mirtazapine	MIR	56·8%
Sertraline	SER	56·6%
Citalopram	CIT	53·6%
Escitalopram	ESC	53·0%
Paroxetine	PAR	52·7%
Nefazodone	NEF	51·4%
Imipramine	IMP	43·7%
Amitriptyline	AMI	41·6%
Placebo	PBO	38·8%
Clomipramine	CLO	31·5%
Nortriptyline	NOR	3·7%

***** Larger SUCRAs denote more effective interventions.

Cumulative probability plots (Random Effects model):



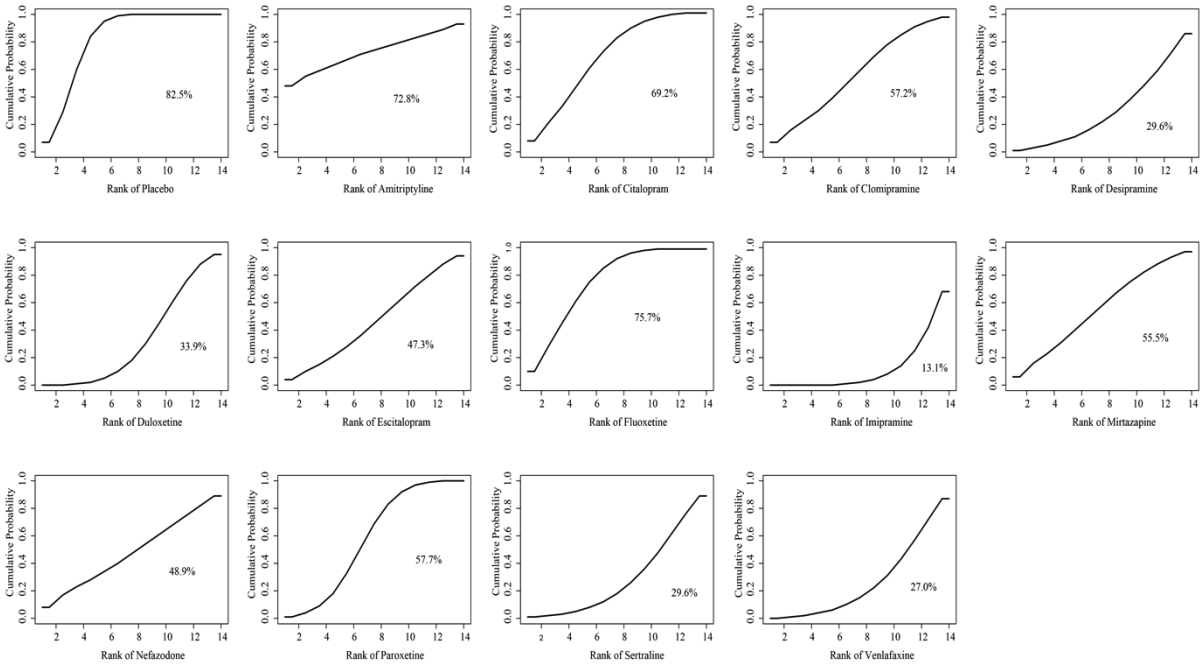
Discontinuation due to adverse events

Treatment ranking:

Drugs	Abbreviation	SUCRA (%)
Placebo	PBO	82·5%
Fluoxetine	FLU	75·7%
Amitriptyline	AMI	72·8%
Citalopram	CIT	69·2%
Paroxetine	PAR	57·7%
Clomipramine	CLO	57·2%
Mirtazapine	MIR	55·5%
Nefazodone	NEF	48·9%
Escitalopram	ESC	47·3%
Duloxetine	DUL	33·9%
Desipramine	DES	29·6%
Sertraline	SER	29·6%
Venlafaxine	VEN	27·0%
Imipramine	IMP	13·1%

***** Larger SUCRAs denote more tolerabale interventions.

Cumulative probability plots (Random Effects model):



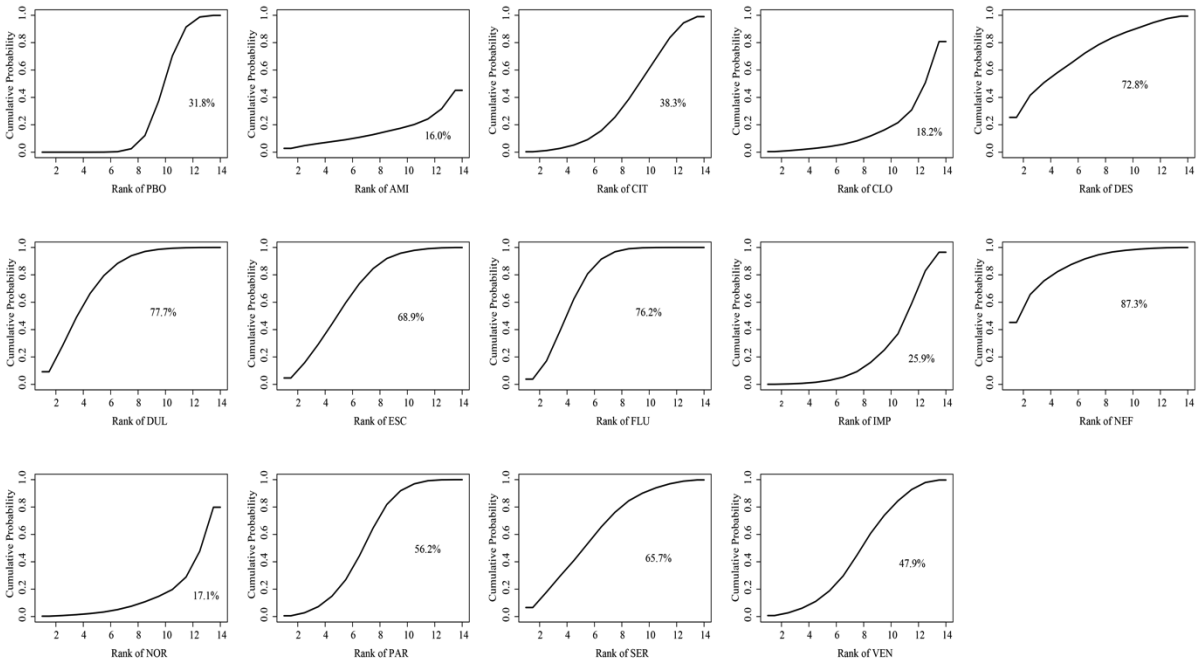
Response rate

Treatment ranking:

Drugs	Abbreviation	SUCRA (%)
Nefazodone	NEF	87·3%
Duloxetine	DUL	77·7%
Fluoxetine	FLU	76·2%
Desipramine	DES	72·8%
Escitalopram	ESC	68·9%
Sertraline	SER	65·7%
Paroxetine	PAR	56·2%
Venlafaxine	VEN	47·9%
Citalopram	CIT	38·3%
Placebo	PBO	31·8%
Imipramine	IMP	25·9%
Clomipramine	CLO	18·2%
Nortriptyline	NOR	17·1%
Amitriptyline	AMI	16·0%

***** Larger SUCRAs denote more effective interventions.

Cumulative probability plots (Random Effects model):



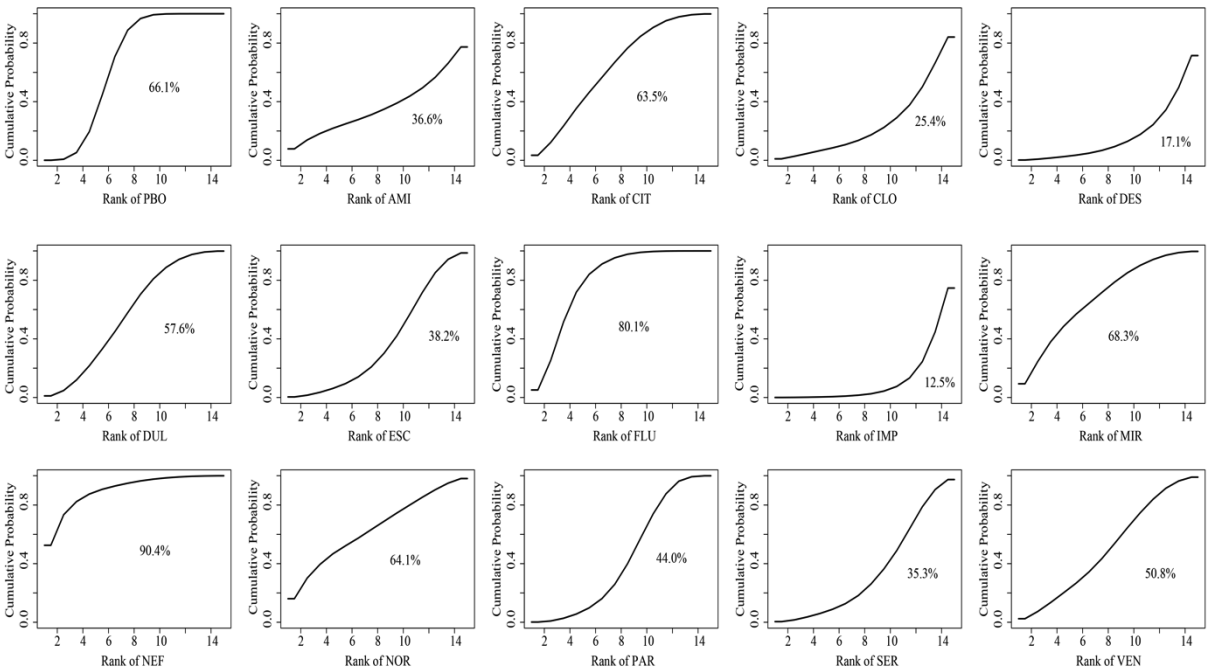
All-cause discontinuation

Treatment ranking:

Drugs	Abbreviation	SUCRA (%)
Nefazodone	NEF	90·4%
Fluoxetine	FLU	80·1%
Mirtazapine	MIR	68·3%
Placebo	PBO	66·1%
Nortriptyline	NOR	64·1%
Citalopram	CIT	63·5%
Duloxetine	DUL	57·6%
Venlafaxine	VEN	50·8%
Paroxetine	PAR	44·0%
Escitalopram	ESC	38·2%
Amitriptyline	AMI	36·6%
Sertraline	SER	35·3%
Clomipramine	CLO	25·4%
Desipramine	DES	17·1%
Imipramine	IMP	12·5%

***** Larger SUCRAs denote more tolerabale interventions.

Cumulative probability plots (Random Effects model):



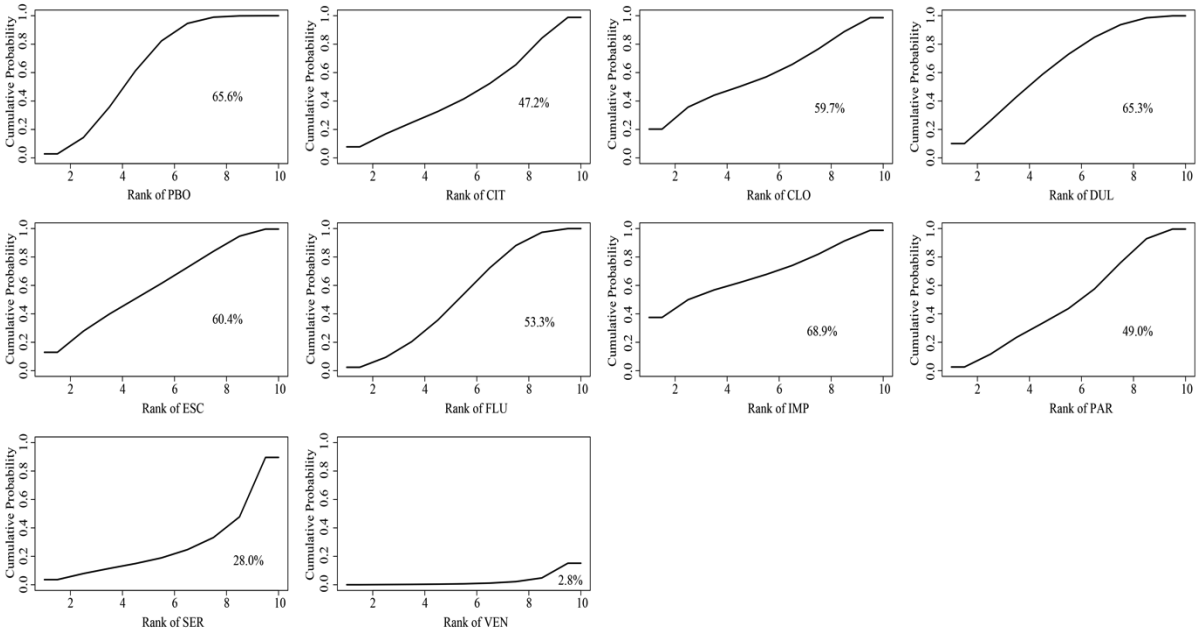
Suicidal behavior or ideation

Treatment ranking:

Drugs	Abbreviation	SUCRA (%)
Imipramine	IMP	68·9%
Placebo	PBO	65·6%
Duloxetine	DUL	65·3%
Escitalopram	ESC	60·4%
Clomipramine	CLO	59·7%
Fluoxetine	FLU	53·3%
Paroxetine	PAR	49·0%
Citalopram	CIT	47·2%
Sertraline	SER	28·0%
Venlafaxine	VEN	2·8%

***** Larger SUCRAs denote safer interventions.

Cumulative probability plots (Random Effects model):



APPENDIX 14

Contribution matrix and contributions summary of risk of bias assessments for each outcome

a. The contribution matrix for each outcome

The contributions (expressed as percentage) of direct comparisons (column) to the effect estimates of mixed or indirect comparisons (row) were calculated with the methods of Chaimani et al (PLoS ONE 8(10): e76654).

AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo

Mean overall change in symptoms (efficacy)

	Comparison	N	PBO vs AMI	PBO vs CIT	PBO vs DES	PBO vs DUL	PBO vs ESC	PBO vs FLU	PBO vs IMP	PBO vs MIR	PBO vs NEF	PBO vs NOR	PBO vs PAR	PBO vs SER	PBO vs VEN	CLO vs PAR	DUL vs FLU	FLU vs NOR	FLU vs VEN	IMP vs PAR
Direct comparison	PBO vs AMI	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs CIT	2	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs DES	2	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs DUL	2	0	0	0	45.2	0	20.7	0	0	0	0.7	0	0	3.7	0	25.2	0.7	3.7	0
	PBO vs ESC	2	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs FLU	8	0	0	0	26	0	33.5	0	0	0	1.2	0	0	6	0	26	1.2	6	0
	PBO vs IMP	2	0	0	0	0	0	0	43.2	0	0	0	28.4	0	0	0	0	0	0	28.4
	PBO vs MIR	2	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0
	PBO vs NEF	1	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
	PBO vs NOR	2	0	0	0	4.2	0	5.4	0	0	0	73.7	0	0	1	0	4.2	10.6	1	0
	PBO vs PAR	4	0	0	0	0	0	0	11.4	0	0	0	77.2	0	0	0	0	0	0	11.4
	PBO vs SER	2	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0
	PBO vs VEN	2	0	0	0	4.9	0	6.3	0	0	0	0.2	0	0	72	0	4.9	0.2	11.4	0
	CLO vs PAR	1	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0
	DUL vs FLU	2	0	0	0	19.5	0	16	0	0	0	0.6	0	0	2.9	0	57.6	0.6	2.9	0
	FLU vs NOR	1	0	0	0	14.9	0	19.2	0	0	0	37.6	0	0	3.5	0	14.9	6.3	3.5	0
	FLU vs VEN	1	0	0	0	15.6	0	20.1	0	0	0	0.7	0	0	36.5	0	15.6	0.7	10.7	0
	IMP vs PAR	1	0	0	0	0	0	0	32.2	0	0	0	32.2	0	0	0	0	0	0	35.7
Indirect comparison	PBO vs CLO		0	0	0	0	0	0	6	0	0	0	40.9	0	0	47	0	0	0	6
	AMI vs CIT		50	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs CLO		32	0	0	0	0	0	4.1	0	0	0	27.9	0	0	32	0	0	0	4.1
	AMI vs DES		50	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs DUL		41.3	0	0	26.5	0	12.1	0	0	0	0.4	0	0	2.2	0	14.8	0.4	2.2	0
	AMI vs ESC		50	0	0	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs FLU		40	0	0	15.6	0	20.1	0	0	0	0.7	0	0	3.6	0	15.6	0.7	3.6	0
	AMI vs IMP		41.7	0	0	0	0	0	25.2	0	0	0	16.6	0	0	0	0	0	0	16.6
	AMI vs MIR		50	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0	0
	AMI vs NEF		50	0	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0
	AMI vs NOR		45.7	0	0	2.3	0	2.9	0	0	0	40	0	0	0.5	0	2.3	5.7	0.5	0
	AMI vs PAR		47	0	0	0	0	0	6	0	0	0	40.9	0	0	0	0	0	0	6
	AMI vs SER		50	0	0	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	AMI vs VEN		45.5	0	0	2.7	0	3.4	0	0	0	0.1	0	0	39.3	0	2.7	0.1	6.2	0
	CIT vs CLO		0	32	0	0	0	0	4.1	0	0	0	27.9	0	0	32	0	0	0	4.1
	CIT vs DES		0	50	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	CIT vs DUL		0	41.3	0	26.5	0	12.1	0	0	0	0.4	0	0	2.2	0	14.8	0.4	2.2	0
	CIT vs ESC		0	50	0	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0
	CIT vs FLU		0	40	0	15.6	0	20.1	0	0	0	0.7	0	0	3.6	0	15.6	0.7	3.6	0
	CIT vs IMP		0	41.7	0	0	0	0	25.2	0	0	0	16.6	0	0	0	0	0	0	16.6
	CIT vs MIR		0	50	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0	0
	CIT vs NEF		0	50	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0
	CIT vs NOR		0	45.7	0	2.3	0	2.9	0	0	0	40	0	0	0.5	0	2.3	5.7	0.5	0
	CIT vs PAR		0	47	0	0	0	0	6	0	0	0	40.9	0	0	0	0	0	0	6
	CIT vs SER		0	50	0	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	CIT vs VEN		0	45.5	0	2.7	0	3.4	0	0	0	0.1	0	0	39.3	0	2.7	0.1	6.2	0
	CLO vs DES		0	0	32	0	0	0	4.1	0	0	0	27.9	0	0	32	0	0	0	4.1
	CLO vs DUL		0	0	0	18.1	0	8.3	3.6	0	0	0.3	24.5	0	1.5	28.2	10.1	0.3	1.5	3.6
	CLO vs ESC		0	0	0	0	32	0	4.1	0	0	0	27.9	0	0	32	0	0	0	4.1
	CLO vs FLU		0	0	0	10.7	0	13.8	3.5	0	0	0.5	24	0	2.5	27.6	10.7	0.5	2.5	3.5
	CLO vs IMP		0	0	0	0	0	0	19.2	0	0	0	19.2	0	0	40.4	0	0	0	21.2
	CLO vs MIR		0	0	0	0	0	0	4.1	32	0	0	27.9	0	0	32	0	0	0	4.1
	CLO vs NEF		0	0	0	0	0	0	4.1	0	32	0	27.9	0	0	32	0	0	0	4.1
	CLO vs NOR		0	0	0	1.5	0	1.9	3.9	0	0	26.4	26.3	0	0.3	30.2	1.5	3.8	0.3	3.9
	CLO vs SER		0	0	0	0	0	0	4.1	0	0	0	27.9	32	0	32	0	0	0	4.1
	CLO vs VEN		0	0	0	1.8	0	2.3	3.9	0	0	0.1	26.2	0	25.9	30.1	1.8	0.1	4.1	3.9
	DES vs DUL		0	0	41.3	26.5	0	12.1	0	0	0	0.4	0	0	2.2	0	14.8	0.4	2.2	0
	DES vs ESC		0	0	50	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0
	DES vs FLU		0	0	40	15.6	0	20.1	0	0	0	0.7	0	0	3.6	0	15.6	0.7	3.6	0
	DES vs IMP		0	0	41.7	0	0	0	25.2	0	0	0	16.6	0	0	0	0	0	0	16.6
	DES vs MIR		0	0	50	0	0	0	0	50	0	0	0	0	0	0	0	0	0	0
	DES vs NEF		0	0	50	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0

