PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis
AUTHORS	Zhou, Xinyu; Cipriani, Andrea; Zhang, Yuqing; Cuijpers, Pim; Hetrick, Sarah; Weisz, John; Pu, Juncai; Del Giovane, Cinzia; Furukawa, Toshi; Barth, Jürgen; Coghill, David; Leucht, Stefan; Yang, Lining; Ravindran, Arun; Xie, Peng

VERSION 1 - REVIEW

REVIEWER	Matej Stuhec, Ph.D., Pharm.D. 1. Faculty of Pharmacy Ljubljana, Slovenia, European Union. 2. Ormoz's Psychiatric Hospital, Slovenia, European Union.
REVIEW RETURNED	12-Mar-2017

GENERAL COMMENTS	The authors have written about an understudied and very important clinical topic: "Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis". There are few data on this important topic and therefore this topic is interesting for future publication. The authors make a strong case for the need for a network meta-analysis and have proposed to use many state of the science procedures for searching the literature and analyzing the resulting data. This meta-analysis is an upgrade to the two previous following meta-analyses. This paper provides important information from evidence based medicine that could be considered a bridge between real practice (treatment) and guidelines (recommendations; Ia or A evidence). The purpose of the research is well defined and I'm sure the objectives will be met. Generally the paper has high issues with the standard of writing. However, in the current form presented, it requires a minor revision before consideration for publication. The manuscript could be strengthened by attending to the following matters: A) General remarks: Positive: - Few data on this topic - Meta-analyses are needed on this topic - New evidence and study design - Potential to be cited in the near future Negative: - Some minor mistakes and few methodological questions - Problems with different psychotherapy options (heterogeneity could be expected)

	B) Specific remarks: TITLE: "Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis." According to the MEDLINE searching this tittle is also appropriate for searching and there is no network meta-analysis finding with searching strategy: 'efficacy AND acceptability AND antidepressants AND children AND meta-analysis' (only 9 findings but without network meta-analysis). In this finding we found 5 different meta-analyses: 1) Braz J Med Biol Res. 2016 May 24;49(6) non network 2) BMJ Open. 2015 Sep 9;5(9):e007768. network 3) J Affect Disord. 2015 Jun 1;178:149-59. ; non network, ADHD patients 4) Clin Ther. 2014 Jul 1;36(7):1087-1095.e4. non network; SSRI therapy has a superior efficacy and is better tolerated compared with TCA therapy in young patients. 5) Curr Med Res Opin. 2014 Jun;30(6):971-95. network However in this field one important paper has been published in the Lancet (Lancet. 2016 Aug 27;388(10047):881-90.) in last year, although psychotherapy was excluded. Abstract Introduction: I would suggest that the authors change the first sentence to: Major depression disorder (MDD) or non-psychotic unipolar major depressive disorder is common in children and adolescents … Methods and analysis: / Dissemination: I would suggest that the authors add the following sentence: 'This is the newest network meta-analysis and therefore these results are very important in term of evidence-based medicine'. Key words: OK BACKGROUND Please explain an abbreviation when used first time (CBT, IPT). Was one of the main aim also to add the newest trials, which can change current available evidence? According to the available data one of the aim of this research could be also the following: According to the lack of data where efficacy of antidepressants in this population have been proven, the aim of this research was to add an additional data on antidepressants efficacy in this important population. Usually the guidelines are written according to the evidence based medicine (EBM), where the meta-analyses have the very important role and with these meta-analyses we are getting closer to Ia evidence level. I think this is very important aim of this research (clinical implication). I think one of the important finding of this meta-analysis is an answer on important question: To prescribe or not to prescribe in addition to the 2 previous meta-analyses? Usually the efficacy (SMD) of antidepressants is bigger in the adolescents than in children (NNT 10 vs. 20). Often more adolescents are treated with antidepressants than children. In my point of view, if more adolescents are included in this study, SMD is bigger than in trials with many children (Br J Psychiatry. 2008 Jul;193(1):10-7.). METHODS

