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

Andrea Cipriani, PhD,[1] Xinyu Zhou, PhD,[2] Cinzia Del Giovane, PhD,[3] Sarah E. Hetrick, DPsych,[4] Bin Qin, MD,[2] Craig Whittington, PhD,[5] Prof David Coghill, MD,[6] Yuqing Zhang, MD, [2] Prof Philip Hazell, PhD,[7] Stefan Leucht, MD,[8] Prof Pim Cuijpers, PhD,[9] Juncai Pu, MD,[2] David Cohen, PhD,[10] Arun V. Ravindran, PhD,[11] Yiyun Liu, MD,[2] Prof Kurt D. Michael, PhD,[12] Lining Yang, MD,[2] Lanxiang Liu, MD,[2] Prof Peng Xie, MD [2]

[1] Department of Psychiatry, University of Oxford, Oxford, UK; [2] Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University, Chongqing, China; [3] Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Italy; [4] Orygen, The National Centre of Excellence in Youth Mental Health, University of Melbourne, Australia; [5] Research Department of Clinical, Educational and Health Psychology, University College London, UK; [6] Division of Neuroscience, School of Medicine, University of Dundee, UK & Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Australia; [7] Discipline of Psychiatry, Sydney Medical School, Concord West, Australia; [8] Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany; [9] Department of Clinical, Neuro and Developmental Psychology, VU University Amsterdam, The Netherlands; [10] Department of Child and Adolescent Psychiatry, Hôpital Pitié–Salpétrière, Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Paris, France ; [11] Department of Psychiatry, University of Toronto and Division of Mood and Anxiety Disorders, Centre for Addiction and Mental Health, Toronto, Canada; [12] Department of Psychology, Appalachian State University, Boone, NC, USA.

Correspondence to:

Andrea Cipriani
Department of Psychiatry, University of Oxford
Warneford Hospital
Oxford, UK
Tel: +44 (0)1865 226393
Email: andrea.cipriani@psych.ox.ac.uk

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

Andrea Cipriani and Xinyu Zhou contributed equally to this work.

Abstract

Background: Major depressive disorder (MDD) is one of the most common mental disorders among children and adolescents. However, the question of whether to use pharmacological interventions in this population and which drug should be preferred is still matter of controversy. Consequently, we aimed to compare and rank antidepressants and placebo for MDD in young people.

Methods: We did a network meta-analysis to synthesise both direct and indirect evidence from relevant trials. We searched PubMed, the Cochrane Library, Web of Science, Embase, CINAHL, PsycINFO, LiLACS, regulatory agencies' websites and international registers for published and unpublished double-blind randomised controlled trials up to May 31st 2015, for the acute treatment of MDD in children and adolescents. The primary outcomes were efficacy (change in depressive symptoms) and tolerability (discontinuations due to adverse events). We also examined response rate, all-cause dropouts and suicidality. We assessed the quality of evidence using the GRADE framework. This study is registered with PROSPERO, number CRD42015016023.

Findings: We deemed 34 trials eligible, including 5,260 participants and 14 antidepressant treatments. The quality of evidence was rated as very low in the majority of comparisons. For efficacy, only fluoxetine was statistically significantly more effective than placebo (standardised mean difference: -0·50, 95% credible intervals [CrIs] -0·98 to -0·03). In terms of tolerability, fluoxetine was also better than duloxetine and imipramine (odds ratio [OR] 0·31, 95% CrI 0·13 to 0·95 and 0·23, 95% CrI 0·04 to 0·78, respectively), while imipramine, venlafaxine, and duloxetine had more discontinuations due to adverse events than placebo (OR 5·49, 95% CrI 1·96 to 20·86; 3·19, 95% CrI 1·01 to 18·70 and 2·80, 95% CrI 1·20 to 9·42,

respectively). In terms of heterogeneity, the global I^2 values were 38·63% for efficacy and 0% for tolerability.

Interpretation: Balancing the risk-benefit profile of antidepressants in the acute treatment of MDD, these drugs do not seem to offer a clear advantage for children and adolescents. Fluoxetine is probably the only antidepressant to consider when a pharmacological treatment is indicated, however patients should be carefully monitored for the risk of increased suicidality.

Funding: National Basic Research Program of China (973 Program) (Grant No. 2009CB918300).

Key words: Antidepressants, depression, children, adolescents, network meta-analysis

Introduction

Major depressive disorder (MDD) is common in young people with an estimated point prevalence between 2-3% in school-age children (6-12 years) and 3-9% in adolescents (13-18 years).[1] Compared with adults, children and adolescents with MDD are still under-diagnosed and under-treated,[2] possibly because they tend to present with rather undifferentiated depressive symptoms, e.g., irritability, aggressive behaviors and school refusal.[3] Consequences of depressive episodes in these patients include serious impairments in social functioning, as well as suicidal ideation and attempts.[4] Even though psychological treatments are still considered the first line treatment in many clinical guidelines,[5,6] antidepressants are widely used in the treatment of depression in children and adolescents and the rate of prescription has increased over time.[7] However, in 2004, the Food and Drug Administration (FDA) cautioned practitioners on the use of antidepressants in children and adolescents about increased suicide risk.[8] As a consequence, the question of whether to use antidepressant agents for the treatment of MDD in young people and, if so, which antidepressant would be preferred, remains controversial.[3]

Previous pairwise meta-analyses have tried to evaluate the magnitude of efficacy of all types of antidepressants[9,10] and also to identify factors associated with treatment efficacy.[11] However, they have been inconclusive because they were not able to generate clear hierarchies among available treatments, as many antidepressants have not been compared head to head. Therefore, we conducted a network meta-analysis to comprehensively compare and rank antidepressants for the acute treatment of MDD in children and adolescents.

Methods

Search strategy and selection criteria

We identified double-blind randomised controlled trials (RCTs) published up to May 31, 2015, comparing any antidepressant with placebo or another active antidepressant as oral monotherapy in the acute treatment of children and adolescents (aged from 6 to 18 years old at enrollment in the primary study), with a primary diagnosis of MDD according to standardized diagnostic criteria by searching PubMed, the Cochrane Central Register of Controlled Trials, Web of Science, Embase, CINAHL, PsycINFO, and LiLACS from date of inception. We also screened international trial registers, relevant reports on the FDA website and hand-searched key scientific journals in the field for published and unpublished studies (see Appendix 1 and 2 for details on the review protocol and the search strategy). There was no restriction on language. For data about suicidality we also referred to the Columbia re-analysis of the FDA report[12] and additionally searched the Medicines and Healthcare Products Regulatory Agency database and the pharmaceutical company websites for unpublished data. Study authors and drug manufacturers were contacted to supplement incomplete reports of the original papers or provide data for unpublished studies.

Study selection, data extraction and quality assessment/risk of bias

We included all the following antidepressant interventions, but only if administered within the therapeutic dose range: amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline and venlafaxine. Trials involving patients with comorbid non-affective psychiatric disorders were included; however, RCTs recruiting participants with treatment resistant depression, with treatment duration of less than 4 weeks, or with an overall sample size of less than 10 patients were excluded. Four investigators (AC, SEH, BQ, YL) selected studies independently, and four investigators (YZ, BQ, YL, LY) independently reviewed the main reports and supplementary materials, extracted the relevant information from the included trials using a predefined data extraction sheet and assessed the risk of bias, using the Cochrane risk

of bias tool.[13] Any discrepancies were resolved by consensus and arbitration by a panel of other investigators within the review team (AC, SEH, DC, SL, XZ, PX).