	DES vs NOR		0	0	45.7	2.3	0	2.9	0	0	0	40	0	0	0.5	0	2.3	5.7	0.5	0
	DES vs PAR		0	0	47	0	0	0	6	0	0	0	40.9	0	0	0	0	0	0	6
	DES vs SER		0	0	50	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	DES vs VEN		0	0	45.5	2.7	0	3.4	0	0	0	0.1	0	0	39.3	0	2.7	0.1	6.2	0
	DUL vs ESC		0	0	0	26.5	41.3	12.1	0	0	0	0.4	0	0	2.2	0	14.8	0.4	2.2	0
	DUL vs IMP		0	0	0	22.8	0	10.4	21.4	0	0	0.4	14.1	0	1.9	0	12.7	0.4	1.9	14.1
	DUL vs MIR		0	0	0	26.5	0	12.1	0	41.3	0	0.4	0	0	2.2	0	14.8	0.4	2.2	0
	DUL vs NEF		0	0	0	26.5	0	12.1	0	0	41.3	0.4	0	0	2.2	0	14.8	0.4	2.2	0
	DUL vs NOR		0	0	0	25.6	0	9.9	0	0	0	37.3	0	0	1.8	0	17.6	5.9	1.8	0
	DUL vs PAR		0	0	0	25.2	0	11.5	5	0	0	0.4	34.2	0	2.1	0	14	0.4	2.1	5
	DUL vs SER		0	0	0	26.5	0	12.1	0	0	0	0.4	0	41.3	2.2	0	14.8	0.4	2.2	0
	DUL vs VEN		0	0	0	26.1	0	9.8	0	0	0	0.4	0	0	36.3	0	18.6	0.4	8.5	0
	ESC vs FLU		0	0	0	15.6	40	20.1	0	0	0	0.7	0	0	3.6	0	15.6	0.7	3.6	0
	ESC vs IMP		0	0	0	0	41.7	0	25.2	0	0	0	16.6	0	0	0	0	0	0	16.6
	ESC vs MIR		0	0	0	0	50	0	0	50	0	0	0	0	0	0	0	0	0	0
	ESC vs NEF		0	0	0	0	50	0	0	0	50	0	0	0	0	0	0	0	0	0
	ESC vs NOR		0	0	0	2.3	45.7	2.9	0	0	0	40	0	0	0.5	0	2.3	5.7	0.5	0
	ESC vs PAR		0	0	0	0	47	0	6	0	0	0	40.9	0	0	0	0	0	0	6
	ESC vs SER		0	0	0	0	50	0	0	0	0	0	0	50	0	0	0	0	0	0
	ESC vs VEN		0	0	0	2.7	45.5	3.4	0	0	0	0.1	0	0	39.3	0	2.7	0.1	6.2	0
	FLU vs IMP		0	0	0	13.5	0	17.3	20.8	0	0	0.6	13.7	0	3.1	0	13.5	0.6	3.1	13.7
	FLU vs MIR		0	0	0	15.6	0	20.1	0	40	0	0.7	0	0	3.6	0	15.6	0.7	3.6	0
	FLU vs NEF		0	0	0	15.6	0	20.1	0	0	40	0.7	0	0	3.6	0	15.6	0.7	3.6	0
	FLU vs PAR		0	0	0	14.8	0	19.1	4.9	0	0	0.7	33.2	0	3.4	0	14.8	0.7	3.4	4.9
	FLU vs SER		0	0	0	15.6	0	20.1	0	0	0	0.7	0	40	3.6	0	15.6	0.7	3.6	0
	IMP vs MIR		0	0	0	0	0	0	25.2	41.7	0	0	16.6	0	0	0	0	0	0	16.6
	IMP vs NEF		0	0	0	0	0	0	25.2	0	41.7	0	16.6	0	0	0	0	0	0	16.6
	IMP vs NOR		0	0	0	1.9	0	2.5	23.3	0	0	33.8	15.4	0	0.4	0	1.9	4.9	0.4	15.4
	IMP vs SER		0	0	0	0	0	0	25.2	0	0	0	16.6	41.7	0	0	0	0	0	16.6
	IMP vs VEN		0	0	0	2.3	0	2.9	23.2	0	0	0.1	15.3	0	33.2	0	2.3	0.1	5.3	15.3
	MIR vs NEF		0	0	0	0	0	0	0	50	50	0	0	0	0	0	0	0	0	0
	MIR vs NOR		0	0	0	2.3	0	2.9	0	45.7	0	40	0	0	0.5	0	2.3	5.7	0.5	0
	MIR vs PAR		0	0	0	0	0	0	6	47	0	0	40.9	0	0	0	0	0	0	6
	MIR vs SER		0	0	0	0	0	0	0	50	0	0	0	50	0	0	0	0	0	0
	MIR vs VEN		0	0	0	2.7	0	3.4	0	45.5	0	0.1	0	0	39.3	0	2.7	0.1	6.2	0
	NEF vs NOR		0	0	0	2.3	0	2.9	0	0	45.7	40	0	0	0.5	0	2.3	5.7	0.5	0
	NEF vs PAR		0	0	0	0	0	0	6	0	47	0	40.9	0	0	0	0	0	0	6
	NEF vs SER		0	0	0	0	0	0	0	0	50	0	0	50	0	0	0	0	0	0
	NEF vs VEN		0	0	0	2.7	0	3.4	0	0	45.5	0.1	0	0	39.3	0	2.7	0.1	6.2	0
	NOR vs PAR		0	0	0	2.2	0	2.8	5.6	0	0	37.8	37.6	0	0.5	0	2.2	5.4	0.5	5.6
	NOR vs SER		0	0	0	2.3	0	2.9	0	0	0	40	0	45.7	0.5	0	2.3	5.7	0.5	0
	NOR vs VEN		0	0	0	0.4	0	0.6	0	0	0	43	0	0	42	0	0.4	6.3	7.3	0
	PAR vs SER		0	0	0	0	0	0	6	0	0	0	40.9	47	0	0	0	0	0	6
	PAR vs VEN		0	0	0	2.5	0	3.2	5.5	0	0	0.1	37.4	0	37.1	0	2.5	0.1	5.9	5.5
	SER vs VEN		0	0	0	2.7	0	3.4	0	0	0	0.1	0	45.5	39.3	0	2.7	0.1	6.2	0
total			6.1	6.1	6.1	6.4	6.1	5.2	4.9	6.1	6.1	5.5	11.6	6.1	6	6.1	5.1	0.9	1.7	3.9

Discontinuation due to adverse events (tolerability)

	Comparison	N	PBO vs AMI	PBO vs CIT	PBO vs DES	PBO vs DUL	PBO vs ESC	PBO vs FLU	PBO vs IMP	PBO vs MIR	PBO vs NEF	PBO vs PAR	PBO vs SER	PBO vs VEN	CLO vs PAR	DUL vs FLU	IMP vs PAR
Direct comparison	PBO vs AMI	1	99.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs CIT	2	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs DES	2	0	0	99.6	0	0	0	0	0	0	0.1	0	0	0	0	0
	PBO vs DUL	2	0	0	0	70.5	0	14.7	0	0	0	0	0	0	0	14.7	0
	PBO vs ESC	2	0	0	0	0	99.9	0	0	0	0	0	0	0	0	0	0
	PBO vs FLU	6	0	0	0	16.7	0	66.6	0	0	0	0	0	0	0	16.7	0
	PBO vs IMP	1	0	0	0	0	0	0	37.1	0	0	31.4	0	0	0	0	31.4
	PBO vs MIR	2	0	0	0	0	0	0	0	99.9	0	0	0	0	0	0	0
	PBO vs NEF	1	0	0	0	0	0	0	0	0	99.9	0	0	0	0	0	0
	PBO vs PAR	4	0	0	0	0	0	0	16.4	0	0	67.3	0	0	0	0	16.4
	PBO vs SER	1	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0
	PBO vs VEN	1	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0
	CLO vs PAR	1	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0
	DUL vs FLU	2	0	0	0	38.5	0	38.5	0	0	0	0	0	0	0	23	0
	IMP vs PAR	1	0	0	0	0	0	0	25.7	0	0	25.7	0	0	0	0	48.6
Indirect comparison	PBO vs CLO		0	0	0	0	0	0	8.9	0	0	36.6	0	0	45.5	0	8.9
	AMI vs CIT		49.9	50	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs CLO		31.2	0	0	0	0	0	6.1	0	0	25.2	0	0	31.3	0	6.1
	AMI vs DES		50	0	50	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs DUL		45.9	0	0	38.1	0	8	0	0	0	0	0	0	0	8	0
	AMI vs ESC		49.9	0	0	0	50	0	0	0	0	0	0	0	0	0	0
	AMI vs FLU		45.4	0	0	9.1	0	36.3	0	0	0	0	0	0	0	9.1	0
	AMI vs IMP		40.6	0	0	0	0	0	22	0	0	18.6	0	0	0	0	18.7
	AMI vs MIR		49.9	0	0	0	0	0	0	50	0	0	0	0	0	0	0
	AMI vs NEF		49.9	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	AMI vs PAR		45.5	0	0	0	0	0	8.9	0	0	36.6	0	0	0	0	8.9
	AMI vs SER		49.9	0	0	0	0	0	0	0	0	0	50	0	0	0	0
	AMI vs VEN		49.9	0	0	0	0	0	0	0	0	0	0	50	0	0	0
	CIT vs CLO		0	31.3	0	0	0	0	6.1	0	0	25.2	0	0	31.3	0	6.1
	CIT vs DES		0	50	49.9	0	0	0	0	0	0	0	0	0	0	0	0
	CIT vs DUL		0	46	0	38.1	0	8	0	0	0	0	0	0	0	8	0
	CIT vs ESC		0	50	0	0	50	0	0	0	0	0	0	0	0	0	0
	CIT vs FLU		0	45.4	0	9.1	0	36.3	0	0	0	0	0	0	0	9.1	0
	CIT vs IMP		0	40.7	0	0	0	0	22	0	0	18.6	0	0	0	0	18.7
	CIT vs MIR		0	50	0	0	0	0	0	50	0	0	0	0	0	0	0
	CIT vs NEF		0	50	0	0	0	0	0	0	50	0	0	0	0	0	0
	CIT vs PAR		0	45.5	0	0	0	0	8.9	0	0	36.6	0	0	0	0	8.9
	CIT vs SER		0	50	0	0	0	0	0	0	0	0	50	0	0	0	0
	CIT vs VEN		0	50	0	0	0	0	0	0	0	0	0	50	0	0	0
	CLO vs DES		0	0	31.2	0	0	0	6.1	0	0	25.2	0	0	31.3	0	6.1
	CLO vs DUL		0	0	0	24.6	0	5.1	5.8	0	0	23.9	0	0	29.7	5.1	5.8
	CLO vs ESC		0	0	0	0	31.3	0	6.1	0	0	25.2	0	0	31.3	0	6.1
	CLO vs FLU		0	0	0	5.9	0	23.5	5.8	0	0	23.7	0	0	29.4	5.9	5.8
	CLO vs IMP		0	0	0	0	0	0	14.7	0	0	14.7	0	0	42.6	0	27.9
	CLO vs MIR		0	0	0	0	0	0	6.1	31.3	0	25.2	0	0	31.3	0	6.1
	CLO vs NEF		0	0	0	0	0	0	6.1	0	31.3	25.2	0	0	31.3	0	6.1
	CLO vs SER		0	0	0	0	0	0	6.1	0	0	25.2	31.3	0	31.3	0	6.1
	CLO vs VEN		0	0	0	0	0	0	6.1	0	0	25.2	0	31.3	31.3	0	6.1
	DES vs DUL		0	0	45.9	38.1	0	7.9	0	0	0	0	0	0	0	8	0
	DES vs ESC		0	0	49.9	0	50	0	0	0	0	0	0	0	0	0	0
	DES vs FLU		0	0	45.3	9.1	0	36.3	0	0	0	0	0	0	0	9.1	0
	DES vs IMP		0	0	40.6	0	0	0	22	0	0	18.6	0	0	0	0	18.7
	DES vs MIR		0	0	49.9	0	0	0	0	50	0	0	0	0	0	0	0
	DES vs NEF		0	0	49.9	0	0	0	0	0	50	0	0	0	0	0	0
	DES vs PAR		0	0	45.4	0	0	0	8.9	0	0	36.6	0	0	0	0	8.9
	DES vs SER		0	0	49.9	0	0	0	0	0	0	0	50	0	0	0	0
	DES vs VEN		0	0	49.9	0	0	0	0	0	0	0	0	50	0	0	0
	DUL vs ESC		0	0	0	38.1	46	8	0	0	0	0	0	0	0	8	0
	DUL vs IMP		0	0	0	31.4	0	6.6	20.6	0	0	17.4	0	0	0	6.6	17.4
	DUL vs MIR		0	0	0	38.1	0	8	0	46	0	0	0	0	0	8	0

	DUL vs NEF		0	0	0	38.1	0	8	0	0	46	0	0	0	0	8	0
	DUL vs PAR		0	0	0	34.9	0	7.3	8.3	0	0	34	0	0	0	7.3	8.3
	DUL vs SER		0	0	0	38.1	0	8	0	0	0	0	46	0	0	8	0
	DUL vs VEN		0	0	0	38.1	0	8	0	0	0	0	0	46	0	8	0
	ESC vs FLU		0	0	0	9.1	45.4	36.3	0	0	0	0	0	0	0	9.1	0
	ESC vs IMP		0	0	0	0	40.7	0	22	0	0	18.6	0	0	0	0	18.7
	ESC vs MIR		0	0	0	0	50	0	0	50	0	0	0	0	0	0	0
	ESC vs NEF		0	0	0	0	50	0	0	0	50	0	0	0	0	0	0
	ESC vs PAR		0	0	0	0	45.5	0	8.9	0	0	36.6	0	0	0	0	8.9
	ESC vs SER		0	0	0	0	50	0	0	0	0	0	50	0	0	0	0
	ESC vs VEN		0	0	0	0	50	0	0	0	0	0	0	50	0	0	0
	FLU vs IMP		0	0	0	7.5	0	30.1	20.4	0	0	17.2	0	0	0	7.5	17.2
	FLU vs MIR		0	0	0	9.1	0	36.3	0	45.4	0	0	0	0	0	9.1	0
	FLU vs NEF		0	0	0	9.1	0	36.3	0	0	45.4	0	0	0	0	9.1	0
	FLU vs PAR		0	0	0	8.4	0	33.4	8.2	0	0	33.6	0	0	0	8.4	8.2
	FLU vs SER		0	0	0	9.1	0	36.3	0	0	0	0	45.4	0	0	9.1	0
	FLU vs VEN		0	0	0	9.1	0	36.3	0	0	0	0	0	45.4	0	9.1	0
	IMP vs MIR		0	0	0	0	0	0	22	40.7	0	18.6	0	0	0	0	18.7
	IMP vs NEF		0	0	0	0	0	0	22	0	40.6	18.6	0	0	0	0	18.7
	IMP vs SER		0	0	0	0	0	0	22	0	0	18.6	40.7	0	0	0	18.7
	IMP vs VEN		0	0	0	0	0	0	22	0	0	18.6	0	40.7	0	0	18.7
	MIR vs NEF		0	0	0	0	0	0	0	50	50	0	0	0	0	0	0
	MIR vs PAR		0	0	0	0	0	0	8.9	45.5	0	36.6	0	0	0	0	8.9
	MIR vs SER		0	0	0	0	0	0	0	50	0	0	50	0	0	0	0
	MIR vs VEN		0	0	0	0	0	0	0	50	0	0	0	50	0	0	0
	NEF vs PAR		0	0	0	0	0	0	8.9	0	45.5	36.6	0	0	0	0	8.9
	NEF vs SER		0	0	0	0	0	0	0	0	50	0	50	0	0	0	0
	NEF vs VEN		0	0	0	0	0	0	0	0	50	0	0	50	0	0	0
	PAR vs SER		0	0	0	0	0	0	8.9	0	0	36.6	45.5	0	0	0	8.9
	PAR vs VEN		0	0	0	0	0	0	8.9	0	0	36.6	0	45.5	0	0	8.9
	SER vs VEN		0	0	0	0	0	0	0	0	0	0	50	50	0	0	0
total			6.8	6.8	6.7	6.7	6.8	6.4	5.7	6.8	6.8	12.2	6.8	6.8	6.8	2.5	5.5