	Types of studies OK Types of participants What is with comorbidity with ADHD? Please specify. In my point of view this is a source of bias. For example venlafaxine is more efficacious than escitalopram within patients with MDD and ADHD. About 30-50 % patients with ADHD have also MDD or anxiety disorders and therefore this conclusion can have a great impact on the final drug efficacy. Were all patients treatment-naive patients? Types of interventions The authors mean venlafaxine ER form or IR form? Please specify. Studies where it was not clear what happened to the patients who withdrew from the study were also excluded? Please clarify this important issue. Different outcomes can be a source of pharmaceutical marketing bias (e.g. favourite research for some companies). With careful consideration before research the authors can reduce these type of bias. If the authors will include the 3 different results from the same trials, 'trials bias' should be calculated and discussed in the discussion (e.g. placebo patients are the same in all 3 different results). Please make comments on this question and discuss in the limitations part of the discussion section. Medication effect and adverse events are often dose-dependent. The authors should consider: *to use mg/kg/day; *to proceed different analysis for studies with titration period, and those without. Types of outcome measures Usually we have the brief data from scales' differences between finish and start of the trials. However in some trials we have only number of participants to finish these trials successfully according to the defined outcomes (e.g. in 30% reduction in HAM-D17). How the authors will convert different outcomes to appropriate numbers? Please make comments on this question. Data Sources and Search Strategy Very clear. Risk of bias assessment OK. Very clear. Statistical analysis OK. Very clear. RESULTS Very clear, well presented and easy to read. TABLES and FIGURES. Very clear including Prisma's Table. REFERENCES Please check the references again according to the guidelines. There are some mistakes, especially with space (once Psychiatry 2014; 13(3): 306-9 and once Eur Psychiatry 2007;22(1):1-8.)

REVIEWER	Georgina Cox Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Australia I have collaborated with one of the authors (Sarah Hetrick) on a number of Cochrane reviews and Orygen related projects.
REVIEW RETURNED	20-Apr-2017

GENERAL COMMENTS	This network meta-analysis aims to compare the efficacy and acceptability of antidepressants, psychological interventions and their combination in the treatment of depressive disorder in children and adolescents. Overall, the protocol is well written and I have very few comments to add. I have specified a handful below that I do not envisage taking the authors long to address. I look forward to reviewing the outcome of the analysis, which will be a welcome edition to the literature. General comment The words phrases 'children and adolescents' and 'young people' are used interchangeably. Generally young people refers to those up to the age of 25. Introduction Overall the introduction is well written and incorporates relevant literature and current issues in the field. 'For example, a report from the American Academy of Child and Adolescent Psychiatry (AACAP) suggested that depressive disorder is responsible for over 500,000 suicide attempts by children and adolescents a year' I would suggest changing the wording to 'contributed to' rather than responsible for. Pg. 8: "Literature supports the notion that psychotherapy has its own side-effects". Please state what these are. Method Pg. 10: "For the pharmacological interventions, the control condition always is pill placebo, and these for psychological control conditions will include waiting-list (WL), treatment as usual (TAU), psychological placebo or attention placebo, as well as no-treatment (NT)". Reword sentence as it does not currently make sense. "…because the onset of benefit for most antidepressants often takes at least 4 weeks". Please provide a reference for this. Pg. 11. Suicide-related outcomes. Some trials use continuous scales of suicidal ideation as an outcome measure. Will this type of data be suitable for inclusion? If not why not? Data sources and search strategy These are all appropriate and likely to capture all relevant trials. Risk of bias assessment This is appropriate.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

The authors have written about an understudied and very important clinical topic: "Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis". There are few data on this important topic and therefore this topic is interesting for future publication. The authors make a strong case for the need for a network meta-analysis and have proposed to use many state of the science procedures for searching the literature and analyzing the resulting data. This meta-analysis is an upgrade to the two previous following meta-analyses. This paper provides important information from evidence based medicine that could be considered a bridge between real practice (treatment) and guidelines (recommendations; Ia or A evidence). The purpose of the research is well defined and I'm sure the objectives will be met. Generally the paper has high issues with the standard of writing. However, in the current form presented, it requires a minor revision before consideration for publication.

A) General remarks:

Positive:

- Few data on this topic

- Meta-analyses are needed on this topic
- New evidence and study design
- Potential to be cited in the near future
Negative:
- Some minor mistakes and few methodological questions
-Problems with different psychotherapy options (heterogeneity could be expected)

Authors' response
We are grateful to Reviewer #1 for his positive comments about our manuscript. We have revised the manuscript accordingly. Please see the following responses.