Outcomes

We considered the mean overall change in depressive symptoms from baseline to endpoint and the proportion of patients who discontinued treatment due to any adverse events for our primary analyses. To measure improvement in depressive symptoms we used the following rating scales: 1) the Children's Depression Rating Scale Revised (CDRS-R) is a clinician-rated scale adapted for children and adolescents from the Hamilton Depression Rating Scale (HAMD), which is a tool validated and commonly used in adults (both CDRS-R and HAMD have good reliability and validity - Appendix 1); 2) the Beck Depression Inventory and the Children's Depression Inventory are the two most commonly used among depression symptom severity self-rated scales. Where depression symptoms had been measured using more than one standardised rating scale, we used a pre-defined hierarchy, based on psychometric properties, frequency of use in children and adolescents and consistency of use across included trials (Appendix 3). Secondary outcomes included response rate (estimated as the proportion of patients who achieved a reduction of 50% or more in depression rating score, or who scored much or very much improved on the Clinical Global Impression (CGI)), all-cause discontinuation and suicidal behaviour or ideation (Appendix 1). We defined acute treatment as eight-week treatment for both efficacy and tolerability analyses.[14] If eight-week data were not available, we used data ranging between four and sixteen weeks (we gave preference to the time point given in the original study as the study endpoint).

Statistical analysis

Details of the applied statistical approaches are provided in Appendix 1 and 4. First, we conducted pairwise meta-analyses using the random-effects model with STATA 13·0. The

standardised mean difference (SMD) was calculated as the effect size for continuous outcomes and the odds ratio (OR) was calculated for dichotomous outcomes, both with a 95% confidence interval (CI). We assessed the presence of heterogeneity statistically within each pairwise comparison using the I^2 statistic and p value from a standard test.[13] We also used the funnel plot and Egger's test to detect publication bias, if at least ten studies were available.[13] Second, we performed a random-effects network meta-analysis within a Bayesian framework with WinBUGS 1·4·3 and further analysis with STATA 13·0 and R 3·2·2. We summarised the results of network meta-analysis using effect sizes (SMD or OR) and their credible intervals (CrI).[15] See Appendix 4 for details about the WinBUGS codes used. The pooled estimates were obtained using the Markov Chains Monte Carlo method. Two Markov chains were run simultaneously with different arbitrarily chosen initial values. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic were assessed.[16] A common heterogeneity parameter was assumed for all comparisons and we assessed the global heterogeneity using the I^2 statistic with 'gemtc' in R 3·2·2.[17] Inconsistency between direct and indirect sources of evidence was statistically assessed globally (by comparing the fit and parsimony of consistency and inconsistency models) and locally (by calculating the difference between direct and indirect estimates in all closed loops in the network).[18] The node splitting method also was used to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence.[19] We estimated the ranking probabilities for all treatments of being at each possible rank for each intervention. The treatment hierarchy were summarized and reported as surface under the cumulative ranking curve (SUCRA).[20] We also performed the comparison-adjusted funnel plot for the network meta-analysis, to detect the presence of any dominant publication bias in network meta-analysis.[20] In addition, we assessed the quality of evidence contributing to each network estimate 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 for the primary

outcomes.[21]

To determine whether the results were affected by study characteristics, we performed subgroup network meta-analyses in WinBUGS for primary outcomes according to the following variables (see Appendix 5 for details): (i) gender ratio; (ii) age group; (iii) treatment duration; (iv) severity of symptoms; (v) comorbid psychiatric disorder; (vi) quality of study; (vii) sample size; and (viii) sponsorship. In addition, we performed sensitivity network meta-analyses for primary outcomes by omitting (i) the unpublished trials and (ii) the trials where response was imputed.

Role of the funding source

The funders of the study had no role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit for publication. AC, XZ, CDG, and PX had full access to all the data, and AC and PX were responsible for the decision to submit for publication.

Results

Overall 5,794 citations were identified by the search and 165 potentially eligible articles were retrieved in full text (Figure 1). We then excluded 138 reports, but managed to include four additional studies from trial registers and pharmaceutical companies' website, ending up with 31 publications describing 34 parallel RCTs (5,260 patients) published between 1986 and 2014 and comparing 14 antidepressants or placebo (Figure 1 and Table 1). Among the included trials, seven were unpublished trials and two were not in English (see Appendix 6 for the reference list of included studies). The mean study sample size was 159 participants, ranging between 23 and 463 patients. About half of the total sample was female (n=2783; 52·9%) and the mean age was 13·0 (SD 2·87) years. Overall, 3,106 participants were randomised to an

active drug and 2,154 to placebo. The median duration of the acute treatment was 8 weeks (range: 5-12 weeks) and the great majority of trials (n=28; 82·4%) enrolled children and adolescents with moderate-to-severe depressive symptoms. Half of the trials (n=17) recruited patients from Northern America, 14·7% (n=5) from cross-continental and 11·8% (n=4) from Europe (of the remaining trials, four recruited participants from other countries and four trials did not specify). The majority of trials (n=22; 64·7%) were funded by pharmaceutical companies. In terms of study quality, ten trials were rated as high risk of bias, twenty trials as moderate and four as low (Appendix 7).

Figure 2 shows the network of eligible comparisons for efficacy (see Appendix 8 for the graphical representation of the other networks). All antidepressant drugs, except for clomipramine, had at least one placebo-controlled trial and five of them were directly compared with at least one other active drug. Detailed results of pairwise meta-analyses are given in the Appendix 9. Fluoxetine, sertraline and escitalopram were statistically more efficacious than placebo; paroxetine showed a significant benefit in terms of efficacy compared with clomipramine, and fluoxetine was superior to nortriptyline. For tolerability, duloxetine, imipramine, sertraline and venlafaxine were less tolerated than placebo; and paroxetine than imipramine (Appendix 9b).