Response rate

Comparison		N	PBO vs AMI	PBO vs CIT	PBO vs DES	PBO vs DUL	PBO vs ESC	PBO vs FLU	PBO vs IMP	PBO vs NEF	PBO vs NOR	PBO vs PAR	PBO vs SER	PBO vs VEN	CLO vs PAR	DUL vs FLU	FLU vs NOR	FLU vs VEN	IMP vs PAR
Direct comparison	PBO vs AMI	1	99.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs CIT	2	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs DES	2	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs DUL	2	0	0	0	50.6	0	20	0	0	0.6	0	0	2.5	0	23.1	0.6	2.5	0
	PBO vs ESC	1	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs FLU	7	0	0	0	25.5	0	37.3	0	0	1.1	0	0	4.7	0	25.5	1.1	4.7	0
	PBO vs IMP	3	0	0	0	0	0	0	46.8	0	0	26.6	0	0	0	0	0	0	26.6
	PBO vs NEF	1	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
	PBO vs NOR	2	0	0	0	11.1	0	16.2	0	0	28.1	0	0	2.1	0	11.1	29.4	2.1	0
	PBO vs PAR	3	0	0	0	0	0	0	11.8	0	0	76.4	0	0	0	0	0	0	11.8
	PBO vs SER	2	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0
	PBO vs VEN	2	0	0	0	4.4	0	6.4	0	0	0.2	0	0	73.6	0	4.4	0.2	10.9	0
	CLO vs PAR	1	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0
	DUL vs FLU	2	0	0	0	23.2	0	20	0	0	0.6	0	0	2.5	0	50.6	0.6	2.5	0
	FLU vs NOR	1	0	0	0	10.6	0	15.5	0	0	28	0	0	2	0	10.6	31.3	2	0
	FLU vs VEN	1	0	0	0	15	0	21.9	0	0	0.6	0	0	37.5	0	15	0.6	9.3	0
	IMP vs PAR	1	0	0	0	0	0	0	33.5	0	0	33.5	0	0	0	0	0	0	33
Indirect comparison	PBO vs CLO		0	0	0	0	0	0	6.3	0	0	40.6	0	0	46.9	0	0	0	6.3
	AMI vs CIT		50	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs CLO		31.9	0	0	0	0	0	4.3	0	0	27.6	0	0	31.9	0	0	0	4.3
	AMI vs DES		50	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs DUL		42.4	0	0	29.1	0	11.5	0	0	0.3	0	0	1.5	0	13.3	0.3	1.5	0
	AMI vs ESC		49.9	0	0	0	50	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs FLU		40.7	0	0	15.1	0	22.1	0	0	0.6	0	0	2.8	0	15.1	0.6	2.8	0
	AMI vs IMP		42.3	0	0	0	0	0	27	0	0	15.3	0	0	0	0	0	0	15.4
	AMI vs NEF		50	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0
	AMI vs NOR		36.5	0	0	7.1	0	10.3	0	0	17.8	0	0	1.3	0	7.1	18.7	1.3	0
	AMI vs PAR		46.8	0	0	0	0	0	6.3	0	0	40.6	0	0	0	0	0	0	6.3
	AMI vs SER		50	0	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	AMI vs VEN		45.8	0	0	2.4	0	3.5	0	0	0.1	0	0	39.9	0	2.4	0.1	5.9	0
	CIT vs CLO		0	31.9	0	0	0	0	4.3	0	0	27.6	0	0	31.9	0	0	0	4.3
	CIT vs DES		0	50	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	CIT vs DUL		0	42.4	0	29.1	0	11.5	0	0	0.3	0	0	1.5	0	13.3	0.3	1.5	0
	CIT vs ESC		0	50	0	0	50	0	0	0	0	0	0	0	0	0	0	0	0
	CIT vs FLU		0	40.7	0	15.1	0	22.1	0	0	0.6	0	0	2.8	0	15.1	0.6	2.8	0
	CIT vs IMP		0	42.3	0	0	0	0	27	0	0	15.4	0	0	0	0	0	0	15.4
	CIT vs NEF		0	50	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0
	CIT vs NOR		0	36.5	0	7.1	0	10.3	0	0	17.8	0	0	1.3	0	7.1	18.7	1.3	0
	CIT vs PAR		0	46.9	0	0	0	0	6.3	0	0	40.6	0	0	0	0	0	0	6.3
	CIT vs SER		0	50	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	CIT vs VEN		0	45.8	0	2.4	0	3.5	0	0	0.1	0	0	39.9	0	2.4	0.1	5.9	0
	CLO vs DES		0	0	31.9	0	0	0	4.3	0	0	27.6	0	0	31.9	0	0	0	4.3
	CLO vs DUL		0	0	0	19.7	0	7.8	3.8	0	0.2	24.8	0	1	28.7	9	0.2	1	3.8
	CLO vs ESC		0	0	0	0	31.9	0	4.3	0	0	27.6	0	0	31.9	0	0	0	4.3
	CLO vs FLU		0	0	0	10.4	0	15.1	3.7	0	0.4	24.1	0	1.9	27.8	10.4	0.4	1.9	3.7
	CLO vs IMP		0	0	0	0	0	0	20.1	0	0	20.1	0	0	39.9	0	0	0	19.8
	CLO vs NEF		0	0	0	0	0	0	4.3	31.9	0	27.6	0	0	31.9	0	0	0	4.3
	CLO vs NOR		0	0	0	5	0	7.3	3.5	0	12.6	22.4	0	0.9	25.8	5	13.2	0.9	3.5

	CLO vs SER		0	0	0	0	0	0	4.3	0	0	27.6	31.9	0	31.9	0	0	0	4.3
	CLO vs VEN		0	0	0	1.6	0	2.3	4	0	0.1	26.1	0	26.2	30.1	1.6	0.1	3.9	4
	DES vs DUL		0	0	42.4	29.1	0	11.5	0	0	0.3	0	0	1.5	0	13.3	0.3	1.5	0
	DES vs ESC		0	0	50	0	50	0	0	0	0	0	0	0	0	0	0	0	0
	DES vs FLU		0	0	40.7	15.1	0	22.1	0	0	0.6	0	0	2.8	0	15.1	0.6	2.8	0
	DES vs IMP		0	0	42.3	0	0	0	27	0	0	15.3	0	0	0	0	0	0	15.4
	DES vs NEF		0	0	50	0	0	0	0	50	0	0	0	0	0	0	0	0	0
	DES vs NOR		0	0	36.5	7.1	0	10.3	0	0	17.8	0	0	1.3	0	7.1	18.7	1.3	0
	DES vs PAR		0	0	46.9	0	0	0	6.3	0	0	40.6	0	0	0	0	0	0	6.3
	DES vs SER		0	0	50	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	DES vs VEN		0	0	45.8	2.4	0	3.5	0	0	0.1	0	0	39.9	0	2.4	0.1	5.9	0
	DUL vs ESC		0	0	0	29.1	42.4	11.5	0	0	0.3	0	0	1.5	0	13.3	0.3	1.5	0
	DUL vs IMP		0	0	0	25.2	0	10	23.4	0	0.3	13.3	0	1.3	0	11.5	0.3	1.3	13.3
	DUL vs NEF		0	0	0	29.1	0	11.5	0	42.4	0.3	0	0	1.5	0	13.3	0.3	1.5	0
	DUL vs NOR		0	0	0	24.5	0	0.5	0	0	23.9	0	0	0.1	0	25.2	25.8	0.1	0
	DUL vs PAR		0	0	0	27.6	0	10.9	5.4	0	0.3	34.8	0	1.4	0	12.6	0.3	1.4	5.4
	DUL vs SER		0	0	0	29.1	0	11.5	0	0	0.3	0	42.4	1.5	0	13.3	0.3	1.5	0
	DUL vs VEN		0	0	0	28.7	0	8.9	0	0	0.3	0	0	37.9	0	16.6	0.3	7.4	0
	ESC vs FLU		0	0	0	15.1	40.7	22.1	0	0	0.6	0	0	2.8	0	15.1	0.6	2.8	0
	ESC vs IMP		0	0	0	0	42.3	0	27	0	0	15.3	0	0	0	0	0	0	15.4
	ESC vs NEF		0	0	0	0	50	0	0	50	0	0	0	0	0	0	0	0	0
	ESC vs NOR		0	0	0	7.1	36.5	10.3	0	0	17.8	0	0	1.3	0	7.1	18.7	1.3	0
	ESC vs PAR		0	0	0	0	46.9	0	6.3	0	0	40.6	0	0	0	0	0	0	6.3
	ESC vs SER		0	0	0	0	50	0	0	0	0	0	50	0	0	0	0	0	0
	ESC vs VEN		0	0	0	2.4	45.8	3.5	0	0	0.1	0	0	39.9	0	2.4	0.1	5.9	0
	FLU vs IMP		0	0	0	13.2	0	19.3	22.6	0	0.6	12.9	0	2.4	0	13.2	0.6	2.4	12.9
	FLU vs NEF		0	0	0	15.1	0	22.1	0	40.7	0.6	0	0	2.8	0	15.1	0.6	2.8	0
	FLU vs PAR		0	0	0	14.4	0	21	5.2	0	0.6	33.4	0	2.7	0	14.4	0.6	2.7	5.2
	FLU vs SER		0	0	0	15.1	0	22.1	0	0	0.6	0	40.7	2.8	0	15.1	0.6	2.8	0
	IMP vs NEF		0	0	0	0	0	0	27	42.3	0	15.4	0	0	0	0	0	0	15.4
	IMP vs NOR		0	0	0	6.2	0	9.1	20.5	0	15.7	11.7	0	1.2	0	6.2	16.5	1.2	11.7
	IMP vs SER		0	0	0	0	0	0	27	0	0	15.4	42.3	0	0	0	0	0	15.4
	IMP vs VEN		0	0	0	2	0	3	25	0	0.1	14.2	0	34.2	0	2	0.1	5.1	14.2
	NEF vs NOR		0	0	0	7.1	0	10.3	0	36.5	17.8	0	0	1.3	0	7.1	18.7	1.3	0
	NEF vs PAR		0	0	0	0	0	0	6.3	46.9	0	40.6	0	0	0	0	0	0	6.3
	NEF vs SER		0	0	0	0	0	0	0	50	0	0	50	0	0	0	0	0	0
	NEF vs VEN		0	0	0	2.4	0	3.5	0	45.8	0.1	0	0	39.9	0	2.4	0.1	5.9	0
	NOR vs PAR		0	0	0	6.7	0	9.8	4.7	0	17	30.1	0	1.2	0	6.7	17.8	1.2	4.7
	NOR vs SER		0	0	0	7.1	0	10.3	0	0	17.8	0	36.5	1.3	0	7.1	18.7	1.3	0
	NOR vs VEN		0	0	0	5.7	0	8.3	0	0	19.5	0	0	33.5	0	5.7	20.6	6.6	0
	PAR vs SER		0	0	0	0	0	0	6.3	0	0	40.6	46.9	0	0	0	0	0	6.3
	PAR vs VEN		0	0	0	2.2	0	3.3	5.8	0	0.1	37.4	0	37.6	0	2.2	0.1	5.6	5.8
	SER vs VEN		0	0	0	2.4	0	3.5	0	0	0.1	0	45.8	39.9	0	2.4	0.1	5.9	0
total			6.4	6.4	6.4	7.4	6.4	6.5	5.4	6.4	3.3	11.8	6.4	6.2	6.4	5.7	3.4	1.6	3.9

All-cause discontinuation (acceptability)

	Comparison	N	PBO vs AMI	PBO vs CIT	PBO vs DES	PBO vs DUL	PBO vs ESC	PBO vs FLU	PBO vs IMP	PBO vs MIR	PBO vs NEF	PBO vs NOR	PBO vs PAR	PBO vs SER	PBO vs VEN	CLO vs PAR	DUL vs FLU	FLU vs NOR	FLU vs VEN	IMP vs PAR
Direct comparison	PBO vs AMI	1	99.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs CIT	2	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs DES	2	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs DUL	2	0	0	0	31.7	0	30.9	0	0	0	1.3	0	0	0.8	0	33.1	1.3	0.8	0
	PBO vs ESC	2	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0
	PBO vs FLU	8	0	0	0	21.6	0	49.8	0	0	0	2.1	0	0	1.4	0	21.6	2.1	1.4	0
	PBO vs IMP	2	0	0	0	0	0	0	14.1	0	0	0	43	0	0	0	0	0	0	43
	PBO vs MIR	2	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0
	PBO vs NEF	1	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
	PBO vs NOR	1	0	0	0	7.2	0	16.5	0	0	0	44.1	0	0	0.5	0	7.2	24.1	0.5	0
	PBO vs PAR	4	0	0	0	0	0	0	5.4	0	0	0	89.1	0	0	0	0	0	0	5.4
	PBO vs SER	2	0	0	0	0	0	0	0	0	0	0	0	99.9	0	0	0	0	0	0
	PBO vs VEN	1	0	0	0	0.7	0	1.6	0	0	0	0.1	0	0	94.5	0	0.7	0.1	2.4	0
	CLO vs PAR	1	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0
	DUL vs FLU	2	0	0	0	16.6	0	15.5	0	0	0	0.7	0	0	0.4	0	65.8	0.7	0.4	0
	FLU vs NOR	1	0	0	0	10.1	0	23.3	0	0	0	34.1	0	0	0.6	0	10.1	21.1	0.6	0
	FLU vs VEN	1	0	0	0	12.4	0	28.6	0	0	0	1.2	0	0	42.3	0	12.4	1.2	1.9	0
	IMP vs PAR	1	0	0	0	0	0	0	15.9	0	0	0	15.9	0	0	0	0	0	0	68.1
Indirect comparison	PBO vs CLO		0	0	0	0	0	0	2.8	0	0	0	45.8	0	0	48.6	0	0	0	2.8
	AMI vs CIT		50	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs CLO		32.7	0	0	0	0	0	1.9	0	0	0	30.8	0	0	32.7	0	0	0	1.9
	AMI vs DES		50	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs DUL		39.3	0	0	19.2	0	18.8	0	0	0	0.8	0	0	0.5	0	20.1	0.8	0.5	0
	AMI vs ESC		50	0	0	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0
	AMI vs FLU		42.8	0	0	12.3	0	28.5	0	0	0	1.2	0	0	0.8	0	12.3	1.2	0.8	0
	AMI vs IMP		36.3	0	0	0	0	0	9	0	0	0	27.4	0	0	0	0	0	0	27.4
	AMI vs MIR		50	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0	0
	AMI vs NEF		50	0	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0
	AMI vs NOR		40.5	0	0	4.3	0	9.8	0	0	0	26.2	0	0	0.3	0	4.3	14.3	0.3	0
	AMI vs PAR		48.6	0	0	0	0	0	2.8	0	0	0	45.8	0	0	0	0	0	0	2.8
	AMI vs SER		50	0	0	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	AMI vs VEN		49.2	0	0	0.3	0	0.8	0	0	0	0	0	0	48	0	0.4	0	1.2	0
	CIT vs CLO		0	32.7	0	0	0	0	1.9	0	0	0	30.8	0	0	32.7	0	0	0	1.9
	CIT vs DES		0	50	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	CIT vs DUL		0	39.3	0	19.2	0	18.8	0	0	0	0.8	0	0	0.5	0	20.1	0.8	0.5	0
	CIT vs ESC		0	50	0	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0
	CIT vs FLU		0	42.8	0	12.3	0	28.5	0	0	0	1.2	0	0	0.8	0	12.3	1.2	0.8	0
	CIT vs IMP		0	36.3	0	0	0	0	9	0	0	0	27.4	0	0	0	0	0	0	27.4
	CIT vs MIR		0	50	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0	0
	CIT vs NEF		0	50	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0
	CIT vs NOR		0	40.6	0	4.3	0	9.8	0	0	0	26.2	0	0	0.3	0	4.3	14.3	0.3	0
	CIT vs PAR		0	48.6	0	0	0	0	2.8	0	0	0	45.8	0	0	0	0	0	0	2.8
	CIT vs SER		0	50	0	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
	CIT vs VEN		0	49.2	0	0.4	0	0.8	0	0	0	0	0	0	48	0	0.4	0	1.2	0
	CLO vs DES		0	0	32.7	0	0	0	1.9	0	0	0	30.8	0	0	32.7	0	0	0	1.9
	CLO vs DUL		0	0	0	13.6	0	13.3	1.6	0	0	0.6	26.2	0	0.4	27.8	14.2	0.6	0.4	1.6
	CLO vs ESC		0	0	0	0	32.7	0	1.9	0	0	0	30.8	0	0	32.7	0	0	0	1.9
	CLO vs FLU		0	0	0	8.5	0	19.6	1.7	0	0	0.8	27.8	0	0.5	29.5	8.5	0.8	0.5	1.7
	CLO vs IMP		0	0	0	0	0	0	8.7	0	0	0	8.6	0	0	45.7	0	0	0	37
	CLO vs MIR		0	0	0	0	0	0	1.9	32.7	0	0	30.8	0	0	32.7	0	0	0	1.9
	CLO vs NEF		0	0	0	0	0	0	1.9	0	32.7	0	30.8	0	0	32.7	0	0	0	1.9
	CLO vs NOR		0	0	0	3	0	6.9	1.6	0	0	18.3	26.8	0	0.2	28.4	3	10	0.2	1.6
	CLO vs SER		0	0	0	0	0	0	1.9	0	0	0	30.8	32.7	0	32.7	0	0	0	1.9
	CLO vs VEN		0	0	0	0.2	0	0.5	1.9	0	0	0	30.5	0	31.6	32.4	0.2	0	0.8	1.9
	DES vs DUL		0	0	39.3	19.2	0	18.8	0	0	0	0.8	0	0	0.5	0	20.1	0.8	0.5	0
	DES vs ESC		0	0	50	0	50	0	0	0	0	0	0	0	0	0	0	0	0	0
	DES vs FLU		0	0	42.8	12.3	0	28.5	0	0	0	1.2	0	0	0.8	0	12.3	1.2	0.8	0
	DES vs IMP		0	0	36.3	0	0	0	9	0	0	0	27.4	0	0	0	0	0	0	27.4
	DES vs MIR		0	0	50	0	0	0	0	50	0	0	0	0	0	0	0	0	0	0
	DES vs NEF		0	0	50	0	0	0	0	0	50	0	0	0	0	0	0	0	0	0