TITLE: "Comparative efficacy and acceptability of antidepressants, psychological interventions, and their combination for depressive disorder in children and adolescents: protocol for a network meta-analysis."
According to the MEDLINE searching this title is also appropriate for searching and there is no network meta-analysis finding with searching strategy: 'efficacy AND acceptability AND antidepressants AND children AND meta-analysis' (only 9 findings but without network meta-analysis).
In this finding we found 5 different meta-analyses:
1) Braz J Med Biol Res. 2016 May 24;49(6) non network
2) BMJ Open. 2015 Sep 9;5(9):e007768. network
3) J Affect Disord. 2015 Jun 1;178:149-59. ; non network, ADHD patients
4) Clin Ther. 2014 Jul 1;36(7):1087-1095.e4. non network; SSRI therapy has a superior efficacy and is better tolerated compared with TCA therapy in young patients.
5) Curr Med Res Opin. 2014 Jun;30(6):971-95 . network
However in this field one important paper has been published in the Lancet (Lancet. 2016 Aug 27;388(10047):881-90.) in last year, although psychotherapy was excluded.

Authors' response
Among these six meta-analyses, four articles (1. Braz J Med Biol Res 2016; 2. BMJ Open 2015; 4. Clin Ther 2014; 6. Lancet 2016) were published by my team. As you might know, we have investigated the efficacy and acceptability of antidepressants and psychological interventions for depressive disorder in children and adolescents, respectively. This NMA will be the first NMA of antidepressants, psychological interventions, and their combination for the treatment of depressive disorders in children and adolescents.

Introduction: I would suggest that the authors change the first sentence to:
Major depression disorder (MDD) or non-psychotic unipolar major depressive disorder is common in children and adolescents …

Authors' response
Since the aim of our study would be not covered by this introduction, we prefer to keep the sentence as it is. We focus on patients with the diagnosis of depressive disorders, including major depressive disorder (MDD), dysthymia, and other specified types.

Methods and analysis:
Dissemination: I would suggest that the authors add the following sentence: 'This is the newest network meta-analysis and therefore these results are very important in term of evidence-based medicine '.
Key words: OK

Authors' response

Following Reviewer's advice , we have revised the dissemination part (please see page 4, paragraph 1, line 1).

BACKGROUND
Please explain an abbreviation when used first time (CBT, IPT).

Authors' response
We have revised accordingly (please see page 6, paragraph 2, lines 3 and 4).

Was one of the main aim also to add the newest trials, which can change current available evidence? According to the available data one of the aim of this research could be also the following: According to the lack of data where efficacy of antidepressants in this population have been proven, the aim of this research was to add an additional data on antidepressants efficacy in this important population.

Authors' response
The main aim of this study is not only to update the data on antidepressants and psychotherapies trials, but also to add data on the combination of antidepressants and psychotherapies as a combined intervention strategy. This is the first meta-analysis that supplies comprehensive and systematic evidence to compare the three different intervention approaches (antidepressants, psychotherapies, combination).

Usually the guidelines are written according to the evidence based medicine (EBM), where the meta-analyses have the very important role and with these meta-analyses we are getting closer to Ia evidence level. I think this is very important aim of this research (clinical implication).

Authors' response
In this network meta-analysis, we will only include randomised controlled trials to get the best evidence. We will also assess the quality of evidence contributing to primary outcomes with the GRADE framework. This is now the standard way of assessing the quality of the retrieved evidence, which is endorsed by the Cochrane Collaboration and many scientific journals, and which is based on the following dimensions: study limitations, imprecision, heterogeneity or inconsistency, indirectness, and publication bias.

I think one of the important finding of this meta-analysis is an answer on important question: To prescribe or not to prescribe in addition to the 2 previous meta-analyses? Usually the efficacy (SMD) of antidepressants is bigger in the adolescents than in children (NNT 10 vs. 20). Often more adolescents are treated with antidepressants than children. In my point of view, if more adolescents are included in this study, SMD is bigger than in trials with many children (Br J Psychiatry. 2008 Jul;193(1):10-7.).