Figure 3 presents the league table with the results of the network meta-analyses for the primary outcomes. In terms of efficacy, only fluoxetine was better than placebo (SMD = -0·50; 95% CrI -0·98 to -0·03). Nortriptyline was significantly less effective than many other antidepressants and also placebo (SMDs ranging between -1·64 and -1·14). In terms of tolerability, fluoxetine was statistically significantly better tolerated than duloxetine and imipramine (OR 0·31, 95% CrI 0·13 to 0·95 and 0·23, 95% CrI 0·04 to 0·78, respectively), and citalopram and paroxetine were significantly better tolerated than imipramine alone (OR 0·27, 95% CrI 0·04 to 0·96 and 0·22, 95% CrI 0·08 to 0·87, respectively); interestingly, imipramine, venlafaxine and duloxetine were significantly less well tolerated than placebo (OR 5·49, 95%

CrI 1·96 to 20·86; 3·19, 95% CrI 1·01 to 18·70 and 2·80, 95% CrI 1·20 to 9·42, respectively). Results from secondary outcomes did not show material differences and confirmed the findings from primary outcomes (the only exception was nefazodone which was more efficacious and better tolerated in the secondary analyses, but this evidence was based on only one unpublished trial of limited quality, which constitutes a major limitation for the reliability of findings with this drug –Appendix 10). In Figure 4 we present the network meta-analyses results of the suicide-related outcome (see Table 2 for the actual number of patients with suicidal behavior or ideation). Venlafaxine was associated with a significantly increased risk of suicidal behavior/ideation compared to placebo (OR 0·13, 95% CrI 0·00 to 0·55) and many other antidepressants (namely, escitalopram, imipramine, duloxetine, fluoxetine and paroxetine). Fluoxetine, paroxetine, citalopram and sertraline were also associated with an increased risk of suicidality compared with placebo (ORs ranging between 0·57, 95% CrI 0·06 to 2·05 for sertraline and 0·90, 95% CrI 0·49 to 1·49 for fluoxetine), but the difference was not statistically significant.

The common heterogeneity SD was 0.68 (95% CrI, 0·47 to 0·94) for efficacy, 0·42 (95% CrI, 0·02 to 0·94) for tolerability, 0·22 (95% CrI, 0·01 to 0·50) for response rate, 0·32 (95% CrI, 0·03 to 0·67) for all-cause discontinuation, and 0·30 (95% CrI, 0·01 to 0·84) for suicide-related outcome. The global I^2 values were 38·63% for efficacy and 0% for tolerability. The test of global inconsistency showed a significant difference between the consistency and inconsistency models for efficacy ($p<0·0001$), but not for tolerability ($p=0·8432$) (Appendix 11 and 12). Tests of local inconsistency revealed that the percentages for inconsistent loops were to be expected based on the empirical data (two of four comparison loops for the efficacy outcome and zero of two for tolerability outcome; for details of the assessments of consistency, Appendix 11b). The test of inconsistency from the node-splitting model showed significant difference between some comparisons in primary efficacy, but not for tolerability (Appendix 11c). The comparison-adjusted funnel plots of the network meta-analysis for

primary outcomes were not suggestive of any publication bias (Appendix 12).

The ranking of treatments based on cumulative probability plots and SUCRAs is presented in Appendix 13. In terms of efficacy, the most effective treatment was fluoxetine (76·6%) and he least effective was nortriptyline (3·7%). In terms of tolerability, fluoxetine was the best drug (75·7%) and imipramine the worst (13·3%). According to GRADE, the quality of evidence for primary outcomes were rated as very low for most comparisons. It was very low for overall ranking of treatment in terms of efficacy and low for tolerability (Appendix 14 and 15). We also explored the influence of several potential moderator variables for the primary outcomes in subgroup analyses, which did not produce material differences for most of these comparisons (Appendix 16). Pre-planned sensitivity analyses did not affect the main results (Appendix 17).

Discussion

This network meta-analysis represents the most comprehensive synthesis of data for currently available pharmacological treatments for children and adolescents with acute MDD. Our results can be summarized as follows: only fluoxetine was statistically significantly more effective than placebo, however, and the corresponding standardised mean difference of 0·50 is considered to be a medium effect size.[22] However, the large confidence interval and its upper limit close to the point of no difference raise the question whether this estimate is robust enough to inform clinical practice. In comparison with placebo, fluoxetine was significantly more effective in trials without industry sponsors, however a possible explanation is that trials without industry sponsors tend to have a smaller sample size, which may result in an exaggerated treatment effect.[23] Compared with other antidepressants, fluoxetine was significantly more effective than nortriptyline and in terms of discontinuations due to adverse events it was better tolerated than imipramine. However, the clinical interpretation of these findings is limited not only by the uncertainty around these estimates but also by the potential

bias due to selective reporting and the small number of trials in each node. We did our best to retrieve all available unpublished information and also contacted study authors for supplemental data, but we cannot rule out the possibility that some unpublished studies are still missing or that published reports may overestimate the efficacy of treatments.[1024] Moreover, poor methodology and risk of bias within individual studies, as well as potential selective reporting are important factors to be considered when interpreting the results from this review. Without access to individual patient level data, we cannot be confident about the accuracy of information contained in published studies or even clinical study reports.

Since 2003, many international agencies, including the European Medicines Agency, the FDA in the US and the Medicines and Healthcare Products Regulatory Agency in the UK, have added a black box warning (the most serious type of warning) to the prescription drug labeling of antidepressants, indicating that they may increase the risk of suicidal thinking and behavior in some children and adolescents with MDD.[8] Our analysis found robust evidence to suggest a significantly increased risk for suicidality (suicidal behavior or ideation) for young people treated with venlafaxine. Fluoxetine, paroxetine, citalopram and sertraline were also found to be associated with increases in the risk of suicidality, but the differences were not statistically significant. Unfortunately, due to the lack of the data on suicidality for many antidepressants, it was not possible to comprehensively assess the risk of suicidality for all drugs. However, from a clinical perspective, the decision making process should always consider the overall clinical picture and patient management plans need to balance the risks and benefits. Children and adolescents taking antidepressant medications should be closely monitored regardless of the treatment chosen, particularly at the beginning of treatment.[5]

This study has some limitations. First, in the GRADE framework, many comparisons were assessed as low or very low quality, which largely restricts the interpretation of these results. In the network we found some inconsistency for efficacy, which was mainly determined by the loop of fluoxetine-nortriptyline-placebo (we did not find heterogeneity for the tolerability

outcome, probably because dropout rate is a harder outcome). We believe that this inconsistency may be a consequence of a cohort effect that relates to differing methodologies in the oldest studies compared to those conducted more recently. In fact, some evidence suggests that clinical trial quality of psychopharmacologic studies has changed significantly over the past 30 years[25] and other network meta-analyses confirmed similar findings.[26] Second, the review was restricted to trials involving children and adolescents with MDD. We excluded studies in which participants were described as having subsyndromal depressive symptoms, which is a significant proportion of patients seen in real world clinical settings. Similarly, we excluded patients with treatment resistant depression. We did this to reduce heterogeneity and inconsistency among trials in the network meta-analysis, but acknowledge that it limits the external validity of the results. In addition, omission of trials of treatment resistant depression may have led to an overestimation of efficacy in the present meta-analysis because treatment resistant patients are clearly a difficult to treat population. Third, we are aware of the recently published Restoring Study 329,[23] which revealed different results when the original protocol was enacted to analyze the data compared with the Original Study 329. Because Restoring Study 329 was published after our last update of the search, we included the original study data, which were biased in favour of paroxetine over placebo. Findings from our review, however, were not affected by the misleading results from this single study, as in our analysis paroxetine showed no differences in efficacy from placebo (and also an increased – though non-significant - risk of suicidality). The example of Restoring Study 329 supports the added value of network meta-analysis, which provides a more reliable estimate in terms of comparative efficacy.[27] Finally, there were too few studies to be able to perform a network meta-analysis that addressed the clinically important issue of antidepressant therapy for preventing relapse in child and adolescent depression. It should be noted that some of the adverse effects of antidepressants occur over a longer period, meaning that positive results from short term studies need to be taken with great caution. However, there is some long term

data suggesting that fluoxetine can be well tolerated and effective in reducing the risk of relapse in children and adolescents with MDD after 32 weeks of treatment.[28] These data should be critically analysed and contextualized at the individual patient level (many adolescent patients treated with MDD are treated with medications in adulthood and efficacy of drugs can change over time),[14] but they support in principle the use of fluoxetine as a long term treatment, if effective in the acute phase.