DES vs NOR		0	0	40.6	4.3	0	9.8	0	0	0	26.2	0	0	0.3	0	4.3	14.3	0.3	0
DES vs PAR		0	0	48.6	0	0	0	2.8	0	0	0	45.8	0	0	0	0	0	0	2.8
DES vs SER		0	0	50	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0
DES vs VEN		0	0	49.2	0.3	0	0.8	0	0	0	0	0	0	48	0	0.4	0	1.2	0
DUL vs ESC		0	0	0	19.2	39.3	18.8	0	0	0	0.8	0	0	0.5	0	20.1	0.8	0.5	0
DUL vs IMP		0	0	0	14.8	0	14.5	7.5	0	0	0.6	22.8	0	0.4	0	15.5	0.6	0.4	22.8
DUL vs MIR		0	0	0	19.2	0	18.8	0	39.3	0	0.8	0	0	0.5	0	20.1	0.8	0.5	0
DUL vs NEF		0	0	0	19.2	0	18.8	0	0	39.3	0.8	0	0	0.5	0	20.1	0.8	0.5	0
DUL vs NOR		0	0	0	17.1	0	10.5	0	0	0	27.8	0	0	0.3	0	27.4	16.6	0.3	0
DUL vs PAR		0	0	0	18.8	0	18.3	2.2	0	0	0.8	36.2	0	0.5	0	19.6	0.8	0.5	2.2
DUL vs SER		0	0	0	19.2	0	18.8	0	0	0	0.8	0	39.3	0.5	0	20.1	0.8	0.5	0
DUL vs VEN		0	0	0	19.3	0	18.4	0	0	0	0.8	0	0	38.5	0	20.7	0.8	1.5	0
ESC vs FLU		0	0	0	12.3	42.8	28.5	0	0	0	1.2	0	0	0.8	0	12.3	1.2	0.8	0
ESC vs IMP		0	0	0	0	36.3	0	9	0	0	0	27.4	0	0	0	0	0	0	27.4
ESC vs MIR		0	0	0	0	50	0	0	50	0	0	0	0	0	0	0	0	0	0
ESC vs NEF		0	0	0	0	50	0	0	0	50	0	0	0	0	0	0	0	0	0
ESC vs NOR		0	0	0	4.3	40.6	9.8	0	0	0	26.2	0	0	0.3	0	4.3	14.3	0.3	0
ESC vs PAR		0	0	0	0	48.6	0	2.8	0	0	0	45.8	0	0	0	0	0	0	2.8
ESC vs SER		0	0	0	0	50	0	0	0	0	0	0	50	0	0	0	0	0	0
ESC vs VEN		0	0	0	0.4	49.2	0.8	0	0	0	0	0	0	48	0	0.4	0	1.2	0
FLU vs IMP		0	0	0	9.3	0	21.5	8	0	0	0.9	24.4	0	0.6	0	9.3	0.9	0.6	24.4
FLU vs MIR		0	0	0	12.3	0	28.5	0	42.8	0	1.2	0	0	0.8	0	12.3	1.2	0.8	0
FLU vs NEF		0	0	0	12.3	0	28.5	0	0	42.8	1.2	0	0	0.8	0	12.3	1.2	0.8	0
FLU vs PAR		0	0	0	12	0	27.8	2.4	0	0	1.2	39.4	0	0.8	0	12.1	1.2	0.8	2.4
FLU vs SER		0	0	0	12.3	0	28.5	0	0	0	1.2	0	42.8	0.8	0	12.3	1.2	0.8	0
IMP vs MIR		0	0	0	0	0	0	9	36.3	0	0	27.4	0	0	0	0	0	0	27.4
IMP vs NEF		0	0	0	0	0	0	9	0	36.3	0	27.4	0	0	0	0	0	0	27.4
IMP vs NOR		0	0	0	3.3	0	7.5	7.7	0	0	20.1	23.4	0	0.2	0	3.3	11	0.2	23.4
IMP vs SER		0	0	0	0	0	0	9	0	0	0	27.4	36.3	0	0	0	0	0	27.4
IMP vs VEN		0	0	0	0.3	0	0.6	8.9	0	0	0	27	0	35	0	0.3	0	0.9	27
MIR vs NEF		0	0	0	0	0	0	0	50	50	0	0	0	0	0	0	0	0	0
MIR vs NOR		0	0	0	4.3	0	9.8	0	40.6	0	26.2	0	0	0.3	0	4.3	14.3	0.3	0
MIR vs PAR		0	0	0	0	0	0	2.8	48.6	0	0	45.8	0	0	0	0	0	0	2.8
MIR vs SER		0	0	0	0	0	0	0	50	0	0	0	50	0	0	0	0	0	0
MIR vs VEN		0	0	0	0.4	0	0.8	0	49.2	0	0	0	0	48	0	0.4	0	1.2	0
NEF vs NOR		0	0	0	4.3	0	9.8	0	0	40.6	26.2	0	0	0.3	0	4.3	14.3	0.3	0
NEF vs PAR		0	0	0	0	0	0	2.8	0	48.6	0	45.8	0	0	0	0	0	0	2.8
NEF vs SER		0	0	0	0	0	0	0	0	50	0	0	50	0	0	0	0	0	0
NEF vs VEN		0	0	0	0.4	0	0.8	0	0	49.2	0	0	0	48	0	0.4	0	1.2	0
NOR vs PAR		0	0	0	4.2	0	9.6	2.3	0	0	25.6	37.4	0	0.3	0	4.2	14	0.3	2.3
NOR vs SER		0	0	0	4.3	0	9.8	0	0	0	26.2	0	40.6	0.3	0	4.3	14.3	0.3	0
NOR vs VEN		0	0	0	4	0	9.3	0	0	0	26.7	0	0	40	0	4	14.6	1.3	0
PAR vs SER		0	0	0	0	0	0	2.8	0	0	0	45.8	48.6	0	0	0	0	0	2.8
PAR vs VEN		0	0	0	0.3	0	0.8	2.7	0	0	0	45.1	0	46.7	0	0.3	0	1.2	2.7
SER vs VEN		0	0	0	0.3	0	0.8	0	0	0	0	0	49.2	48	0	0.4	0	1.2	0
total		6	6	6	4.9	6	7.6	2	6	6	4.1	13.8	6	6.1	6	5.4	2.4	0.4	5.2

Suicidal behavior or ideation

Comparison		N	PBO vs CIT	PBO vs DUL	PBO vs ESC	PBO vs FLU	PBO vs IMP	PBO vs PAR	PBO vs SER	PBO vs VEN	CLO vs PAR	DUL vs FLU	IMP vs PAR
Direct comparison	PBO vs CIT	2	100	0	0	0	0	0	0	0	0	0	0
	PBO vs DUL	2	0	47.1	0	26.4	0	0	0	0	0	26.4	0
	PBO vs ESC	2	0	0	100	0	0	0	0	0	0	0	0
	PBO vs FLU	6	0	21.9	0	56.2	0	0	0	0	0	21.9	0
	PBO vs IMP	1	0	0	0	0	27.1	36.4	0	0	0	0	36.4
	PBO vs PAR	4	0	0	0	0	12	76	0	0	0	0	12
	PBO vs SER	2	0	0	0	0	0	0	99.9	0	0	0	0
	PBO vs VEN	2	0	0	0	0	0	0	0	99.9	0	0	0
	CLO vs PAR	1	0	0	0	0	0	0	0	0	100	0	0
	DUL vs FLU	2	0	26.5	0	26.5	0	0	0	0	0	47	0
	IMP vs PAR	1	0	0	0	0	22.5	22.5	0	0	0	0	55
Indirect comparison	PBO vs CLO		0	0	0	0	6.4	40.4	0	0	46.8	0	6.4
	CIT vs CLO		31.9	0	0	0	4.3	27.5	0	0	31.9	0	4.3
	CIT vs DUL		42.4	27.2	0	15.2	0	0	0	0	0	15.2	0
	CIT vs ESC		50	0	50	0	0	0	0	0	0	0	0
	CIT vs FLU		43.8	12.3	0	31.5	0	0	0	0	0	12.3	0
	CIT vs IMP		38.9	0	0	0	16.6	22.3	0	0	0	0	22.3
	CIT vs PAR		46.8	0	0	0	6.4	40.4	0	0	0	0	6.4
	CIT vs SER		50	0	0	0	0	0	50	0	0	0	0
	CIT vs VEN		50	0	0	0	0	0	0	50	0	0	0
	CLO vs DUL		0	18.3	0	10.3	3.9	24.7	0	0	28.6	10.3	3.9
	CLO vs ESC		0	0	31.9	0	4.3	27.5	0	0	31.9	0	4.3
	CLO vs FLU		0	8.2	0	21.1	4	25.3	0	0	29.3	8.2	4
	CLO vs IMP		0	0	0	0	12.7	12.7	0	0	43.7	0	31
	CLO vs SER		0	0	0	0	4.3	27.5	31.9	0	31.9	0	4.3
	CLO vs VEN		0	0	0	0	4.3	27.5	0	31.9	31.9	0	4.4
	DUL vs ESC		0	27.2	42.4	15.2	0	0	0	0	0	15.2	0
	DUL vs IMP		0	21.9	0	12.2	14.6	19.5	0	0	0	12.3	19.5
	DUL vs PAR		0	25.7	0	14.4	5.5	34.6	0	0	0	14.4	5.5
	DUL vs SER		0	27.2	0	15.2	0	0	42.4	0	0	15.2	0
	DUL vs VEN		0	27.2	0	15.2	0	0	0	42.4	0	15.2	0
	ESC vs FLU		0	12.3	43.8	31.5	0	0	0	0	0	12.3	0
	ESC vs IMP		0	0	38.9	0	16.6	22.3	0	0	0	0	22.3
	ESC vs PAR		0	0	46.8	0	6.4	40.4	0	0	0	0	6.4
	ESC vs SER		0	0	50	0	0	0	50	0	0	0	0
	ESC vs VEN		0	0	50	0	0	0	0	50	0	0	0
	FLU vs IMP		0	9.8	0	25.2	15	20.1	0	0	0	9.8	20.1
	FLU vs PAR		0	11.6	0	29.8	5.6	35.7	0	0	0	11.6	5.6
	FLU vs SER		0	12.3	0	31.5	0	0	43.8	0	0	12.3	0
	FLU vs VEN		0	12.3	0	31.5	0	0	0	43.8	0	12.3	0
	IMP vs SER		0	0	0	0	16.6	22.3	38.9	0	0	0	22.3
	IMP vs VEN		0	0	0	0	16.6	22.3	0	38.9	0	0	22.3
	PAR vs SER		0	0	0	0	6.4	40.4	46.8	0	0	0	6.4
	PAR vs VEN		0	0	0	0	6.4	40.4	0	46.8	0	0	6.4
	SER vs VEN		0	0	0	0	0	0	50	50	0	0	0
total			9.3	8	9.3	9.3	5.6	17.2	9.3	9.3	9.3	5.9	7.6

b. Contributions summary of risk of bias assessments for each outcome

Risk of bias assessment* for any direct comparisons included in the network for each outcome

	Mean overall change in symptoms	Discontinuation due to adverse events	Response rate	All-cause discontinuation	Suicidal behavior or ideation
AMI vs PBO	Moderate	Moderate	Moderate	Moderate	NA
CIT vs PBO	High	High	High	High	High
CLO vs PAR	Low	Low	Low	Low	Low
DES vs PBO	Moderate	Moderate	Moderate	Moderate	NA
DUL vs PBO	Low	Low	Low	Low	Low
DUL vs FLU	Low	Low	Low	Low	Low
ESC vs PBO	Moderate	Moderate	Moderate	Moderate	Moderate
FLU vs NOR	Moderate	NA	Moderate	Moderate	NA
FLU vs PBO	Moderate	Moderate	Moderate	Moderate	Moderate
FLU vs VEN	Moderate	NA	Moderate	Moderate	NA
IMP vs PBO	High	High	High	High	High
IMP vs PAR	High	High	High	High	High
MIR vs PBO	High	Moderate	NA	Moderate	NA
NEF vs PBO	Moderate	Moderate	Moderate	Moderate	NA
NOR vs PBO	Moderate	NA	Moderate	Moderate	NA
PAR vs PBO	Moderate	Moderate	Moderate	Moderate	Moderate
SER vs PBO	High	High	High	High	High
VEN vs PBO	High	High	High	High	High

*The overall risk of bias for each direct comparison was based on the risk of bias of individual studies contributing to that comparison, and was classified as high, moderate or low.

AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo, NA= no available.

The contribution of direct comparisons to mixed or indirect comparisons by risk of bias classification and outcome*

	Mean overall change in symptoms			Discontinuation due to adverse events			Response rate			All-cause discontinuation			Suicidal behavior or ideation		
	Low (%)	Moderate (%)	High (%)	Low (%)	Moderate (%)	High (%)	Low (%)	Moderate (%)	High (%)	Low (%)	Moderate (%)	High (%)	Low (%)	Moderate (%)	High (%)
PBO vs AMI	0	100	0	0	99·7	0	0	99·9	0	0	99·9	0	…	…	…
PBO vs CIT	0	0	100	0	0	100	0	0	100	0	0	100	0	0	100
PBO vs DES	0	100	0	0	99·7	0	0	100	0	0	100	0	…	…	…
PBO vs DUL	70·4	25·8	3·7	85·2	14·7	0	73·7	23·7	2·5	64·8	34·3	0·8	73·5	26·4	0
PBO vs ESC	0	100	0	0	99·9	0	0	100	0	0	100	0	0	100	0
PBO vs FLU	52	41·9	6	33·4	66·6	0	51	44·2	4·7	43·2	55·4	1·4	43·8	56·2	0
PBO vs IMP	0	28·4	71·6	0	31·4	68·5	0	26·6	73·4	0	43	57·1	0	36·4	63·5
PBO vs MIR	0	0	100	0	99·9	0	…	…	…	0	100	0	…	…	…
PBO vs NEF	0	100	0	0	99·9	0	0	100	0	0	100	0	…	…	…
PBO vs NOR	8·4	90·7	1	…	…	…	22·2	75·8	2·1	14·4	85·2	0·5	…	…	…
PBO vs PAR	0	77·2	22·8	0	67·3	32·8	0	76·4	23·6	0	89·1	10·8	0	76	24
PBO vs SER	0	0	100	0	0	100	0	0	100	0	0	99·9	0	0	99·9
PBO vs VEN	9·8	18·1	72	0	0	100	8·8	17·7	73·6	1·4	4·2	94·5	0	0	99·9
CLO vs PAR	100	0	0	100	0	0	100	0	0	100	0	0	100	0	0
DUL vs FLU	77·1	20·1	2·9	61·5	38·5	0	73·8	23·7	2·5	82·4	17·3	0·4	73·5	26·5	0
FLU vs NOR	29·8	66·6	3·5	…	…	…	21·2	76·8	2	20·2	79·1	0·6	…	…	…
FLU vs VEN	31·2	32·2	36·5	18·2	36·3	45·4	30	32·4	37·5	24·8	32·9	42·3	24·6	31·5	43·8