Authors' response
We thank the reviewer for highlighting such an important issue. Indeed, concerns about tolerability may make clinicians cautious about prescribing medication for children. In this study, to investigate whether age is related to the magnitude of the treatment effect , we plan to conduct the network meta-regression of data on primary outcomes for the age of participants (children vs. adolescents) (please see page 16, paragraph 1, lines 1 and 2).

Types of participants
What is with comorbidity with ADHD? Please specify. In my point of view this is a source of bias. For example venlafaxine is more efficacious than escitalopram within patients with MDD and ADHD. About 30-50 % patients with ADHD have also MDD or anxiety disorders and therefore this conclusion can have a great impact on the final drug efficacy.

Authors' response
In our protocol, comorbidity of depressive disorders with ADHD is defined as one patient who is concurrently diagnosed with depressive disorders and ADHD according to standardised criteria (such as DMS-V and ICD-10). To clarify this issue, we have revised the sentences as following: "Trials focusing on child or adolescent bipolar disorder will also be excluded, but not those involving patients with other comorbid psychiatric disorders as diagnosed according to standardised criteria (e.g., anxiety disorder, or attention deficit hyperactivity disorder)".
This is indeed a potential source of bias, which is difficult to detect and eliminate. As we know, a considerable proportion of young patients with depressive disorders have at least one secondary diagnosis of psychiatric disorders, such as anxiety disorders, ADHD, and substance abuse. However, the authors of most trials did not separately report the data of patients with comorbidity, and often do not even report the proportion of patients with comorbidity for any other psychiatric disorder(s). Nonetheless, we will also conduct a sensitivity analysis to exclude trials where only include patients comorbidity with other psychiatric disorders, as following, "In the sensitivity analysis,…, and trials where only included patients comorbidity with other psychiatric disorders."(please see page 16, paragraph 1, lines 6 and 7).

Were all patients treatment-naive patients?

Authors' response
No, we will not limit our meta-analysis to only those trials with treatment-naive patients since this information is most often not reported in papers.

Types of interventions
The authors mean venlafaxine ER form or IR form? Please specify.

Authors' response
We mean venlafaxine ER form. As far as we know, only venlafaxine ER has been used in trials for children and adolescents.

Studies where it was not clear what happened to the patients who withdrew from the study were also excluded? Please clarify this important issue.

Authors' response
No, we will not exclude these studies, and we will classify all patients who withdrew from the study as non-responders (that is "ITT analysis"). As described in the paper, missing dichotomous outcome data will be managed according to the intention to treat (ITT) principle, and all the dropouts after randomisation will be considered to be non-responders. Missing continuous outcome data will be analysed using the completer data. (please see page 14, paragraph 2, lines 1 to 3).

Different outcomes can be a source of pharmaceutical marketing bias (e.g. favourite research for some companies). With careful consideration before research the authors can reduce these type of bias. If the authors will include the 3 different results from the same trials, 'trials bias' should be calculated and discussed in the discussion (e.g. placebo patients are the same in all 3 different results). Please make comments on this question and discuss in the limitations part of the discussion section.

Authors' response
We thank the reviewer for pointing out the dangers associated with commercial biases in reporting of the trials. First we will search for all published and unpublished reports of the trials and will spot out any discrepancies among them; we will then abide by the intention-to-treat principle and obtain such

results; if missing, we will contact the original investigators for such data. All these procedures have been clearly described in our protocol. We have also pre-specified our primary outcomes of interest as “(1) Efficacy (as a continuous outcome), measured by the overall mean change scores on depressive symptom scales (self- or assessor-rated), e.g., Children’s Depression Rating Scale (CDRS-R) and Hamilton Depression Rating Scale (HAMD) from baseline to endpoint. (2) Acceptability of treatment, defined as the proportion of patients who drop out of the study by any cause during the delivery of the intervention” in the protocol. This will allow us to avoid overestimation of treatment efficacy due to selective outcome reporting by the original authors.

Medication effect and adverse events are often dose-dependent. The authors should consider:
*to use mg/kg/day;
*to proceed different analysis for studies with titration period, and those without.