The findings of this comprehensive network meta-analysis provide limited evidence that fluoxetine may reduce depressive symptoms in children and adolescents with MDD and the extent to which this reduction is clinically meaningful is still uncertain. Notwithstanding these caveats, fluoxetine may be still considered the 'best bet' among antidepressants when a pharmacological treatment is indicated. Other antidepressants do not seem to be suitable as routine treatment options. In the clinical care of young people with MDD, clinical guidelines recommend psychotherapy (especially cognitive-behavioral or interpersonal therapy)[5,29] as the first line intervention and fluoxetine should be considered only for those patients with moderate to severe depression (especially adolescents),[11] who do not have access to psychotherapy (like in low and middle income countries)[30] or have failed to respond to non-pharmacological interventions. Antidepressants are understudied in this population, and further research on moderators of treatment effect and possible novel interventions are needed. In all these cases, however, clinicians should carefully monitor for the emergence or exacerbation of suicidality and balance the risk-benefit profile of antidepressants during the acute treatment phase.

Acknowledgments:

We thank Professor Graham J. Emslie and Faculty Associate Taryn Mayes from the University of Texas (UT) Southwestern Medical Center in Dallas for providing unpublished data in this review. We also thank Professor Salvatore Gentile from the Department of Mental Health, ASL Salerno Mental Health Center, Italy for his valuable advice. Andrea Cipriani is supported by the NIHR Oxford Cognitive Health Clinical Research Facility.

Contributors

PX, XZ, BQ, CW, DCoh, YL, CDG, KDM, and YZ conceived and designed the study. AC and PX did the study. AC, XZ, BQ, YZ, JP, YL, LY and LL selected the articles and extracted the data. AC, CDG, and XZ analysed the data. AC, XZ and PX wrote the first draft of the report, and SEH, DCog, CW, SL, PH, SL, PC, AVR, and KDM helped to write the final version. All authors read and met the ICMJE criteria for authorship. All authors agree with the results and conclusions of the report.

382 **References**

383 1 Costello JE, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression?
384 *J Child Psychol Psychiatry* 2006; **47:** 1263–71.

385 2 Olfson M, Blanco C, Wang S, Laje G, Correll CU. National trends in the mental health care
386 of children, adolescents, and adults by office-based physicians. *JAMA Psychiatry* 2014;
387 **71**: 81-90.

388 3 Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet* 2012; **379**:
389 1056-67.

390 4 Hopkins K, Crosland P, Elliott N, Bewley S; Clinical Guidelines Update Committee B.
391 Diagnosis and management of depression in children and young people: summary of
392 updated NICE guidance. BMJ. 2015 Mar 4;350:h824.

393 5 National Institute for Health and Clinical Excellence, Depression: Management of
394 Depression in Primary and Secondary Care. Clinical Practice Guideline Number 23,
395 National Institute for Clinical Excellence, London, 2004.

396 6 American Academy of Child and Adolescent Psychiatry. Practice parameters for the
397 assessment and treatment of children and adolescents with depressive disorders. *J Am*
398 *Acad Child Adolesc Psychiatry* 2007; **46**: 1503–26

399 7 Bachmann CJ, Aagaard L, Burcu M, et al. Trends and patterns of antidepressant use in
400 children and adolescents from five western countries, 2005–2012. *Eur*
401 *Neuropsychopharmacol* 2016; **26:** 411–419..

402 8 U.S. Food and Drug Administration. Suicidality in children and adolescents being treated
403 with antidepressant medications. 15 October 2004.
404 www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalprodu
405 cts/ucm155488.htm. (accessed October 18, 2015)

406 9 Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation
407 antidepressants for depressive disorders in children and adolescents. *Cochrane*

Database Syst Rev 2012; **11:** CD004851.

10 Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004; **363**: 1341–5.

11 Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ. Efficacy of antidepressants in juvenile depression: meta-analysis. Br J Psychiatry. 2008; **193:** 10-7.

12 Hammad TA. Relationship between psychotropic drugs and pediatric suicidality. 16 August 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf (Accessed October 25, 2015).

13 Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0, updated March, 2011. http://handbook.cochrane.org (accessed October 20, 2015).

14 Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; **373:** 746–58.

15 Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008; **17:** 279–301.

16 Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. *J Comput Graph Stat* 1998; **7:** 434–55.

17 Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network meta-analysis using R: a review of currently available automated packages. *PLoS One* 2014; **9**: e115065.

18 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PloS One* 2013; **8:** e76654.

19 Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; **29**: 932–44.

20 Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for

presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64:** 163–71.

21 Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the Quality of Evidence from a Network Meta-Analysis. *PLoS One* 2014; **9:** e99682.

22 Cohen J. Statistical power analysis for the behavioral sciences (2nd ed). Hillsdale, NJ: Erlbaum, 1988.

23 Biau DJ, Kernéis S, Porcher R. Statistics in brief: the importance of sample size in the planning and interpretation of medical research. *Clin Orthop Relat Res* 2008; **466**: 2282–8.

24 Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015; **351**: h4320.

25 Brunoni AR, Tadini L, Fregni F. Changes in clinical trials methodology over time: a systematic review of six decades of research in psychopharmacology. *PLoS One* 2010; **5:** e9479.

26 Samara MT, Dold M, Gianatsi M, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. *JAMA Psychiatry* 2016; **73:** 199-210.

27 Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013; **159**: 130–7.

28 Emslie GJ, Heiligenstein JH, Hoog SL, et al. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 2004; **43**: 1397–405.

29 Zhou X, Hetrick SE, Cuijpers P, et al. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry* 2015; **14**: 207–22.

30 Kakuma R, Minas H, van Ginneken N, et al. Human resources for mental health care: current situation and strategies for action. *Lancet* 2011; 378: 1654-63.

Research in context panel

Evidence before this study

Even though psychological treatments are still considered the first line treatment, antidepressants are widely used in the treatment of depression in children and adolescents. Previous pairwise meta-analyses have been inconclusive because they could not generate clear hierarchies among available treatments, as many antidepressants have not been compared head to head.

Added value of this study

Our study provides a comprehensive systematic review and network meta-analysis of all available double-blind randomised trials, comparing any antidepressant with placebo or another active antidepressant as oral monotherapy in the acute treatment of major depression in children and adolescents (aged from 6 to 18 years). Our findings emphasise the fact that there are some significant differences with placebo and among antidepressants in the reduction of risk of specific clinical outcomes. For example, only fluoxetine is statistically significantly more effective than placebo and some other acitive drugs in reducing depressive symptoms or the number of discontinuations due to adverse events over a period of 8 weeks. Furthermore, we found robust evidence to suggest a significantly increased risk for suicidality (suicidal behavior or ideation) for young people treated with venlafaxine.