IMP vs PAR	0	32·2	67·9	0	25·7	74·3	0	33·5	66·5	0	15·9	84	0	22·5	77·5
PBO vs CLO	47	40·9	12	45·5	36·6	17·8	46·9	40·6	12·6	48·6	45·8	5·6	46·8	40·4	12·8
AMI vs CIT	0	50	50	0	49·9	50	0	50	50	0	50	50	…	…	…
AMI vs CLO	32	59·9	8·2	31·3	56·4	12·2	31·9	59·5	8·6	32·7	63·5	3·8	…	…	…
AMI vs DES	0	100	0	0	100	0	0	100	0	0	100	0	…	…	…
AMI vs DUL	41·3	56·4	2·2	46·1	53·9	0	42·4	56	1·5	39·3	60·2	0·5	…	…	…
AMI vs ESC	0	100	0	0	99·9	0	0	99·9	0	0	100	0	…	…	…
AMI vs FLU	31·2	65·1	3·6	18·2	81·7	0	30·2	66·8	2·8	24·6	74·5	0·8	…	…	…
AMI vs IMP	0	58·3	41·8	0	59·2	40·7	0	57·6	42·4	0	63·7	36·4	…	…	…
AMI vs MIR	0	50	50	0	99·9	0	…	…	…	0	100	0	…	…	…
AMI vs NEF	0	100	0	0	99·9	0	0	100	0	0	100	0	…	…	…
AMI vs NOR	4·6	94·8	0·5	…	…	…	14·2	84·6	1·3	8·6	91·1	0·3	…	…	…
AMI vs PAR	0	87·9	12	0	82·1	17·8	0	87·4	12·6	0	94·4	5·6	…	…	…
AMI vs SER	0	50	50	0	49·9	50	0	50	50	0	50	50	…	…	…
AMI vs VEN	5·4	55·3	39·3	0	49·9	50	4·8	55·4	39·9	0·7	51·2	48	…	…	…
CIT vs CLO	32	27·9	40·2	31·3	25·2	43·5	31·9	27·6	40·5	32·7	30·8	36·5	31·9	27·5	40·5
CIT vs DES	0	50	50	0	49·9	50	0	50	50	0	50	50	…	…	…
CIT vs DUL	41·3	15·1	43·5	46·1	8	46	42·4	13·6	43·9	39·3	20·9	39·8	42·4	15·2	42·4
CIT vs ESC	0	50	50	0	50	50	0	50	50	0	50	50	0	50	50
CIT vs FLU	31·2	25·1	43·6	18·2	36·3	45·4	30·2	26·1	43·5	24·6	31·7	43·6	24·6	31·5	43·8
CIT vs IMP	0	16·6	83·5	0	18·6	81·4	0	15·4	84·7	0	27·4	72·7	0	22·3	77·8
CIT vs MIR	0	0	100	0	50	50	…	…	…	0	50	50	…	…	…
CIT vs NEF	0	50	50	0	50	50	0	50	50	0	50	50	…	…	…

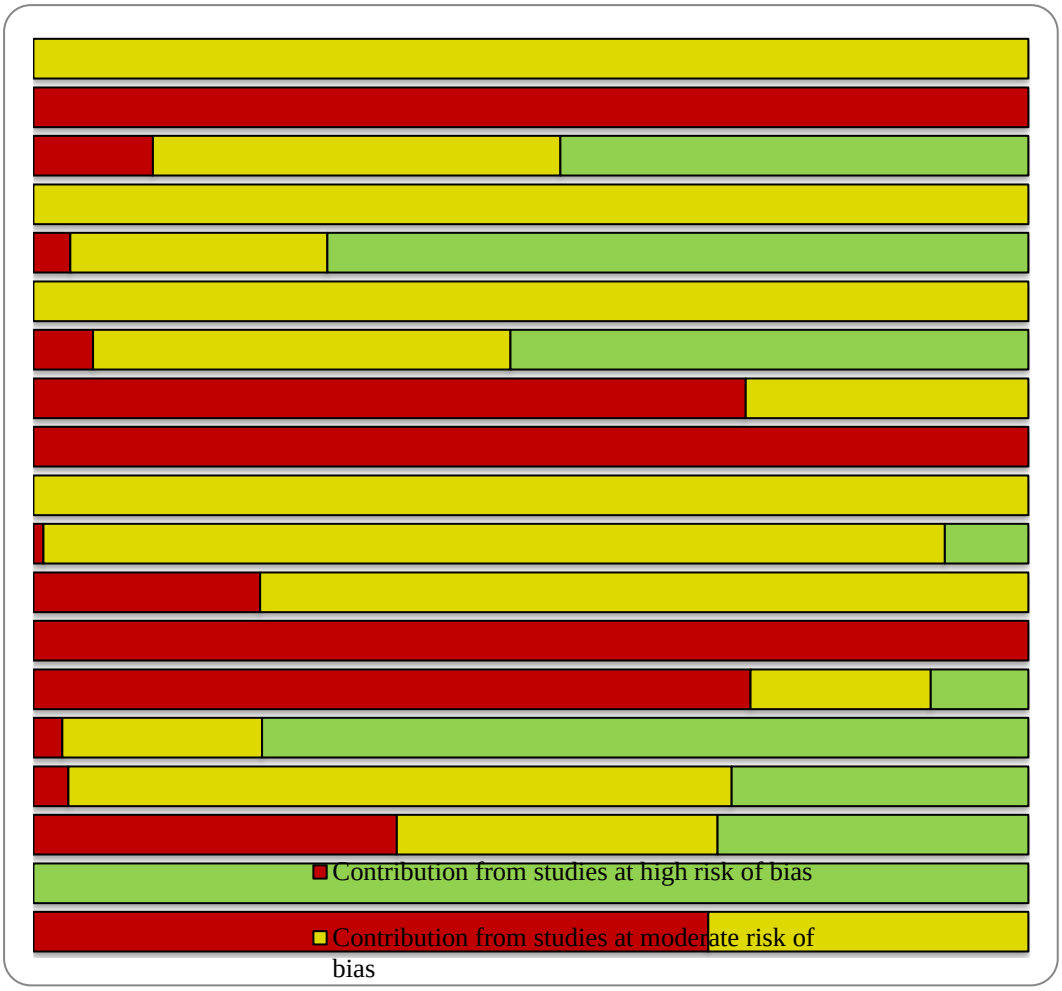
CIT vs NOR	4·6	49·1	46·2	…	…	…	14·2	48·1	37·8	8·6	50·6	40·9	…	…	…
CIT vs PAR	0	40·9	59	0	36·6	63·3	0	40·6	59·5	0	45·8	54·2	0	40·4	59·6
CIT vs SER	0	0	100	0	0	100	0	0	100	0	0	100	0	0	100
CIT vs VEN	5·4	9·8	84·8	0	0	100	4·8	9·6	85·7	0·8	2	97·2	0	0	100
CLO vs DES	32	59·9	8·2	31·3	56·4	12·2	31·9	59·5	8·6	32·7	63·5	3·8	…	…	…
CLO vs DUL	56·4	34·9	8·7	59·4	29	11·6	57·4	34	8·6	55·6	41·1	3·6	57·2	35	7·8
CLO vs ESC	32	59·9	8·2	31·3	56·5	12·2	31·9	59·5	8·6	32·7	63·5	3·8	31·9	59·4	8·6
CLO vs FLU	49	41·3	9·5	41·2	47·2	11·6	48·6	41·9	9·3	46·5	49·5	3·9	45·7	46·4	8
CLO vs IMP	40·4	19·2	40·4	42·6	14·7	42·6	39·9	20·1	39·9	45·7	8·6	45·7	43·7	12·7	43·7
CLO vs MIR	32	27·9	40·2	31·3	56·5	12·2	…	…	…	32·7	63·5	3·8	…	…	…
CLO vs NEF	32	59·9	8·2	31·3	56·5	12·2	31·9	59·5	8·6	32·7	63·5	3·8	…	…	…
CLO vs NOR	33·2	58·7	8·1	…	…	…	35·8	56·4	7·9	34·4	62·2	3·4	…	…	…
CLO vs SER	32	27·9	40·2	31·3	25·2	43·5	31·9	27·6	40·5	32·7	30·8	36·5	31·9	27·5	40·5
CLO vs VEN	33·7	32·8	33·7	31·3	25·2	43·5	33·3	32·5	34·2	32·8	31·8	35·4	31·9	27·5	40·6
DES vs DUL	41·3	56·4	2·2	46·1	53·8	0	42·4	56	1·5	39·3	60·2	0·5	…	…	…
DES vs ESC	0	100	0	0	99·9	0	0	100	0	0	100	0	…	…	…
DES vs FLU	31·2	65·1	3·6	18·2	81·6	0	30·2	66·8	2·8	24·6	74·5	0·8	…	…	…
DES vs IMP	0	58·3	41·8	0	59·2	40·7	0	57·6	42·4	0	63·7	36·4	…	…	…
DES vs MIR	0	50	50	0	99·9	0	…	…	…	0	100	0	…	…	…
DES vs NEF	0	100	0	0	99·9	0	0	100	0	0	100	0	…	…	…
DES vs NOR	4·6	94·8	0·5	…	…	…	14·2	84·6	1·3	8·6	91·2	0·3	…	…	…
DES vs PAR	0	87·9	12	0	82	17·8	0	87·5	12·6	0	94·4	5·6	…	…	…
DES vs SER	0	50	50	0	49·9	50	0	50	50	0	50	50	…	…	…

DES vs VEN	5·4	55·3	39·3	0	49·9	50	4·8	55·4	39·9	0·7	51·2	48	…	…	…
DUL vs ESC	41·3	56·4	2·2	46·1	54	0	42·4	56	1·5	39·3	60·2	0·5	42·4	57·6	0
DUL vs IMP	35·5	27·2	37·4	38	24	38	36·7	25·2	38	30·3	38·9	30·7	34·2	31·7	34·1
DUL vs MIR	41·3	15·1	43·5	46·1	54	0	…	…	…	39·3	60·2	0·5	…	…	…
DUL vs NEF	41·3	56·4	2·2	46·1	54	0	42·4	56	1·5	39·3	60·2	0·5	…	…	…
DUL vs NOR	43·2	54·9	1·8	…	…	…	49·7	50·3	0·1	44·5	55·2	0·3	…	…	…
DUL vs PAR	39·2	48·6	12·1	42·2	41·3	16·6	40·2	47·7	12·2	38·4	56·6	4·9	40·1	49	11
DUL vs SER	41·3	15·1	43·5	46·1	8	46	42·4	13·6	43·9	39·3	20·9	39·8	42·4	15·2	42·4
DUL vs VEN	44·7	19·1	36·3	46·1	8	46	45·3	16·9	37·9	40	21·5	38·5	42·4	15·2	42·4
ESC vs FLU	31·2	65·1	3·6	18·2	81·7	0	30·2	66·8	2·8	24·6	74·5	0·8	24·6	75·3	0
ESC vs IMP	0	58·3	41·8	0	59·3	40·7	0	57·6	42·4	0	63·7	36·4	0	61·2	38·9
ESC vs MIR	0	50	50	0	100	0	…	…	…	0	100	0	…	…	…
ESC vs NEF	0	100	0	0	100	0	0	100	0	0	100	0	…	…	…
ESC vs NOR	4·6	94·8	0·5	…	…	…	14·2	84·6	1·3	8·6	91·2	0·3	…	…	…
ESC vs PAR	0	87·9	12	0	82·1	17·8	0	87·5	12·6	0	94·4	5·6	0	87·2	12·8
ESC vs SER	0	50	50	0	50	50	0	50	50	0	50	50	0	50	50
ESC vs VEN	5·4	55·3	39·3	0	50	50	4·8	55·4	39·9	0·8	51·2	48	0	50	50
FLU vs IMP	27	35·3	37·6	15	47·3	37·6	26·4	35·8	37·9	18·6	48·3	33	19·6	45·3	35·1
FLU vs MIR	31·2	25·1	43·6	18·2	81·7	0	…	…	…	24·6	74·5	0·8	…	…	…
FLU vs NEF	31·2	65·1	3·6	18·2	81·7	0	30·2	66·8	2·8	24·6	74·5	0·8	…	…	…
FLU vs PAR	29·6	57·1	13·2	16·8	67	16·4	28·8	58·3	13·1	24·1	70·4	5·6	23·2	65·5	11·2
FLU vs SER	31·2	25·1	43·6	18·2	36·3	45·4	30·2	26·1	43·5	24·6	31·7	43·6	24·6	31·5	43·8
IMP vs MIR	0	16·6	83·5	0	59·3	40·7	…	…	…	0	63·7	36·4	…	…	…

IMP vs NEF	0	58·3	41·8	0	59·2	40·7	0	57·7	42·4	0	63·7	36·4	…	…	…
IMP vs NOR	3·8	57	39·1	…	…	…	12·4	54·2	33·4	6·6	62·2	31·3	…	…	…
IMP vs SER	0	16·6	83·5	0	18·6	81·4	0	15·4	84·7	0	27·4	72·7	0	22·3	77·8
IMP vs VEN	4·6	23·7	71·7	0	18·6	81·4	4	22·5	73·4	0·6	28·5	70·9	0	22·3	77·8
MIR vs NEF	0	50	50	0	100	0	…	…	…	0	100	0	…	…	…
MIR vs NOR	4·6	49·1	46·2	…	…	…	…	…	…	8·6	91·2	0·3	…	…	…
MIR vs PAR	0	40·9	59	0	82·1	17·8	…	…	…	0	94·4	5·6	…	…	…
MIR vs SER	0	0	100	0	50	50	…	…	…	0	50	50	…	…	…
MIR vs VEN	5·4	9·8	84·8	0	50	50	…	…	…	0·8	51·2	48	…	…	…
NEF vs NOR	4·6	94·8	0·5	…	…	…	14·2	84·6	1·3	8·6	91·2	0·3	…	…	…
NEF vs PAR	0	87·9	12	0	82·1	17·8	0	87·5	12·6	0	94·4	5·6	…	…	…
NEF vs SER	0	50	50	0	50	50	0	50	50	0	50	50	…	…	…
NEF vs VEN	5·4	55·3	39·3	0	50	50	4·8	55·4	39·9	0·8	51·2	48	…	…	…
NOR vs PAR	4·4	84·1	11·7	…	…	…	13·4	75·9	10·6	8·4	86·9	4·9	…	…	…
NOR vs SER	4·6	49·1	46·2	…	…	…	14·2	48·1	37·8	8·6	50·6	40·9	…	…	…
NOR vs VEN	0·8	57·2	42	…	…	…	11·4	55	33·5	8	51·9	40	…	…	…
PAR vs SER	0	40·9	59	0	36·6	63·3	0	40·6	59·5	0	45·8	54·2	0	40·4	59·6
PAR vs VEN	5	46·7	48·1	0	36·6	63·3	4·4	46·5	49·2	0·6	47·1	52·1	0	40·4	59·6
SER vs VEN	5·4	9·8	84·8	0	0	100	4·8	9·6	85·7	0·7	2	97·2	0	0	100
Total Network	17·6	49·3	33·1	16	52·5	31·6	19·5	52·2	28·3	16·3	58·3	25·3	23·2	35·8	41·1

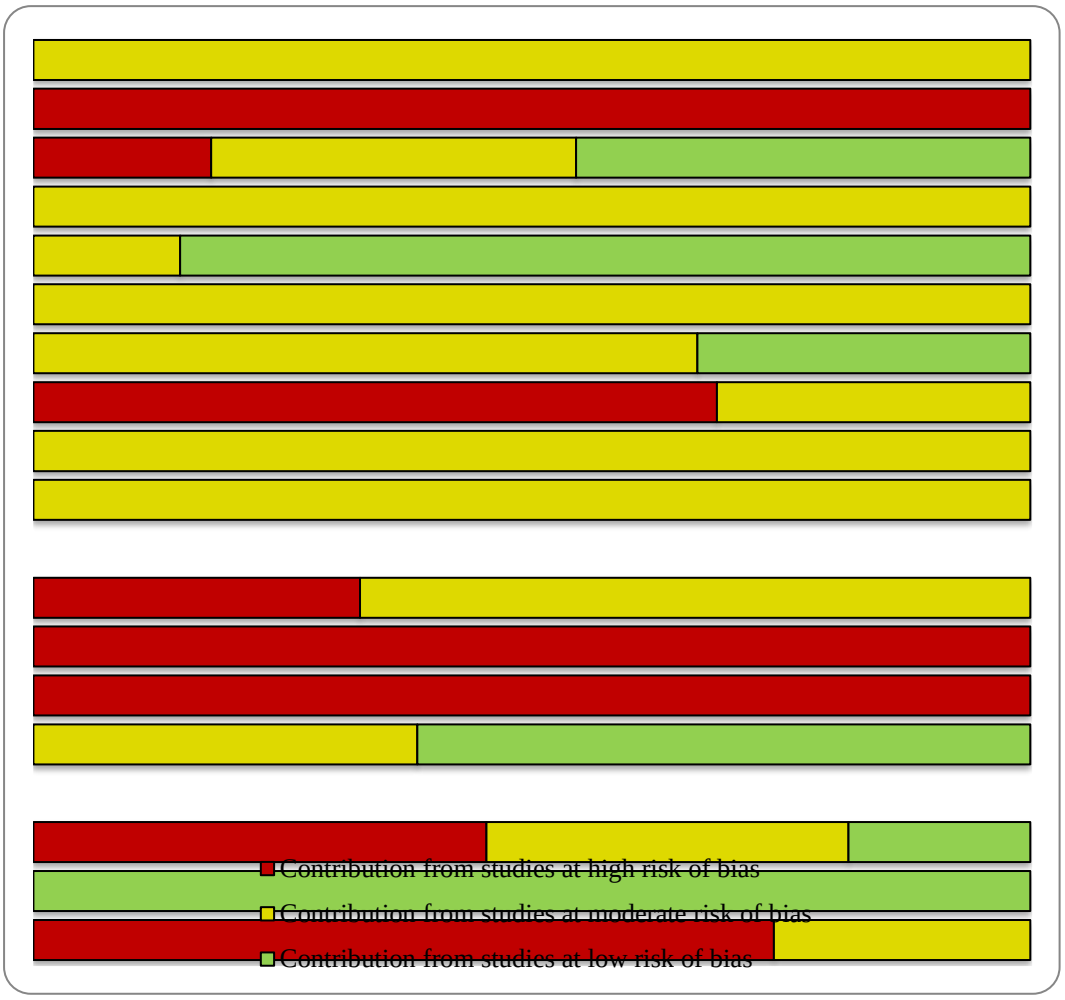
*Contributions of direct comparisons at high, moderate or low risk of bias to mixed or indirect comparisons were calculated as the sum of direct comparisons with corresponding risks of bias, weighted by the contribution matrix; AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo

Contributions summary of direct comparisons for each risk of bias assessment for the mean overall change in symptoms



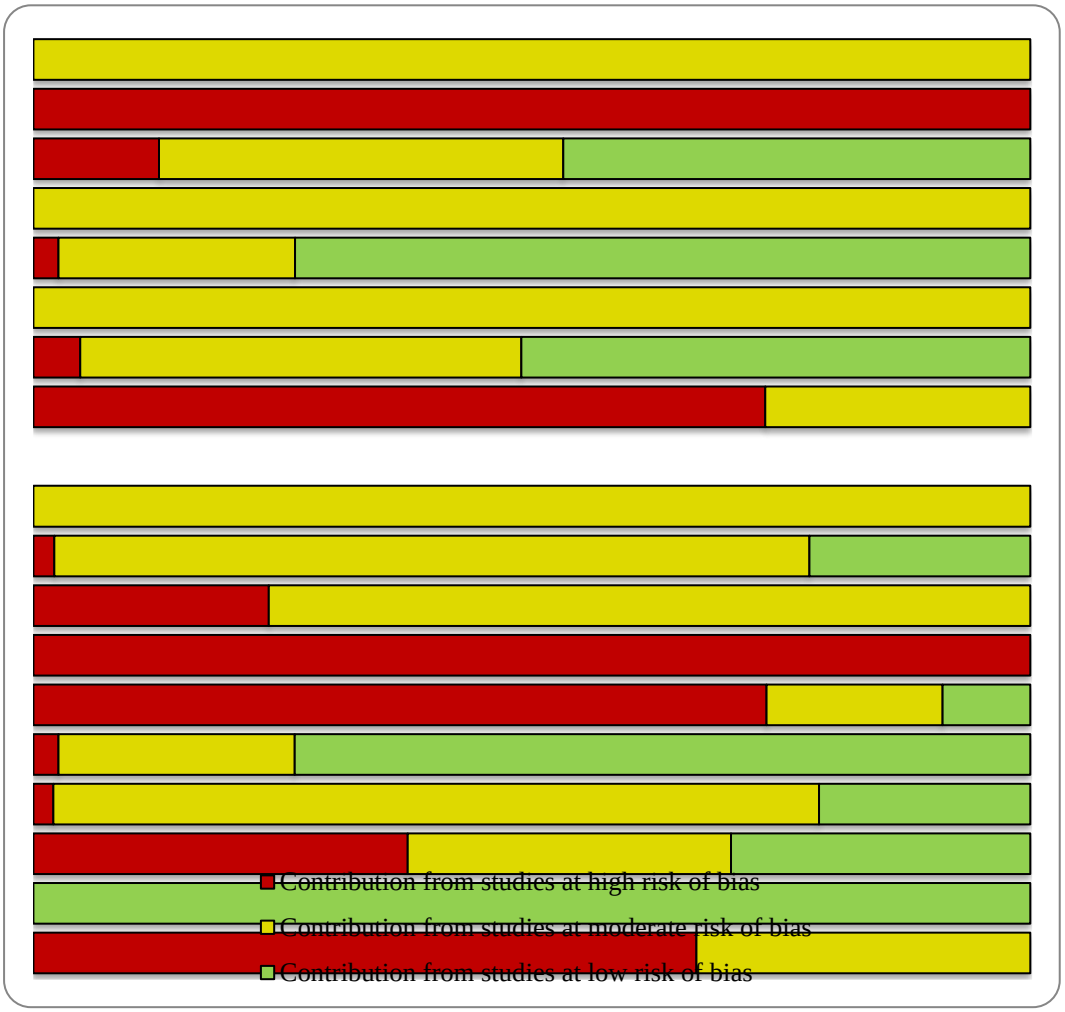
Legend: AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo

Contributions summary of direct comparisons for each risk of bias assessment for discontinuation due to adverse events



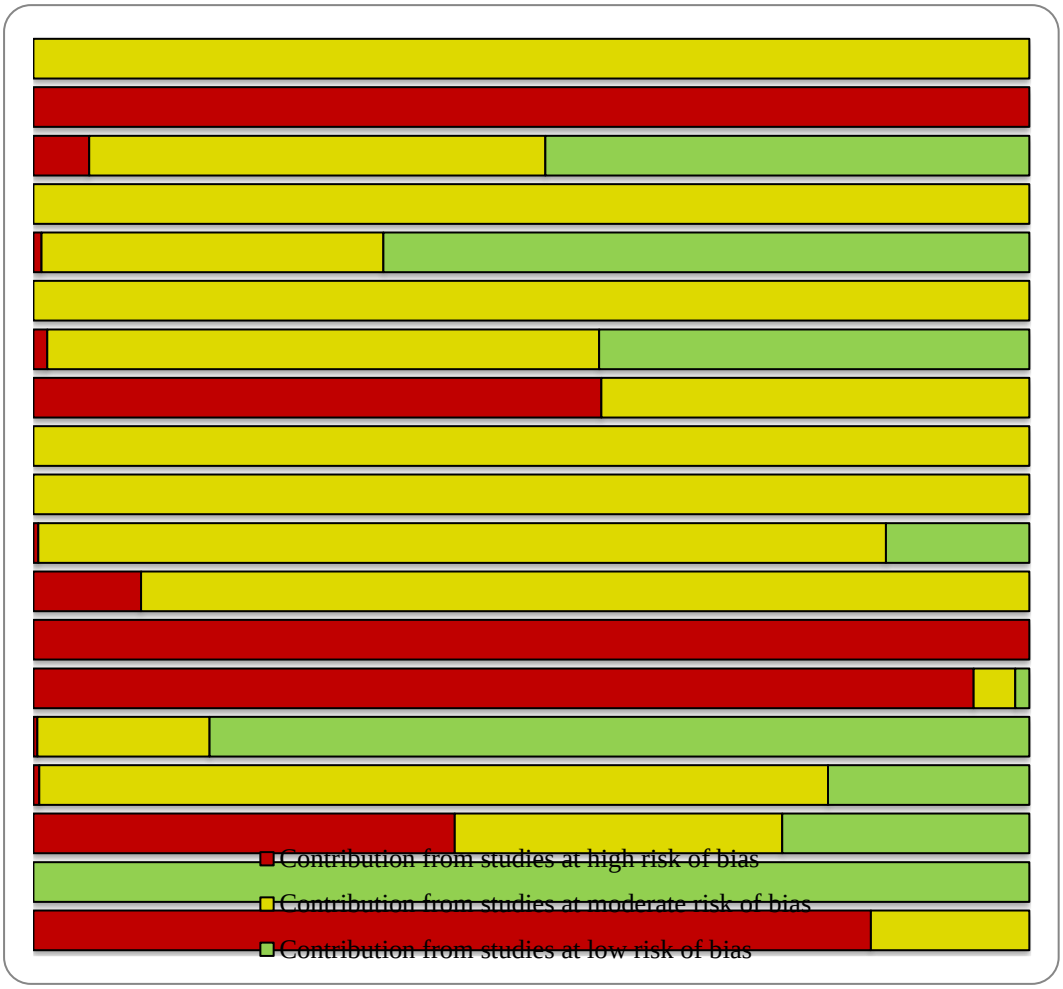
Legend: AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo

Contributions summary of direct comparisons for each risk of bias assessment for response rate



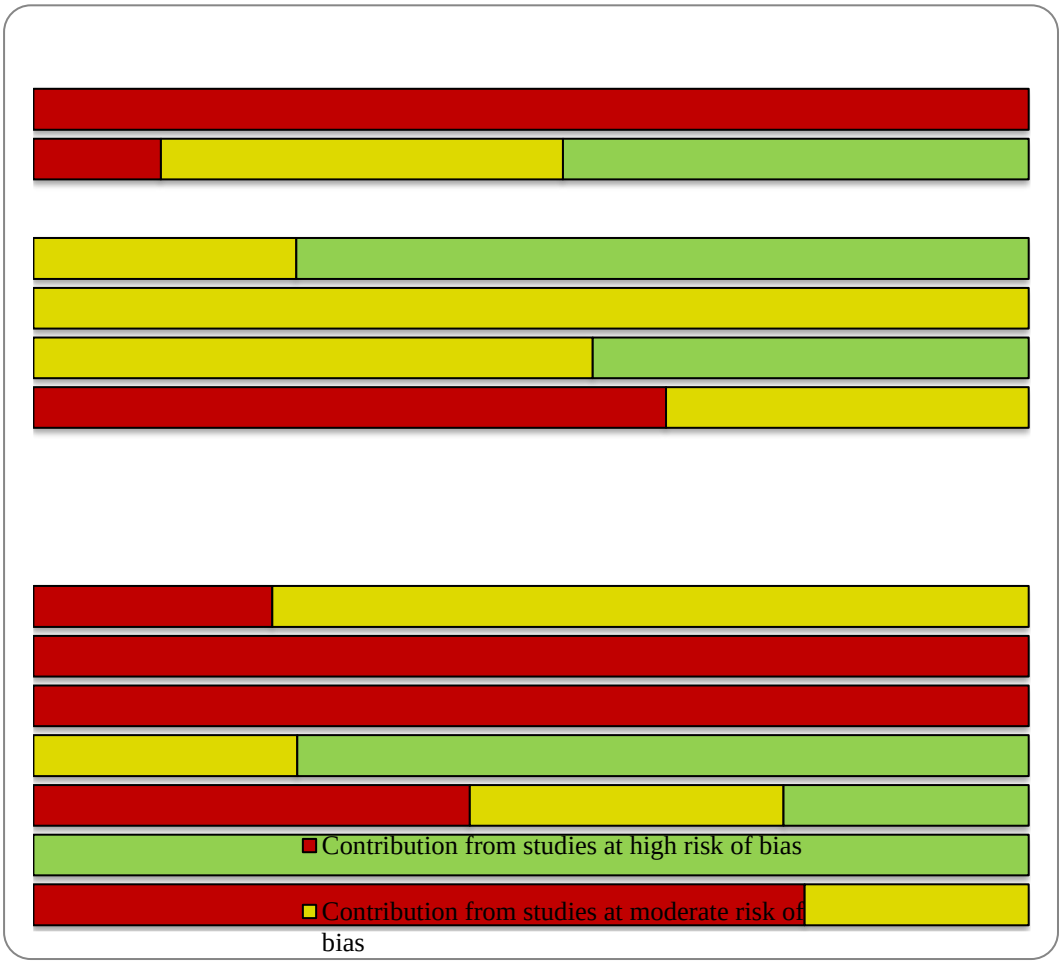
Legend: AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo

Contributions summary of direct comparisons for each risk of bias assessment for all-cause discontinuation



Legend: AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo

Contributions summary of direct comparisons for each risk of bias assessment for suicidal behavior or ideation



Legend: AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, PAR=paroxetine, SER=sertraline, VEN=venlafaxine, PBO=placebo

APPENDIX 15

Evaluation of the quality of evidence using GRADE framework for primary outcomes

The confidence in SMD for mean overall change in symptoms by GRADE system*

Comparison	Study limitations	Imprecision	Heterogeneity and Inconsistency	Indirectness	Publication bias	Confidence in SMD for overall change in depressive symptoms
AMI vs. PBO	0% of the estimate from studies at high risk, and 100% at moderate risk	SMD 0·09, 95% CrI -1·45 to 1·63	Only one head-to-head study, and no heterogeneity. Only direct comparison and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses. Only one monocenter study.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations, imprecision, and indirectness)
CIT vs.PBO	100% of the estimate from studies at high risk, and 0% at moderate risk	SMD -0·18, 95% CrI -1·18 o 0·81	Moderate heterogeneity according to I^2 (60·7%) and P-value (0·11~~1~~09) in direct comparisons. Only direct comparisons and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations (for two levels), imprecision)
CLO vs.PBO	12·0% of the estimate from studies at high risk, and 40·9% at moderate risk	SMD 0·33, 95% CrI -1·26 to 1·91	No head-to-head study and no heterogeneity. Only indirect comparison and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations, and imprecision)
DES vs. PBO	0% of the estimate from studies at high risk, and 100% at moderate risk	SMD -0·44, 95% CrI -1·51 to 0·63	High heterogeneity according to I^2 (80·8%) and P-value (0·02253) in direct comparisons. Only direct comparisons and no	The treatment effect was significantly influenced by clinical modifiers (e.g., co-morbid) in the	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant	Very Low (Downgrade by four levels due to study limitations, imprecision,

			node-splitting inconsistency.	subgroup analyses.	publication bias.	heterogeneity and indirectness)
DUL vs. PBO	3·7% of the estimate from studies at high risk, and 25·.8% at moderate risk	SMD -0·35, 95% CrI -1·25 to 0·54	Mild heterogeneity according to I^2 (27·9%) and P-value (0·23889) in direct comparisons. There is an inconsistency between the direct and indirect estimate (Node-split p=0·0010 and tau =0·0878).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to imprecision and inconsistency)
ESC vs. PBO	0% of the estimate from studies at high risk, and 100% at moderate risk	SMD -0·17, 95% CrI -1·16 to 0·82	Mild heterogeneity according to I^2 (0%) and P-value (0·6070) in direct comparisons. Only direct comparisons and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations and imprecision)
FLU vs. PBO	6% of the estimate from studies at high risk, and 41·9% at moderate risk	SMD -0·50, 95% CrI -0·98 to -0·03	Moderate heterogeneity according to I^2 (67·4%) and P-value (0·0031) in direct comparisons. There is an inconsistency between direct and indirect estimate (Node-split p=0·02409 and tau= 0·3296)	The treatment effects were significantly influenced by some clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by four levels due to study limitations, heterogeneity and inconsistency, and indirectness)
IMP vs. PBO	71·6% of the estimate from studies at high risk, and 28.4% at moderate risk	SMD -0·01, 95% CrI -0·98 to 0·96	Mild heterogeneity according to I^2 (0%) and P-value (0·6430) in direct comparisons. No inconsistency between the direct and indirect estimate (Node-split p= 0·65656 and tau= 0·3098).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations (for two levels), imprecision)
MIR vs.PBO	100% of the estimate	SMD -0·24, 95%	Mild heterogeneity according to I^2	The treatment effects	Undetectable by the routine	Very Low (Downgrade

	from studies at high risk, and 0% at moderate risk	CrI -1·24 to 0·77	(14·0%) and P-value (0·2810) in direct comparisons. Only direct comparison, and no node-splitting inconsistency.	were not significantly influenced by clinical modifiers in the subgroup analyses.	method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	by three levels due to study limitations (for two levels), imprecision)
NEF vs.PBO	0% of the estimate from studies at high risk, and 100% at moderate risk	SMD -0.14, 95% CrI -1·13 to 0·85	Moderate heterogeneity according to I^2 (47·9%) and P-value (0·16596) in direct comparisons. Only direct comparisons, and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations and imprecision)
NOR vs. PBO	1% of the estimate from studies at high risk, and 90·7% at moderate risk	SMD 1·14, 95% CrI 0·26 to 2·02	Mild heterogeneity according to I^2 (0%) and P-value (0·3214) in direct comparisons. There is an inconsistency between direct and indirect estimate (Node-split p=≤ 0·0001 and tau= 0·1450).	The treatment effects were significantly influenced by most clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to tudy limitations, inconsistency and indirectness)
PAR vs.PBO	22·8% of the estimate from studies at high risk, and 77·2% at moderate risk	SMD -0·16, 95% CrI -0·86 to 0·54	Mild heterogeneity according to I^2 (0%) and P-value (0·39273) in direct comparisons. No inconsistency between direct and indirect estimate (Node-split p= 0·691727 and tau= 0·3022).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations, and imprecision)
SER vs. PBO	100% of the estimate from studies at high risk, and 0% at moderate risk	SMD -0·23, 95% CrI -1·22 to 0·76	Mild heterogeneity according to I^2 (0%) and P-value (0·7951) in direct comparisons. Only direct comparisons, and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations (for two levels), imprecision)

VEN vs. PBO	72% of the estimate from studies at high risk, and 18·1% at moderate risk	SMD -0·26, 95% CrI -1·09 to 0·58	Mild heterogeneity according to I^2 (0%) and P-value (0·9094) in direct comparisons. No inconsistency between direct and indirect estimate (Node-split p=0·6192 and tau= 0·3088).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations (for two levels) and imprecision)
FLU vs. DUL	2·9% of the estimate from studies at high risk, and 20·1% at moderate risk	SMD -0·15, 95% CrI -1·04 to 0·74	Mild heterogeneity according to I^2 (0%) and P-value (0·62657) in direct comparisons. There is an inconsistency between direct and indirect estimate (Node-split p= 0·0010 and tau= 0·0878).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to imprecision and inconsistency)
FLU vs. NOR	3·5% of the estimate from studies at high risk, and 66·6% at moderate risk	SMD -1·64, 95% CrI -2·57 to -0·72	Only one head-to-head study and no heterogeneity. There is an inconsistency between direct and indirect estimate (Node-split p<= 0·0001 and tau= 0·1450).	Treatment effects not significantly influenced by clinical modifiers in subgroup analyses. Only one monocenter study.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations, inconsistency, and indirectness)
FLU vs. VEN	36·5% of the estimate from studies at high risk, and 32·2% at moderate risk	SMD -0·25, 95% CrI -1·13 to 0·63	Only one head-to-head study and no heterogeneity. No inconsistency between direct and indirect estimate (Node-split p= 0·6192 and tau= 0·3088).	The treatment effect was significantly influenced by clinical modifiers (e.g., risk bias) in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (downgrade by three levels due to study limitations, imprecision and indirectness)
PAR vs. CLO	0% of the estimate from studies at high risk, and 0% at moderate risk	SMD -0·49, 95% CrI -1·90 to 0·93	Only one head-to-head study and no heterogeneity. No inconsistency between direct and indirect estimate (Node-split p= 0·9978 and tau=	The treatment effects were not significantly influenced by clinical modifiers in the	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant	Moderate (Downgrade by one level due to imprecision)