Authors’ response
The NMA requires that the network be transitive, i.e. all the included treatments be prescribable for any patients included in the network. We therefore will only include trials where antidepressants were prescribed within therapeutic doses. And, we will conduct a subgroup analysis for the dosing schedule (fixed or flexible doses), as following, “Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: …(v) the dosing schedule (fixed or flexible doses).” (please see page 16, paragraph 1, line 3).

Types of outcome measures
Usually we have the brief data from scales' differences between finish and start of the trials. However in some trials we have only number of participants to finish these trials successfully according to the defined outcomes (e.g. in 30% reduction in HAM-D17). How the authors will convert different outcomes to appropriate numbers? Please make comments on this question.

Authors’ response
Although some feasible methods were used to convert different outcomes to appropriate numbers, some experts stated the conversion methods limit the accuracy of data. Therefore, we will not use any conversion methods in this NMA. If there are missing data, we will contact the authors of trials.

REFERENCES
Please check the references again according to the guidelines. There are some mistakes, especially with space (once Psychiatry 2014; 13(3): 306-9 and once Eur Psychiatry 2007;22(1):1-8.)

Authors’ response
We have checked the references again according to the guidelines.

Reviewer #2:

This network meta-analysis aims to compare the efficacy and acceptability of antidepressants, psychological interventions and their combination in the treatment of depressive disorder in children and adolescents. Overall, the protocol is well written and I have very few comments to add. I have specified a handful below that I do not envisage taking the authors long to address. I look forward to reviewing the outcome of the analysis, which will be a welcome edition to the literature.

Authors’ response
Thanks, we are grateful to Reviewer #2 for his/her positive comments about our manuscript.

General comment

The words phrases ‘children and adolescents’ and ‘young people’ are used interchangeably. Generally young people refers to those up to the age of 25.

Authors’ response
Sorry, we have revised accordingly (please see page 2, paragraph 1, line 7, and page 6, paragraph 1, line 3).

Introduction
Overall the introduction is well written and incorporates relevant literature and current issues in the field. “For example, a report from the American Academy of Child and Adolescent Psychiatry (AACAP) suggested that depressive disorder is responsible for over 500,000 suicide attempts by children and adolescents a year” I would suggest changing the wording to ‘contributed to’ rather than responsible for.

Authors’ response
We have revised accordingly (please see page 6, paragraph 1, line 6).

Pg. 8: “Literature supports the notion that psychotherapy has its own side-effects”. Please state what these are.

Authors’ response
Following the Reviewer’s suggestion, we have revised this sentences, as following, “Previous research supports the notion that psychotherapy has its own side-effects, such as worsening of symptoms, and leading to distress for the patients’ family.17” (please see page 7, paragraph 1, line 4)

Method
Pg. 10: “For the pharmacological interventions, the control condition always is pill placebo, and these for psychological control conditions will include waiting-list (WL), treatment as usual (TAU), psychological placebo or attention placebo, as well as no-treatment (NT)”. Reword sentence as it does not currently make sense.

Authors’ response
Thanks for your comments. We have revised this sentence, as following: “For the pharmacological interventions, the control condition is always a pill placebo, whilst the psychological control conditions are waiting-list (WL), treatment as usual (TAU), psychological placebo or attention placebo, or no-treatment (NT).” (please see page 9, paragraph 1, line11-12)

“…because the onset of benefit for most antidepressants often takes at least 4 weeks”. Please provide a reference for this.

Authors’ response
Following the Reviewer’s suggestion, we have quoted the relevant references, (Birmaher B, Brent D; AACAP Work Group on Quality Issues, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(11):1503-26.)”

Pg. 11. Suicide-related outcomes. Some trials use continuous scales of suicidal ideation as an outcome measure. Will this type of data be suitable for inclusion? If not why not?

Authors’ response
No, we will not include continuous outcomes of suicidal ideation because very few trials used such measures.