Implications of all the available evidence

Our study has several implications for clinical practice. First, our findings suggest that fluoxetine should be considered the best available choice when a pharmacological treatment is indicated for moderate to severe depression in people aged less than 18 years who do not have access to psychotherapy or have failed to respond to non-pharmacological interventions.

Other antidepressants do not seem to be suitable as routine treatment options. Second, antidepressants were found to be associated with an increased risk of suicidality in the young population, but the differences were not statistically significant. Due to the lack of the data on suicidality for many antidepressants, it was not possible to comprehensively assess the risk of suicidality for all drugs. However, from a clinical perspective, children and adolescents taking antidepressant medications should be closely monitored regardless of the treatment chosen, particularly at the beginning of treatment. Finally, we found that the methodology of the individual studies was poor. Together with selective reporting, these are important limitations to be considered when interpreting the results from studies in such a population. Without access to individual patient level data, we cannot be totally confident about the accuracy of information contained in published studies or even clinical study reports.

514 **Table 1 Summary of randomised controlled trials included in the systematic review and network meta-analysis**

515

Trial	Publication year	Diagnostic criteria	Treatments, N [dose range]	Treatment duration (weeks)	Age range [mean]	Female (%)	Recruiting area	Setting	Company Sponsor
003-045 Trial 1	2002	DSM-IV	MIR=82 [15-45 mg/d] PBO=44	8	7-18 [12·3]	50·8	Europe	Out	Organon
003-045 Trial 2	2002	DSM-IV	MIR=88 [15-45 mg/d] PBO=45	8	7-18 [12·0]	52·6	Europe	Out	Organon
Almeida-Montes 2005	2005	DSM-IV-TR	FLU=12 [20 mg/d] PBO=11	6	8-14 [11·4]	35·0	Mexico	Out	None[a]
Atkinson 2014	2014	DSM-IV-TR	DUL=117 [60-120 mg/d] FLU=117 [20-40 mg/d] PBO=103	10	7-17 [13·2]	52·2	United States, Finland, France, Germany, Russia, Slovakia, Estonia, Ukraine, South Africa	Out	Eli Lilly
Attari 2006	2006	DSM-IV	FLU=20 [0·5-2 mg/d/kg] NOR=20 [1-2 mg/d /kg]	8	7-16 [12·9]	50·0	Iran	Out	Not stated
B1Y-MC-HCCJ	1986	DSM III	FLU=21 [20-60 mg/d] PBO=19	6	12-17 [15·6]	55·0	Canada	In & Out	Eli Lilly
Berard 2006	2006	DSM-IV	PAR=187 [20-40 mg/d] PBO=99	12	13-18 [15·6]	64·0	Belgium, Italy, Mexico, United Kingdom, Spain, The Netherlands, Canada, South Africa, United Arab Emirates, Argentina.	Out	GlaxoSmithKline
Braconnier 2003	2003	DSM-IV	CLO=58 [75-150 mg/d] PAR=63 [20-40 mg/d]	8	12-20 [16·1]	60·3	France	NA	GlaxoSmithKline
CN104187	2002	DSM-IV	NEF=95 [100-300 mg/d] NEF=95 [200-600 mg/d] PBO=94	8	7-17 [NA]	NA	NA	NA	Bristol-Myers Squibb
Emslie 1997	1997	DSM III-R	FLU=48 [20 mg/d] PBO=48	8	7-17 [12·4]	45·8	United States	Out	None
Emslie 2002a	2002	DSM-IV	FLU=109 [10-20 mg/d] PBO=110	9	8-18 [16·5]	49·3	United States	Out	Eli Lilly

Emslie 2002b	2002	DSM-IV	NEF=99 [100-400 mg/d] PBO=96	8	12-17 [NA]	59·0	NA	NA	Bristol-Myers Squibb
Emslie 2006	2006	DSM-IV	PAR=104 [10-50 mg/d] PBO=102	8	7-17 [12·0]	46·8	United States and Canada	NA	GlaxoSmithKline
Emslie 2007	2007	DSM-IV	VEN=184 [37·5-225 mg/d] PBO=183	8	7-17 [12·3]	45·5	United States	Out	Wyeth Research
Emslie 2009	2009	DSM-IV	ESC=158 [10-20 mg/d] PBO=158	8	12-17 [14·6]	59·0	United States	Out	Forest Laboratories
Emslie 2014	2014	DSM-IV-TR	DUL=108 [60 mg/d] DUL=116 [30 mg/d] FLU=117 [20 mg/d] PBO=122	10	7-17 [13·0]	51·2	United States, Argentina, Canada, Mexico	Out	Eli Lilly
Findling 2009	2009	DSM-IV	FLU=18 [10-20 mg/d] PBO=16	8	12-17 [16·5]	14·7	United States	Out	Eli Lilly
Geller 1990	1990	DSM-III	NOR=12 [45-140 mg/d] PBO=19	8	12-17 [14·3]	45·2	United States	Out	None
Geller 1992	1992	DSM III	NOR=30 [10-140 mg/d] PBO=30	8	6-12 [9·7]	30·0	NA	Out	None
Hongfen 2009	2009	CCMD-3	FLU=30 [20 mg/d] VEN=30 [150 mg/d]	8	12-18 [15·8]	56·0	China	In & Out	Not stated
Hughes 1990	1990	DSM-III	IMP=13 [NA] PBO=14	6	6-12 [NA]	NA	NA	In	None
Keller 2001	2001	DSM-IV	IMP=95 [50-300 mg/d] PAR=93 [20-40 mg/d] PBO=87	8	12-18 [14·9]	62·2	United States, Canada	NA	GlaxoSmithKline
Klein 1998	1988	DSM-III-R	DES=23 [50-300 mg/d] PBO=22	6	13-18 [15·7]	66·7	United States	Out	None
Kutcher 1994	1994	DSM-III-R	DES=30 [200 mg/d] PBO=30	6	15-19 [17·8]	70·0	Canada	Out	None
Kye 1996	1996	K-SADS and RDC	AMI=18 [5 mg/d/kg] PBO=13	8	12-17 [14·8]	29·0	United States	Out	None
March 2004	2004	DSM-IV	FLU =109 [10-40 mg/d] PBO=112	12	12-17 [14·6]	54·4	United States	Out	None
NCT00812812	2009	DSM-IV-TR	PAR=29 [10-40 mg/d] PBO=27	8	7-17 [14·6]	60·7	Japan	NA	GlaxoSmithKline

Puig-Antich 1987	1987	K-SADS and RDC	IMP=20 [3·25-5 mg/d/kg] PBO=22	5	6-12 [9·1]	39·5	United States	In & Out	None
von Knorring 2006	2006	DSM-IV	CIT=124 [10-40 mg/d] PBO =120	12	13-18 [16·0]	NA	Europe	In & Out	Lundbeck
Wagner 2003 trial 1	2003	DSM-IV	SER=97 [50-200 mg/d] PBO=91	10	6-17 [NA]	50·5	United States, Costa Rica, India, Canada, Mexico	Out	Pfizer
Wagner 2003 trial 2	2003	DSM-IV	SER=92 [50-200 mg/d] PBO=96	10	6-17 [NA]	51·6	United States, Costa Rica, India, Canada, Mexico	Out	Pfizer
Wagner 2004	2004	DSM-IV	CIT=93 [20-40 mg/d] PBO=85	8	7-17 [12·1]	53·4	United States	NA	Forest Laboratories
Wagner 2006	2006	DSM-IV	ESC=132 [10-20 mg/d] PBO=136	8	6-17 [12·3]	51·9	United States	Out	Forest Laboratories