			0·2756).	subgroup analyses.	publication bias.	
PAR vs. IMP	67·9% of the estimate from studies at high risk, and 32·2% at moderate risk	SMD -0·15, 95% CrI -1·21 to 0·92	Only one head-to-head study and no heterogeneity. No inconsistency between direct and indirect estimate (Node-split p= 0·5884 and tau= 0·2999).	The treatment effects were significantly influenced by some clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by four levels due to study limitations (two levels), imprecision and indirectness)
Ranking of treatment	33·1% from studies at high risk, and 49·3% at moderate risk	SUCRA plots suggested the imprecision in a ranking of treatments.	Mild heterogeneity for mean overall change in symptoms in network meta-analyses according to global I^2 (38·6%). But, there is a significant inconsistency in test of global inconsistency (p<P =0·0001) and few inconsistency in local inconsistency.	The overall effects were not significantly influenced by clinical modifiers in the subgroup analyses.	The network funnel plot suggested no dominant publication bias	Very low (Downgrade by three levels due to study limitations, imprecision and inconsistency)

* Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One.* 2014 Jul 3;9(7):e99682

The confidence in OR for discontinuation due to adverse events by GRADE system*

Comparison	Study limitations	Imprecision	Heterogeneity and Inconsistency	Indirectness	Publication bias	Confidence in OR for discontinuation due to adverse events
AMI vs. PBO	0% of the estimate from studies at high risk, and 99·7% at moderate risk	OR 0·10, 95% CrI 0·02 to 32·16	Only one head-to-head study, and no heterogeneity. Only direct comparison, and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses. Only one monocenter study.	Undetectable by routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations, imprecision, and indirectness)
CIT vs.PBO	100% of the estimate from studies at high risk, and 0% at moderate risk	OR 1·13, 95% CrI 0·45 to 3·66	Mild heterogeneity according to I^2 (0%) and P-value (0·4895) in direct comparisons. Only direct comparisons, and no node-splitting inconsistency.	The treatment effect was significantly influenced by clinical modifiers (e.g., mean age) in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by four levels due to study limitations (two levels), imprecision and indirectness)
CLO vs.PBO	17·8% of the estimate from studies at high risk, and 36·6% at moderate risk	OR 1·27, 95% CrI 0·36 to 8·33	No head-to-head study and no heterogeneity. Only indirect comparison, and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations, and imprecision)
DES vs. PBO	0% of the estimate from studies at high risk, and 99·7% at moderate risk	OR 2·85, 95% CrI 0·83 to 21·80	Moderate heterogeneity according to I^2 (74·8%) and P-value (0·0463) in direct comparisons. Only direct comparisons, and no	The treatment effect was significantly influenced by clinical modifiers (e.g., co-morbid) in the subgroup	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant	Very Low (Downgrade by four levels due to study limitations, imprecision,

			node-splitting inconsistency.	analyses.	publication bias.	heterogeneity, and indirectness)
DUL vs. PBO	0% of the estimate from studies at high risk, and 14·7% at moderate risk	OR 2·80, 95% CrI 1·20 to 9·42	Mild heterogeneity according to I^2 (0%) and P-value (0·98576) in direct comparisons. No inconsistency between direct and indirect estimate (Node-split p= 0·789890 and tau= 0·0000).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	High
ESC vs. PBO	0% of the estimate from studies at high risk, and 99·9% at moderate risk	OR 1·64, 95% CrI 0·46 to 13·49	Mild heterogeneity according to I^2 (0%) and P-value (0·3594) in direct comparisons. Only direct comparisons and no node-splitting inconsistency.	The treatment effects were significantly influenced by some clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations, imprecision and indirectness)
FLU vs. PBO	0% of the estimate from studies at high risk, and 66·6% at moderate risk	OR 1·03, 95% CrI 0·50 to 2·70	Moderate heterogeneity according to I^2 (27·0%) and P-value (0·2413) in direct comparisons. Only direct comparisons and no node-splitting inconsistency.	The treatment effects were significantly influenced by some clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations, imprecision and indirectness)
IMP vs. PBO	68·5% of the estimate from studies at high risk, and 31·4% at moderate risk	OR 5·49, 95% CrI 1·96 to 20·86	Only one head-to-head study, and no heterogeneity. No inconsistency between direct and indirect estimate (Node-split p= 0·6662 and tau= 0·1630).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations (for two levels))
MIR vs.PBO	0% of the estimate from studies at high risk, and 99·9% at	OR 1·36, 95% CrI 0·41 to 10·99	Mild heterogeneity according to I^2 (0%) and P-value (0·4774) in direct comparisons.	The treatment effects were not significantly influenced by clinical	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not	Low (Downgrade by two levels due to study limitations and

	moderate risk		Only direct comparisons, and no node-splitting inconsistency.	modifiers in the subgroup analyses.	suggestive of any dominant publication bias.	imprecision)
NEF vs.PBO	0% of the estimate from studies at high risk, and 99·9% at moderate risk	OR 1·29, 95% CrI 0·30 to 21·89	Only one head-to-head study, and no heterogeneity. Only direct comparison, and no node-splitting inconsistency.	Treatment effects not significantly influenced by clinical modifiers in subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations, imprecision)
PAR vs.PBO	32·8% of the estimate from studies at high risk, and 67·3% at moderate risk	OR 1·59, 95% CrI 0·77 to 3·95	Mild heterogeneity according to I^2 (0%) and P-value (0·40438) in direct comparisons. No inconsistency between direct and indirect estimate (Node-split p= 0·37765 and tau= 0·0000).	The treatment effects were significantly influenced by some clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by three levels due to study limitations, imprecision and indirectness)
SER vs. PBO	100% of the estimate from studies at high risk, and 0% at moderate risk	OR 2·94, 95% CrI 0·94 to 17·19	Only one head-to-head study, and no heterogeneity. Only direct comparison, and no node-splitting inconsistency.	The treatment effects were significantly influenced by some clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Very Low (Downgrade by four levels due to study limitations (for two levels), imprecision and indirectness)
VEN vs. PBO	100% of the estimate from studies at high risk, and 0% at moderate risk	OR 3·19, 95% CrI 1·01 to 18·70	Only one head-to-head study, and no heterogeneity. Only direct comparison, and no node-splitting inconsistency.	Treatment effects not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations (for two levels))
FLU vs. DUL	0% of the estimate from studies at high risk, and 38·5% at moderate risk	OR 0·31, 95% CrI 0·13 to 0·95	Moderate heterogeneity according to I^2 (56·1%) and P-value (0·13112) in direct comparisons. No inconsistency between the direct and indirect estimate	The treatment effects were significantly influenced by some clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Moderate (Downgrade by one level due to indirectness)

			(Node-split p= 0·7898~~90~~ and tau= 0·0000).			
FLU vs. VEN	45·4% of the estimate from studies at high risk, and 36·3% at moderate risk	OR 0·39, 95% CrI 0·05 to 1·47	No head-to-head study and no heterogeneity. Only indirect comparison, and no node-splitting inconsistency.	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations and imprecision)
PAR vs. CLO	0% of the estimate from studies at high risk, and 0% at moderate risk	OR 0·79, 95% CrI 0·26 to 3·77	Only one head-to-head study, and no heterogeneity. No inconsistency betweendirect and indirect estimate (Node-split p= 0·9948~~5~~ and tau= 0·0000).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Moderate (Downgrade by one level due to imprecision)
PAR vs. IMP	74·3% of the estimate from studies at high risk, and 25·7% at moderate risk	OR 0·22, 95% CrI 0·08 to 0·87	Only one head-to-head study and no heterogeneity. No inconsistency between direct and indirect estimate (Node-split p= 0·5172 and tau= 0·1284).	The treatment effects were not significantly influenced by clinical modifiers in the subgroup analyses.	Undetectable by the routine method. The comparison-adjusted funnel plot for the network is not suggestive of any dominant publication bias.	Low (Downgrade by two levels due to study limitations (for two levels))
Ranking of treatment	31·6% from studies at high risk, and 52·5% at moderate risk	SUCRA plots suggested the imprecision in a ranking of treatments.	Mild heterogeneity for discontinuation due to adverse events in network meta-analyses according to global I^2 (0%). No significant inconsistency in test of global inconsistency (P = 0·8432), and few inconsistency in local inconsistency.	The overall effects were not significantly influenced by clinical modifiers in the subgroup analyses.	The network funnel plot suggested no dominant publication bias.	Low (Downgrade by two levels due to study limitations and imprecision)

* Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One.* 2014 Jul 3;9(7):e99682.

Appendix 16

Subgroup network meta-analyses for primary outcomes

Subgroup network meta-analyses of each drug for mean improvement in symptom compared with placebo with standardized mean difference (95% CrI)*

Characteristics	Fluoxetine	Desipramine	Duloxetine	Venlafaxine	Mirtazapine	Sertraline	Citalopram	Escitalopram	Paroxetine	Nefazodone	Imipramine	Amitriptyline	Clomipramine	Nortriptyline
All trials	**-0·50 (-0·98 to -0·03)**	-0·44 (-1·51 to 0·63)	-0·35 (-1·25 to 0·54)	-0·26 (-1·09 to 0·58)	-0·24 (-1·24 to 0·77)	-0·23 (-1·22 to 0·76)	-0·18 (-1·18 to 0·81)	-0·17 (-1·16 to 0·82)	-0·16 (-0·86 to 0·54)	-0·14 (-1·13 to 0·85)	-0·01 (-0·98 to 0·96)	0·09 (-1·45 to 1·63)	0·33 (-1·26 to 1·91)	**1·14 (0·26 to 2·02)**
Sex Ratio[a]														
Male-to-female ratio < 1	-0·10 (-0·29 to 0·10)	-0·42 (-0·89 to 0·05)	-0·16 (-0·40 to 0·08)	-0·09 (-0·70 to 0·51)	-0·23 (-0·56 to 0·09)	-0·23 (-0·51 to 0·04)	-0·35 (-0·74 to 0·05)	-0·12 (-0·48 to 0·23)	-0·18 (-0·43 to 0·06)	-0·27 (-0·66 to 0·11)	0·06 (-0·30 to 0·42)	…	0·31 (-0·20 to 0·81)	…
Male-to-female ratio > 1	-0·40 (-0·81 to 0·12)	…	…	-0·14 (-0·73 to 0·44)	…	…	…	…	0·05 (-0·77 to 0·87)	…	-0·14 (-1·09 to 0·81)	0·08 (-0·92 to 1·08)	…	-0·13 (-0·82 to 0·53)
Mean Age														
< 13 years	-0·87 (-1·82 to 0·07)	…	-0·61 (-2·15 to 0·93)	-0·14 (-1·35 to 1·07)	-0·24 (-1·45 to 0·98)	-0·22 (-1·91 to 1·49)	-0·35 (-2·07 to 1·36)	-0·13 (-1·82 to 1·57)	0·05 (-1·66 to 1·76)	…	-0·14 (-1·92 to 1·64)	…	…	**1·68 (0·34 to 3·03)**
≥ 13 years	-0·22 (-0·60 to 0·20)	-0·42 (-1·14 to 0·28)	-0·14 (-0·89 to 0·63)	-0·22 (-1·22 to 0·82)	…	-0·34 (-1·19 to 0·52)	-0·01 (-0·86 to 0·84)	-0·21 (-1·05 to 0·62)	-0·20 (-0·71 to 0·29)	…	0·05 (-0·74 to 0·82)	0·09 (-0·96 to 1·13)	0·28 (-0·74 to 1·29)	-0·38 (-1·42 to 0·65)
Treatment durations														
< 8 weeks	-0·20 (-1·20 to 0·79)	-0·43 (-1·39 to 0·51)	…	…	…	…	…	…	…	…	-0·14 (-1·49 to 1·21)	…	…	…
≥8 weeks	**-0·58 (-1·14 to -0·02)**	…	-0·39 (-1·34 to 0·56)	-0·28 (-1·17 to 0·61)	-0·23 (-1·30 to 0·84)	-0·23 (-1·28 to 0·83)	-0·18 (-1·24 to 0·88)	-0·17 (-1·22 to 0·88)	-0·15 (-0·90 to 0·61)	-0·14 (-1·20 to 0·91)	0·08 (-1·27 to 1·42)	0·09 (-1·52 to 1·69)	0·34 (-1·35 to 2·02)	**1·11 (0·17 to 2·04)**
Symptoms Severity														
Mild to moderate	…	…	…	…	…	…	…	…	-0·16 (-0·88 to 0·57)	…	0·07 (-0·89 to 1·03)	0·09 (-1·07 to 1·24)	…	…
Moderate to severe	-0·53 (-1·08 to 0·01)	-0·43 (-1·59 to 0·72)	-0·37 (-1·35 to 0·61)	-0·27 (-1·18 to 0·65)	-0·23 (-1·33 to 0·86)	-0·23 (-1·32 to 0·85)	-0·18 (-1·27 to 0·90)	-0·17 (-1·25 to 0·91)	-0·13 (-1·24 to 0·97)	-0·14 (-1·22 to 0·94)	…	…·	0·35 (-1·55 to 2·25)	**1·13 (0·17 to 2·08)**
Co-morbid														
No co-morbidity	-0·17 (-0·62 to 0·27)	0·08 (-0·62 to 0·80)	…	-0·15 (-0·46 to 0·17)	-0·23 (-0·60 to 0·13)	…	-0·17 (-0·51 to 0·16)	…	-0·34 (-0·97 to 0·29)	-0·14 (-0·47 to 0·18)	…	0·09 (-0·70 to 0·86)	0·15 (-0·66 to 0·96)	**4·04 (3·20 to 4·87)**
With co-morbidity	**-0·27**	**-0·97**	-0·24	…	…	-0·23	…	-0·17	-0·10	…	0·04	…	…	-0·12

	(-0·49 to -0·05)	**(-1·73 to -0·21)**	(-0·56 to 0·08)			(-0·59 to 0·13)		(-0·51 to 0·18)	(-0·39 to 0·19)		(-0·36 to 0·43)			(-0·64 to 0·39)
Risk bias														
Low and unclear risk bias	-0·42 (-1·25 to 0·39)	-0·44 (-1·69 to 0·81)	-0·32 (-1·43 to 0·79)	-0·42 (-2·36 to 1·50)	…	…	…	-0·12 (-1·83 to 1·56)	-0·01 (-1·22 to 1·18)	-0·14 (-1·33 to 1·05)	-0·14 (-1·92 to 1·63)	0·08 (-1·72 to 1·89)	0·47 (-1·62 to 2·55)	**1·90 (0·58 to 3·22)**
High risk bias	**-0·53 (-0·74 to -0·33)**	…	…	-0·14 (-0·41 to 0·13)	-0·24 (-0·54 to 0·07)	-0·23 (-0·49 to 0·03)	-0·17 (-0·43 to 0·09)	-0·21 (-0·53 to 0·10)	-0·27 (-0·58 to 0·04)	…	0·01 (-0·35 to 0·36)	…	…	-0·38 (-1·09 to 0·34)
Sample Size														
≥ 100	-0·80 (-1·67 to 0·06)	-0·43 (-1·75 to 0·89)	…	-0·80 (-2·85 to 1·24)	…	…	…	…	-0·34 (-2·19 to 1·50)	…	-0·14 (-2·00 to 1·73)	0·09 (-1·81 to 1·98)	…	1·03 (-0·09 to 2·15)
< 100	**-0·26 (-0·47 to -0·05)**	…	-0·24 (-0·51 to 0·04)	-0·14 (-0·46 to 0·18)	-0·23 (-0·59 to 0·12)	-0·23 (-0·54 to 0·08)	-0·18 (-0·49 to 0·14)	-0·17 (-0·46 to 0·12)	-0·08 (-0·33 to 0·16)	-0·13 (-0·44 to 0·16)	0·11 (-0·30 to 0·51)	…	0·40 (-0·14 to 0·95)	…
Sponsors														
Without industry sponsors	**-1·17 (-2·12 to -0·21)**	-0·43 (-1·74 to 0·87)	…	-1·17 (-3·22 to 0·88)	…	…	…	…	…	…	-0·14 (-1·98 to 1·71)	0·08 (-1·79 to 1·96)	…	0·92 (-0·20 to 2·03)
With industry sponsors	-0·15 (-0·36 to 0·07)	…	-0·18 (-0·44 to 0·09)	-0·14 (-0·45 to 0·17)	-0·23 (-0·57 to 0·11)	-0·23 (-0·53 to 0·07)	-0·18 (-0·48 to 0·12)	-0·17 (-0·45 to 0·11)	-0·12 (-0·34 to 0·10)	-0·13 (-0·43 to 0·15)	0·09 (-0·30 to 0·47)	…	0·37 (-0·16 to 0·89)	…

*Negative effect sizes indicate superiority of the specific intervention against placebo control.

a We excluded the trials with male-to-female ratio= 1

Subgroup network meta-analyses of each drug for discontinuation due to adverse events compared with placebo with odds ratio (95% CrI)*