VERSION 2 – REVIEW

REVIEWER	Matej Stuhec 1) University of Ljubljana, Faculty of Pharmacy, Slovenia, EU 2) Department for clinical pharmacy, Ormoz's Psychiatric Hospital, Slovenia, EU
REVIEW RETURNED	14-May-2017

GENERAL COMMENTS	The authors accepted all my recommendations. This is well-writen article, which could be very important in term of evidence-based treatment. In addition, I have some comments/remarks, which should be addressed before publication. 1) Reference N21 could be changed by new paper published by the same authors (Cochrane Database Syst Rev. 2014 Nov 30;(11):CD008324) 2) The authors included both inpatients and outpatients (Page 8, line 46). Usually patients treated within the hospitals are more severe patients (differences in Hamilton's score). This can have an impact that antidepressants can have bigger effect size than psychotherapy (over-estimated effect). I will be happy if the authors can comment on this important issue (e.g. how they will resolve this important question within NMA) 3) For venlafaxine please specify form of release (Page 9, line 10): Venlafaxine ER (use in the article instead of venlafaxine). This is very important for citation and also adverse events (e.g. discontinuation all cause with venlafaxine could be bigger than ER form). Also venlafaxine IR was included in many trials. The authors should specify if they excluded these trials. If they excluded them is appropriate approach, if not the result for venlafaxine could be under-estimated 4) What about treatments which are not approved for MDD and were tested for MDD and were effective in some RCTs were excluded (e.g. methylphenidate)? Please specify.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1:

The authors accepted all my recommendations. This is well-writen article, which could be very important in term of evidence-based treatment. In addition, I have some comments/remarks, which should be addressed before publication.
1) Reference N21 could be changed by new paper published by the same authors (Cochrane Database Syst Rev. 2014 Nov 30;(11):CD008324)

Authors' response
We have changed the reference accordingly (please see page 3, paragraph 1, line 1)

2) The authors included both inpatients and outpatients (Page 8, line 46). Usually patients treated within the hospitals are more severe patients (differences in Hamilton's score). This can have an impact that antidepressants can have bigger effect size than psychotherapy (over-estimated effect). I will be happy if the authors can comment on this important issue (e.g. how they will resolve this important question within NMA)

Authors' response
Following Reviewer's advices, we will conduct a network meta-regression meta- analysis based on

the severity of depressive symptom, as following, “Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: …; (v) severity of depressive symptom at baseline.” (please see page 16, paragraph 1, lines 3 to 4).

3) For venlafaxine please specify form of release (Page 9, line 10): Venlafaxine ER (use in the article instead of venlafaxine). This is very important for citation and also adverse events (e.g. discontinuation all cause with venlafaxine could be bigger than ER form). Also venlafaxine IR was included in many trials. The authors should specify if they excluded these trials. If they excluded them is appropriate approach, if not the result for venlafaxine could be under-estimated.

Authors’ response
Thanks for raising this important issue. We considered not to compare the form of release of all pharmacological interventions for the following two reasons.
1. We did not plan to classify the treatments into more detailed classification in both pharmacological interventions (IR versus ER, fixed-dose versus flexible-dose, or different therapeutic doses) and psychological interventions (group vs individual format, face-to-face vs internet-based, or with or without family involvement). These detailed classifications may lead to few RCTs in each node, poor transitivity of the whole network, and may compromise the conclusions.
2. In a network meta-analysis focused on the comparison of efficacy and risk of harms of IR versus ER among adults depressed patients, the authors found no clear differences between the two formulations in adults and therefore they cannot recommend a first choice. (Please see Nussbaumer B, et al. Comparative efficacy and risk of harms of immediate- versus extended-release second-generation antidepressants: a systematic review with network meta-analysis. CNS Drugs. 2014 Aug;28(8):699-712. doi: 10.1007/s40263-014-0169-z.) So maybe it is still hard to know whether the result for venlafaxine could be under-estimated in our network meta-analysis.

4) What about treatments which are not approved for MDD and were tested for MDD and were effective in some RCTs were excluded (e.g. methylphenidate)? Please specify.

Authors’ response
Based on our two previous network meta-analysis, we will only include the common used antidepressants and psychological interventions in clinical practice ([Cipriani A, et al. Lancet 2016;388:881-90.] and [Zhou X, et al. World Psychiatry 2015;14:207-22.9.]), and these eligible interventions will be all antidepressants and psychotherapeutic interventions recommended by current guidelines.

VERSION 3 – REVIEW

REVIEWER	Matej Stuhec Faculty of Pharmacy Ljubljana, Slovenia
REVIEW RETURNED	30-May-2017

GENERAL COMMENTS	The authors clarify all my remarks and therefore I suggest to accept it. Regards!