AMI: Amitriptyline; BDI: Beck Depression Inventory; CCMD-3: Chinese Classification of Mental Disorders-3rd version; CDI: Children Depression Inventory; CDRS-R: Children's Depression Rating Scale-Revised; CIT: Citalopram; CLO: Clomipramine; DES: Desipramine; DSM-III: Diagnostic and Statistical Manual of Mental Disorders-3rd Edition; DSM III-R: Diagnostic and Statistical Manual of Mental Disorders-3rd Edition Revised; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-4th Edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-4th Edition, Text Revision; DSRS: Depression Self-Rating Scale; DUL: Duloxetine; ESC: Escitalopram; FLU: Fluoxetine; HAMD-17: 17-item Hamilton Rating Scale for Depression; IMP: Imipramine; In: Inpatients; K-SADS: Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children; MADRS: Montgomery and Asberg Depression Rating Scale; MIR: Mirtazapine, NA: not available; NEF: Nefazodone; NOR: Nortriptyline; Out: Outpatients; PAR: Paroxetine; PBO: Placebo; RDC: Research Diagnostic Criteria; SER: Sertraline; VEN: Venlafaxine. * For references of included trials, please see Appendix 5.

[a] The authors stated that fluoxetine and placebo were donated by Eli Lilly, but this company was not involved in the design, planning, implementation, collection, analysis and presentation of the results of this study.

526

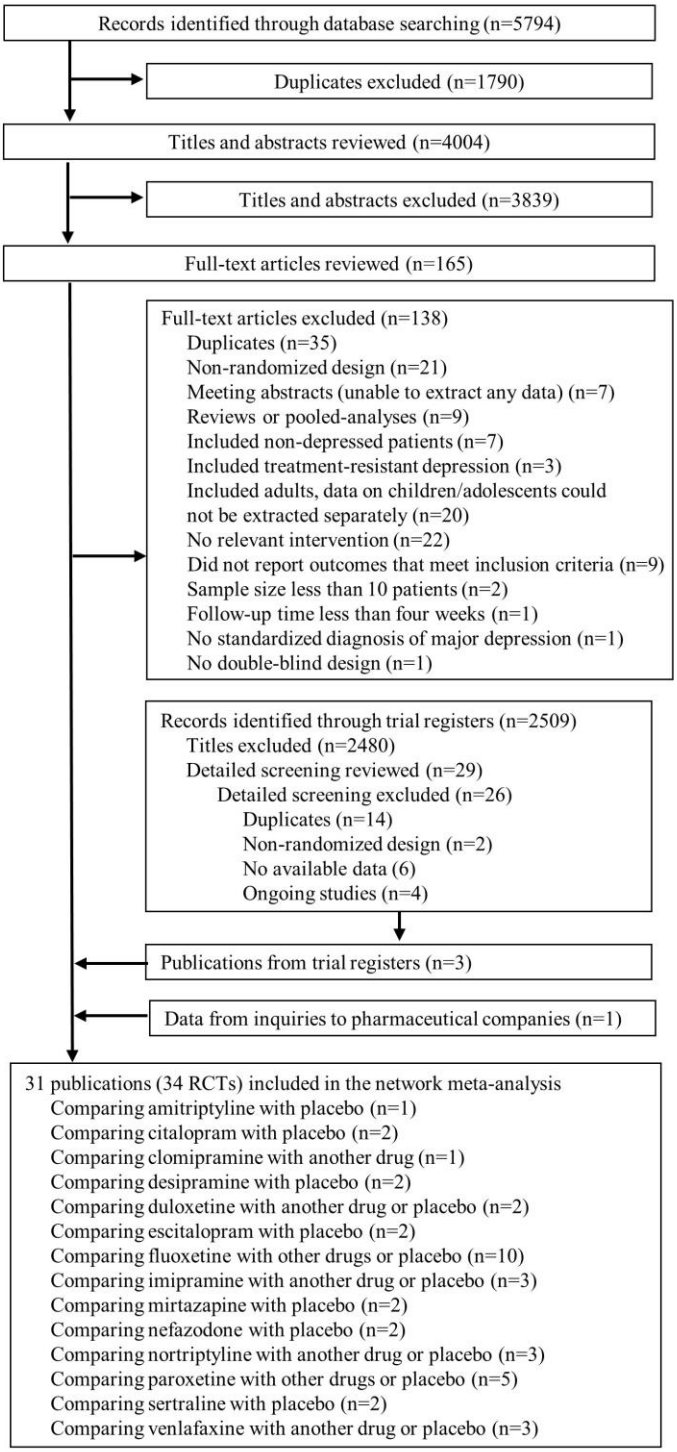
Table 2: Summary of suicide-related outcome with the number of patients with suicidal behavior or ideation

Comparison	No. of trials	Arm 1 Event / No.(%)	Arm 2 Event / No.(%)
Citalopram vs. Placebo	2	10/217 (4·6%)	7/205 (3·4%)
Duloxetine vs. Placebo	2	44/341 (12·9%)	32/225 (14·2%)
Escitalopram vs. Placebo	2	15/290 (5·2%)	15/294 (5·1%)
Fluoxetine vs. Placebo	7	51/521 (9·8%)	44/514 (8·6%)
Imipramine vs. Placebo	2	2/95 (2·1%)	1/87 (1·1%)
Mirtazapine vs. Placebo	2	1/170 (0·6%)	0/89 (0%)
Nefazodone vs. Placebo	2	0/289 (0%)	0/190 (0%)
Paroxetine vs. Placebo	4	13/413 (3·1%)	7/315 (2·2%)
Sertraline vs. Placebo	2	5/189 (2·6%)	2/187 (1·1%)
Venlafaxine vs. Placebo	2	8/184 (4·3%)	0/183 (0%)
Clomipramine vs. Paroxetine	1	7/58 (12·1%)	9/63 (14·3%)
Duloxetine vs. Fluoxetine	2	44/341 (12·9%)	33/234 (14·1%)
Imipramine vs. Paroxetine	1	2/95 (2·1%)	4/93 (4·3%)