Characteristics	Fluoxetine	Desipramine	Duloxetine	Venlafaxine	Mirtazapine	Sertraline	Citalopram	Escitalopram	Paroxetine	Nefazodone	Imipramine	Amitriptyline	Clomipramine
All trials	1·03 (0·50 to 2·70)	2·85 (0·83 to 21·80)	**2·80 (1·20 to 9·42)**	**3·19 (1·01 to 18·70)**	1·36 (0·41 to 10·99)	2·94 (0·94 to 17·19)	1·13 (0·45 to 3·66)	1·64 (0·46 to 13·49)	1·59 (0·77 to 3·95)	1·29 (0·30 to 21·89)	**5·49 (1·96 to 20·86)**	0·10 (0·02 to 32·16)	1·27 (0·36 to 8·33)
Sex Ratio[a]													
Male-to-female ratio < 1	1·05 (0·38 to 4·62)	2·88 (0·81 to 24·98)	**2·89 (1·14 to 11·72)**	…	1·34 (0·40 to 10·39)	2·91 (0·90 to 18·15)	0·63 (0·17 to 5·01)	1·58 (0·46 to 13·12)	1·19 (0·50 to 3·40)	1·28 (0·28 to 25·09)	**5·08 (1·75 to 22·12)**	…	0·93 (0·25 to 7·04)
Male-to-female ratio > 1	0·83 (0·29 to 4·20)	…	…	3·04 (0·87 to 21·36)	…	…	…	…	3·42 (0·82 to 54·08)	…	…	0·07 (0·01 to 30·05)	…
Mean Age													
< 13 years	1·85 (0·62 to 10·17)	…	2·80 (0·89 to17·14)	3·18 (0·98 to 19·63)	1·33 (0·40 to 9·94)	**12·55 (2·70 to 554.0)**	0·62 (0·16 to 4·90)	0·45 (0·09 to 12·42)	3·61 (0·93 to 51·31)	…	…	…	…
≥ 13 years	0·56 (0·20 to 2·28)	2·80 (0·79 to 23·53)	3·03 (0·87 to 24·22)	…	…	0·59 (0·14 to 5·90)	1·23 (0·39 to 6·65)	2·61 (0·50 to 184·77)	1·18 (0·48 to 3·44)	…	**5·05 (1·68 to 22·59)**	0·06 (0·02 to 30·35)	0·90 (0·23 to 7·17)
Treatment durations													
< 8 weeks	2·37 (0·36 to 5000)	2·68 (0·72 to 23·32)	…	…	…	…	…	…	…	…	…	…	…
≥8 weeks	0·87 (0·41 to 2·25)	…	**2·56 (1·15 to 7·97)**	**3·29 (1·11 to 17·51)**	1·35 (0·43 to 9·91)	**3·03 (1·02 to 16·01)**	1·15 (0·49 to 3·43)	1·61 (0·48 to 12·70)	1·64 (0·82 to 3·86)	1·35 (0·33 to 21·70)	**6·22 (2·38 to 22·47)**	0·06 (0·02 to 28·75)	1·35 (0·41 to 7·55)
Symptoms Severity													
Mild to moderate	…	…	…	…	…	…	…	…	1·37 (0·58 to 4·26)	…	**5·56 (1·99 to 23·62)**	0·06 (0·01 to 32·91)	…
Moderate to severe	0·86 (0·38 to 2·51)	2·75 (0·75 to 23·46)	**2·56 (1·04 to 9·44)**	3·07 (0·90 to 20·51)	1·33 (0·40 to 10·69)	2·84 (0·83 to 19·40)	1·09 (0·41 to 3·88)	1·57 (0·44 to 13·70)	1·77 (0·52 to 11·88)	1·26 (0·28 to 24·77)	…	…	1·32 (0·28 to 20·54)
Co-morbid													
No co-morbidity	2·61 (0·41 to 5977)	**9·54 (2·03 to 585)**	…	**3·19 (1·01 to 18·29)**	1·37 (0·42 to 10·00)	…	1·13 (0·45 to 3·62)	…	0·06 (0·01 to 6·33)	1·27 (0·29 to 21·20)	…	0·04 (0·01 to 35·77)	0·05 (0·01 to 8·37)
With co-morbidity	0·87	0·04	**2·55**	…	…	3·01	…	1·61	1·88	…	**6·63**	…	…

	(0·40 to 2·37)	(0·01 to 5·97)	**(1·10 to 8·57)**			(0·96 to 17·77)		(0·46 to 12·74)	(0·90 to 5·06)		**(2·41 to 27·25)**		
Risk bias													
Low and unclear risk bias	1·06 (0·37 to 4·92)	2·71 (0·73 to 23·56)	**2·93 (1·10 to 12·90)**	…	…	…	…	0·42 (0·08 to 12·96)	2·11 (0·81 to 8·87)	1·21 (0·26 to 24·10)	…	0·06 (0·02 to 33·80)	1·61 (0·39 to 18·27)
High risk bias	0·84 (0·30 to 3·82)	…	…	3·12 (0·96 to 18·99)	1·34 (0·40 to 10·51)	2·89 (0·88 to 18·12)	1·11 (0·43 to 3·71)	2·64 (0·52 to 171·14)	0·88 (0·28 to 4·14)	…	**4·47 (1·43 to 22·33)**	…	…
Sample Size													
≥ 100	2·52 (0·49 to 181·29)	2·67 (0·72 to 23·60)	…	…	…	…	…	…	0·04 (0·01 to 6·27)	…	…	0·06 (0·01 to 35·74)	…
< 100	0·65 (0·28 to 1·82)	…	2·24 (0·99 to 6·80)	**3·32 (1·13 to 17·10)**	1·33 (0·42 to 9·77)	**3·09 (1·06 to 15·80)**	1·16 (0·50 to 3·38)	1·62 (0·48 to 12·72)	1·88 (0·94 to 4·70)	1·32 (0·31 to 20·36)	**6·75 (2·66 to 25·00)**	…	1·56 (0·48 to 8·96)
Sponsors													
Without industry sponsors	2·65 (0·49 to 257)	2·65 (0·71 to 23·33)	…	…	…	…	…	…	…	…	…	0·03 (0·02 to 31·54)	…
With industry sponsors	0·81 (0·37 to 2·24)	…	**2·47 (1·11 to 7·60)**	**3·33 (1·15 to 16·75)**	1·36 (0·42 to 9·30)	**3·05 (1·05 to 15·81)**	1·16 (0·50 to 3·38)	1·61 (0·47 to 12·91)	1·65 (0·83 to 3·82)	1·35 (0·33 to 19·81)	**6·23 (2·44 to 21·99)**	…	1·36 (0·43 to 7·50)

*OR<1 indicate superiority of the specific intervention against placebo control.

[a] We excluded the trials with male-to-female ratio= 1

Appendix 17

Sensitivity network meta-analyses

Sensitivity network meta-analysis for response rate outcome by omitting the trials where only data on 'remission', but not on 'response' was reported

NEF											
1·19 (0·55 to 3·09)	**DUL**										
1·02 (0·36 to 4·11)	0·81 (0·33 to 2·79)	**DES**									
1·28 (0·62 to 3·09)	1·09 (0·68 to 1·65)	1·28 (0·41 to 3·10)	**FLU**								
1·31 (0·60 to 3·42)	1·16 (0·58 to 2·10)	1·36 (0·40 to 3·41)	1·00 (0·59 to 1·82)	**ESC**							
1·68 (0·57 to 3·89)	1·23 (0·53 to 2·45)	1·43 (0·38 to 3·84)	1·14 (0·53 to 2·16)	1·12 (0·47 to 2·26)	**SER**						
1·86 (0·74 to 3·88)	1·37 (0·72 to 2·35)	1·59 (0·48 to 3·90)	1·27 (0·74 to 2·02)	1·24 (0·65 to 2·18)	1·07 (0·55 to 2·40)	**PAR**					
2·11 (0·78 to 4·64)	1·54 (0·75 to 2·80)	1·80 (0·51 to 4·58)	1·43 (0·78 to 2·39)	1·40 (0·66 to 2·62)	1·39 (0·57 to 2·84)	1·18 (0·59 to 2·10)	**VEN**				
1·93 (0·88 to 5·31)	1·55 (0·83 to 3·25)	1·47 (0·57 to 5·22)	1·47 (0·84 to 2·86)	1·40 (0·74 to 3·01)	1·32 (0·64 to 3·27)	1·19 (0·66 to 2·44)	1·05 (0·55 to 2·32)	**CIT**			
2·12 (1·09 to 4·74)	**1·70 (1·11 to 2·71)**	1·62 (0·69 to 4·85)	**1·62 (1·20 to 2·24)**	1·53 (0·99 to 2·53)	1·45 (0·81 to 2·86)	1·31 (0·90 to 1·97)	1·16 (0·73 to 1·97)	1·02 (0·63 to 1·77)	**PBO**		
2·33 (1·04 to 6·64)	2·13 (0·97 to 4·09)	2·49 (0·67 to 6·52)	1·98 (0·97 to 3·59)	1·94 (0·87 to 3·79)	1·60 (0·75 to 4·09)	1·46 (0·84 to 2·79)	1·27 (0·65 to 2·95)	1·31 (0·57 to 2·61)	1·20 (0·65 to 2·02)	**IMP**	
2·85 (1·04 to 11·27)	2·28 (0·93 to 7·39)	2·18 (0·71 to 10·74)	2·18 (0·92 to 6·66)	2·06 (0·83 to 6·82)	1·95 (0·74 to 7·19)	1·83 (0·85 to 4·79)	1·56 (0·62 to 5·27)	1·86 (0·54 to 4·70)	1·70 (0·59 to 3·88)	1·14 (0·46 to 3·75)	**CLO**
3·25 (0·72 to 56·37)	2·62 (0·62 to 38·70)	2·52 (0·56 to 46·77)	2·50 (0·60 to 36·82)	2·37 (0·54 to 36·01)	2·24 (0·52 to 36·58)	2·01 (0·48 to 30·11)	1·78 (0·41 to 27·41)	1·57 (0·36 to 24·91)	4·75 (0·37 to 21·72)	1·29 (0·29 to 20·47)	0·91 (0·20 to 17·17)	**AMI**

Treatment Response rate (OR with 95% CrI)

Drugs are reported in order of ranking of response rate. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining treatment and the row-defining treatment. An OR value higher than 1 favors the column-defining treatment. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. Significant results are bolded and underscored. AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, CrI=credibility interval, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, NEF=nefazodone, OR=odds ratio, PAR=paroxetine, PBO=placebo, SER=sertraline, VEN=venlafaxine

Sensitivity network meta-analysis for primary outcomes by omitting the unpublished trials

FLU	0·15 (0·04 to 1·45)	**0·29 (0·12 to 0·88)**	0·35 (0·04 to 1·30)	0·59 (0·20 to 2·94)	0·27 (0·06 to 2·59)	0·33 (0·04 to 1·22)	0·58 (0·14 to 1·61)	**0·18 (0·03 to 0·61)**	0·11 (0·03 to 65·15)	0·87 (0·41 to 2·33)	0·31 (0·08 to 2·91)	…
-0·15 (-1·45 to 1·15)	**DES**	2·28 (0·20 to 9·66)	1·95 (0·12 to 9·18)	1·95 (0·49 to 22·44)	3·71 (0·17 to 18·02)	1·84 (0·11 to 8·78)	3·27 (0·34 to 13·53)	0·99 (0·08 to 4·44)	0·28 (0·09 to 393·86)	2·89 (0·84 to 22·28)	1·01 (0·21 to 19·95)	…
-0·19 (-1·19 to 0·80)	-0·04 (-1·58 to 1·49)	**DUL**	1·13 (0·13 to 4·43)	1·73 (0·56 to 10·26)	2·11 (0·18 to 8·79)	1·06 (0·12 to 4·15)	1·85 (0·40 to 5·71)	0·57 (0·09 to 2·12)	0·31 (0·08 to 205·59)	**2·56 (1·11 to 8·49)**	0·92 (0·23 to 9·73)	…
-0·35 (-1·60 to 0·90)	-0·20 (-1·81 to 1·42)	-0·16 (-1·65 to 1·32)	**SER**	2·02 (0·53 to 18·48)	0·91 (0·18 to 15·17)	1·63 (0·12 to 7·12)	1·37 (0·37 to 10·54)	0·35 (0·09 to 3·65)	0·32 (0·10 to 311·04)	3·00 (0·96 to 17·18)	1·05 (0·23 to 16·39)	…
-0·40 (-1·65 to 0·84)	-0·25 (-1·86 to 1·35)	-0·21 (-1·69 to 1·28)	-0·05 (-1·61 to 1·51)	**CIT**	0·93 (0·08 to 3·75)	0·47 (0·05 to 1·79)	0·82 (0·17 to 2·42)	**0·25 (0·04 to 0·88)**	0·14 (0·03 to 93·72)	1·13 (0·45 to 3·63)	1·02 (0·10 to 4·06)	…
-0·41 (-1·65 to 0·83)	-0·26 (-1·87 to 1·34)	-0·22 (-1·71 to 1·26)	-0·06 (-1·61 to 1·50)	-0·01 (-1·56 to 1·55)	**ESC**	1·04 (0·06 to 5·10)	1·80 (0·18 to 7·72)	0·55 (0·04 to 2·51)	0·20 (0·05 to 203·62)	1·59 (0·45 to 12·82)	0·56 (0·12 to 11·49)	…
-0·44 (-1·69 to 0·81)	-0·29 (-1·90 to 1·31)	-0·24 (-1·73 to 1·24)	-0·09 (-1·65 to 1·48)	-0·04 (-1·60 to 1·52)	-0·02 (-1·57 to 1·53)	**VEN**	1·46 (0·40 to 11·28)	0·37 (0·09 to 3·96)	0·40 (0·10 to 341·53)	**3·21 (1·03 to 18·52)**	1·13 (0·25 to 17·33)	…
-0·47 (-1·53 to 0·58)	-0·32 (-1·78 to 1·15)	-0·28 (-1·61 to 1·06)	-0·12 (-1·53 to 1·29)	-0·07 (-1·49 to 1·35)	-0·06 (-1·47 to 1·35)	-0·03 (-1·45 to 1·38)	**PAR**	**0·24 (0·09 to 0·94)**	0·22 (0·06 to 135·24)	1·81 (0·87 to 4·82)	0·79 (0·27 to 3·71)	…
-0·58 (-1·80 to 0·64)	-0·43 (-2·02 to 1·16)	-0·39 (-1·85 to 1·08)	-0·23 (-1·78 to 1·32)	-0·18 (-1·72 to 1·38)	-0·17 (-1·71 to 1·37)	-0·14 (-1·69 to 1·40)	-0·11 (-1·33 to 1·11)	**IMP**	0·74 (0·18 to 551·57)	**5·95 (2·14 to 23·24)**	2·33 (0·59 to 19·69)	…
-0·66 (-2·43 to 1·11)	-0·51 (-2·56 to 1·53)	-0·47 (-2·42 to 1·48)	-0·31 (-2·32 to 1·70)	-0·26 (-2·27 to 1·75)	-0·25 (-2·25 to 1·75)	-0·22 (-2·23 to 1·79)	-0·19 (-2·09 to 1·70)	-0·08 (-2·08 to 1·92)	**AMI**	0·07 (0·02 to 33·05)	5·84 (0·01 to 21·76)	…
-0·58 (-1·16 to 0·00)	-0·43 (-1·60 to 0·73)	-0·39 (-1·39 to 0·61)	-0·23 (-1·33 to 0·88)	-0·18 (-1·28 to 0·92)	-0·17 (-1·26 to 0·93)	-0·14 (-1·25 to 0·97)	-0·11 (-0·99 to 0·77)	0·00 (-1·08 to 1·08)	0·08 (-1·60 to 1·76)	**PBO**	0·69 (0·10 to 2·36)	…
-0·95 (-2·84 to 0·95)	-0·80 (-2·96 to 1·35)	-0·76 (-2·82 to 1·31)	-0·60 (-2·72 to 1·52)	-0·55 (-2·67 to 1·56)	-0·54 (-2·65 to 1·58)	-0·52 (-2·63 to 1·60)	-0·48 (-2·05 to 1·10)	-0·37 (-2·36 to 1·62)	-0·29 (-2·75 to 2·17)	-0·37 (-2·18 to 1·45)	**CLO**	…
-1·69 (-2·73 to -0·67)	**-1·55 (-3·07 to -0·04)**	**-1·50 (-2·86 to -0·14)**	-1·34 (-2·81 to 0·13)	-1·29 (-2·76 to 0·18)	-1·28 (-2·74 to 0·19)	-1·26 (-2·73 to 0·22)	-1·23 (-2·54 to 0·09)	-1·12 (-2·57 to 0·34)	-1·04 (-2·97 to 0·90)	**-1·12 (-2·09 to -0·14)**	-0·74 (-2·80 to 1·31)	**NOR**

Treatment Efficacy (mean overall change in symptoms, SMD with 95% CrI) Tolerability (discontinuation due to adverse events, OR with 95% CrI)

Drugs are reported in order of efficacy ranking. The estimate is located at the intersection of the column-defining treatment and the row-defining treatment. For efficacy (mean change in symptoms), a SMD below 0 favors the column-defining treatment. For tolerability (discontinuation due to adverse events), an OR below 1 favors the row-defining treatment. To obtain SMDs for comparisons in the opposing direction, negative values should be converted into positive values and vice-versa. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. Significant results are bolded and underscored. AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, CrI=credibility interval, DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, NOR=nortriptyline, OR=odds ratio, PBO=placebo, PAR=paroxetine, SER=sertraline, SMD=standardized mean difference, VEN=venlafaxine.