527

528 ***Figure 1*: Flowchart of Study Selection**

529

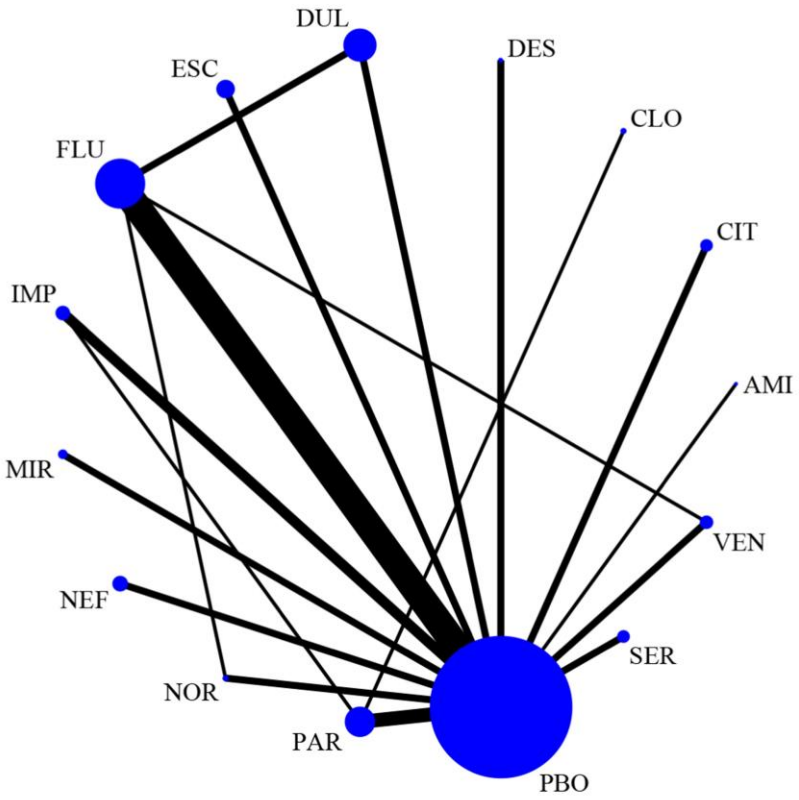


530

531

532

***Figure 2*: Network of Eligible Comparisons for Efficacy**



The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomised participants (sample size). 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.

***Figure 3*: Network Meta-Analysis of Efficacy and Tolerability**

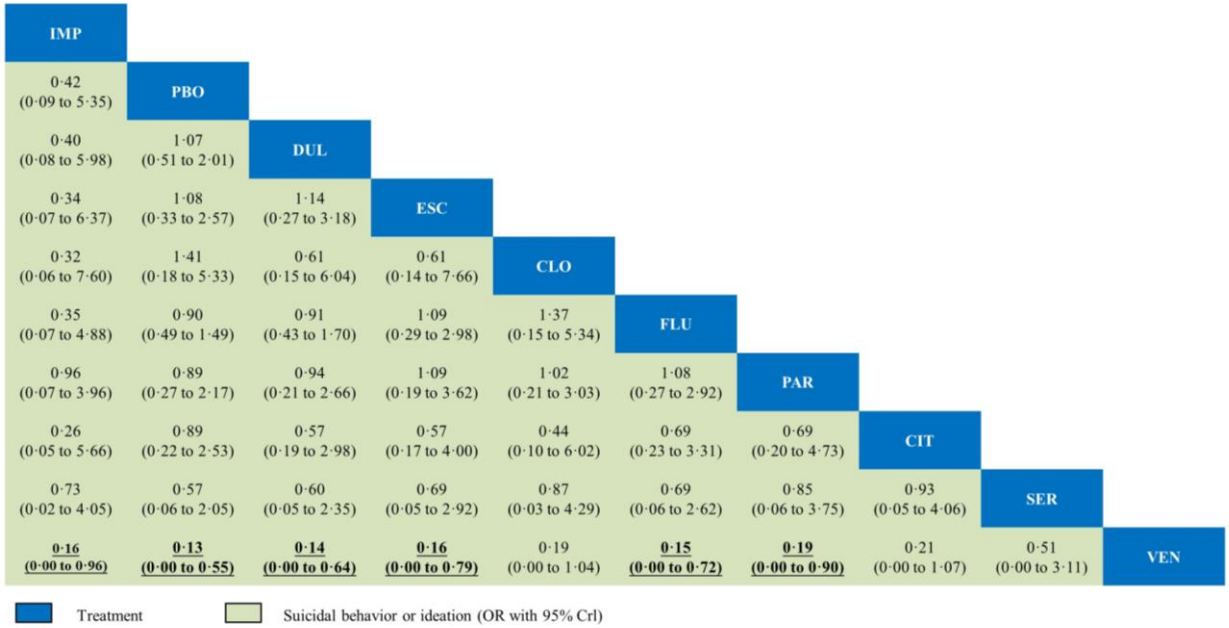
FLU	0·18 (0·04 to 1·75)	**0·31 (0·13 to 0·95)**	0·39 (0·05 to 1·47)	0·91 (0·09 to 3·49)	0·43 (0·06 to 1·58)	0·69 (0·24 to 3·50)	0·30 (0·07 to 3·06)	0·78 (0·21 to 2·18)	0·96 (0·05 to 4·56)	**0·23 (0·04 to 0·78)**	0·11 (0·03 to 77·0)	1·03 (0·50 to 2·70)	0·43 (0·11 to 3·98)	…
-0·06 (-1·23 to 1·11)	**DES**	2·05 (0·18 to 8·72)	1·79 (0·11 to 8·70)	4·23 (0·19 to 20·49)	1·96 (0·12 to 9·40)	1·90 (0·47 to 22·04)	3·55 (0·16 to 17·62)	3·61 (0·39 to 14·96)	4·38 (0·11 to 24·29)	1·09 (0·09 to 4·95)	0·32 (0·09 to 377·5)	2·85 (0·83 to 21·80)	1·17 (0·25 to 22·42)	…
-0·16 (-1·05 to 0·72)	-0·10 (-1·49 to1·28)	**DUL**	1·17 (0·13 to 4·68)	2·73 (0·23 to 11·00)	1·27 (0·14 to 5·05)	1·89 (0·61 to 11·49)	2·27 (0·19 to 9·64)	2·32 (0·53 to 7·26)	2·88 (0·12 to 14·26)	0·68 (0·11 to 2·54)	0·33 (0·09 to224·8)	**2·80 (1·20 to 9·42)**	1·17 (0·30 to 12·58)	…
-0·25 (-1·13 to 0·64)	-0·19 (-1·54 to 1·17)	-0·09 (-1·28 to 1·10)	**VEN**	1·17 (0·23 to 18·93)	0·61 (0·14 to 8·69)	2·13 (0·56 to 20·32)	0·92 (0·19 to 16·01)	1·69 (0·47 to 13·33)	0·71 (0·13 to 22·98)	0·40 (0·10 to 4·39)	0·37 (0·10 to 343·2)	**3·19 (1·01 to 18·70)**	1·30 (0·29 to 21·16)	…
-0·27 (-1·39 to 0·84)	-0·21 (-1·68 to 1·26)	-0·11 (-1·46 to 1·23)	-0·02 (-1·33 to 1·28)	**MIR**	0·93 (0·06 to 4·52)	0·91 (0·23 to 10·97)	0·40 (0·08 to 8·51)	1·71 (0·20 to 7·49)	2·12 (0·05 to 12·37)	0·17 (0·04 to 2·27)	0·18 (0·05 to 151·0)	1·36 (0·41 to 10·99)	0·56 (0·12 to 10·82)	…
-0·28 (-1·38 to 0·82)	-0·22 (-1·68 to 1·24)	-0·12 (-1·46 to 1·21)	-0·03 (-1·34 to 1·27)	-0·01 (-1·43 to 1·40)	**SER**	1·98 (0·52 to 18·57)	0·85 (0·17 to 15·06)	1·56 (0·44 to 12·09)	0·64 (0·11 to 21·50)	0·37 (0·09 to 4·05)	0·35 (0·09 to 304·7)	2·94 (0·94 to 17·19)	1·20 (0·27 to 18·95)	…
-0·33 (-1·43 to 0·78)	-0·27 (-1·72 to 1·20)	-0·17 (-1·50 to 1·17)	-0·08 (-1·38 to 1·22)	-0·06 (-1·47 to 1·35)	-0·05 (-1·45 to 1·35)	**CIT**	0·91 (0·07 to 3·89)	0·93 (0·20 to 2·77)	1·17 (0·05 to 5·60)	**0·27 (0·04 to 0·96)**	0·13 (0·03 to 91·24)	1·13 (0·45 to 3·66)	1·18 (0·11 to 4·76)	…
-0·34 (-1·44 to 0·75)	-0·28 (-1·73 to 1·17)	-0·18 (-1·51 to 1·15)	-0·09 (-1·39 to 1·20)	-0·07 (-1·48 to 1·34)	-0·06 (-1·45 to 1·34)	-0·01 (-1·41 to 1·40)	**ESC**	2·19 (0·22 to 9·23)	2·67 (0·06 to 14·62)	0·63 (0·05 to 2·87)	0·16 (0·05 to 196·9)	1·64 (0·46 to 13·49)	0·68 (0·14 to 13·64)	…
-0·35 (-1·19 to 0·50)	-0·29 (-1·56 to 0·99)	-0·19 (-1·32 to 0·94)	-0·10 (-1·19 to 0·99)	-0·07 (-1·30 to 1·15)	-0·07 (-1·28 to 1·16)	-0·02 (-1·23 to 1·19)	-0·01 (-1·21 to 1·20)	**PAR**	0·35 (0·07 to 6·80)	**0·22 (0·08 to 0·87)**	0·19 (0·05 to 115·6)	1·59 (0·77 to 3·95)	0·79 (0·26 to 3·77)	…
-0·36 (-1·46 to 0·74)	-0·30 (-1·76 to 1·15)	-0·20 (-1·54 to 1·13)	-0·11 (-1·42 to 1·18)	-0·09 (-1·50 to 1·32)	-0·08 (-1·48 to 1·32)	-0·03 (-1·44 to 1·37)	-0·02 (-1·42 to 1·37)	-0·01 (-1·23 to 1·19)	**NEF**	0·16 (0·03 to 4·50)	0·11 (0·04 to 241·2)	1·29 (0·30 to 21·89)	0·52 (0·10 to 20·79)	…
-0·49 (-1·57 to 0·58)	-0·44 (-1·88 to 1·01)	-0·33 (-1·65 to 0·98)	-0·25 (-1·53 to 1·03)	-0·22 (-1·61 to 1·17)	-0·22 (-1·60 to 1·17)	-0·17 (-1·55 to 1·22)	-0·16 (-1·54 to 1·22)	-0·15 (-1·21 to 0·91)	-0·13 (-1·52 to 1·26)	**IMP**	0·67 (0·17 to 471·9)	**5·49 (1·96 to 20·86)**	2·47 (0·62 to 21·47)	…
-0·59 (-2·20 to 1·01)	-0·53 (-2·39 to 1·33)	-0·43 (-2·20 to 1·34)	-0·34 (-2·09 to 1·40)	-0·32 (-2·14 to 1·52)	-0·31 (-2·13 to 1·52)	-0·26 (-2·10 to 1·57)	-0·25 (-2·08 to 1·57)	-0·24 (-1·92 to 1·43)	-0·23 (-2·05 to 1·59)	-0·10 (-1·92 to 1·71)	**AMI**	0·10 (0·02 to 32·16)	6·38 (0·01 to 24·56)	…
-0·51 (-0·99 to -0·03)	-0·45 (-1·52 to 0·62)	-0·35 (-1·24 to 0·54)	-0·26 (-1·10 to 0·58)	-0·24 (-1·25 to 0·77)	-0·23 (-1·21 to 0·77)	-0·18 (-1·18 to 0·82)	-0·17 (-1·15 to 0·81)	-0·16 (-0·86 to 0·54)	-0·15 (-1·14 to 0·85)	-0·01 (-0·98 to 0·95)	0·08 (-1·45 to 1·61)	**PBO**	0·79 (0·12 to 2·75)	…
-0·83 (-2·48 to 0·81)	-0·77 (-2·67 to 1·13)	-0·67 (-2·49 to 1·14)	-0·58 (-2·38 to 1·20)	-0·56 (-2·43 to 1·32)	-0·55 (-2·42 to 1·31)	-0·50 (-2·36 to 1·36)	-0·49 (-2·35 to 1·36)	-0·48 (-1·90 to 0·93)	-0·47 (-2·33 to 1·39)	-0·34 (-2·10 to 1·43)	-0·24 (-2·43 to 1·95)	-0·32 (-1·90 to 1·25)	**CLO**	…
-1·65 (-2·57 to -0·72)	**-1·59 (-2·98 to -0·21)**	**-1·49 (-2·71 to -0·27)**	**-1·40 (-2·60 to -0·20)**	**-1·38 (-2·71 to -0·04)**	**-1·37 (-2·70 to -0·05)**	-1·32 (-2·65 to 0·01)	-1·31 (-2·63 to 0·01)	**-1·30 (-2·43 to -0·18)**	-1·29 (-2·61 to 0·04)	-1·15 (-2·46 to 0·15)	-1·06 (-2·81 to 0·71)	**-1·14 (-2·02 to -0·25)**	-0·82 (-2·61 to 0·99)	**NOR**

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

Drugs are reported in order of efficacy ranking. 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 efficacy (mean overall change in symptoms), a SMD value below 0 favors the column-defining

549 treatment. For tolerability (discontinuation due to adverse events), an OR value below 1 favors the row-defining treatment. To obtain SMDs for comparisons
550 in the opposing direction, negative values should be converted into positive values and vice-versa. To obtain ORs for comparisons in the opposing direction,
551 reciprocals should be taken. Significant results are bolded and underscored. AMI=amitriptyline, CIT=citalopram, CLO=clomipramine, CrI=credibility interval,
552 DES=desipramine, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, MIR=mirtazapine, NEF=nefazodone, NOR=nortriptyline, OR=odds
553 ratio, PBO=placebo, PAR=paroxetine, SER=sertraline, SMD=standardized mean difference, VEN=venlafaxine.
554
555
556
557

***Figure 4*: Network Meta-Analysis of Suicide-related Outcome**



D

Drugs are reported in order of suicide-related outcome ranking. 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 suicidal behavior or ideation, an OR value below 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. Abbreviations: CIT=citalopram, CLO=clomipramine, CrI=credibility interval, DUL=duloxetine, ESC=escitalopram, FLU=fluoxetine, IMP=imipramine, OR=odds ratio, PBO=placebo, PAR=paroxetine, SER=sertraline, VEN=venlafaxine.

565