PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	COMPARATIVE EFFICACY AND ACCEPTABILITY OF FIRST- AND SECOND- GENERATION ANTIDEPRESSANTS IN THE ACUTE TREATMENT OF MAJOR DEPRESSION: PROTOCOL FOR A NETWORK META-ANALYSIS
AUTHORS	Furukawa, Toshi; Salanti, Georgia; Atkinson, Lauren; Leucht, Stefan; Ruhé, Henricus; Turner, Erick; Chaimani, Anna; Ogawa, Yusuke; Takeshima, Nozomi; Hayasaka, Yu; Imai, Hissei; Shinohara, Kiyomi; Suganuma, Aya; Watanabe, Norio; Stockton, Sarah; Geddes, John; Cipriani, Andrea

VERSION 1 - REVIEW

REVIEWER	Gin Malhi University of Sydney, Australia
REVIEW RETURNED	17-Mar-2016

GENERAL COMMENTS	This brief paper outlines a protocol for a systematic review and network analysis that will focus on second generation as well as first generation antidepressants. The group aims to look at efficacy and acceptability in the acute treatment of major depression and involves a number of key people who have extensive experience in this type of analyses. The methods and analysis are sound and the topic is of particular interest given the expansion in the number of new antidepressants available and the ongoing discussion as to whether there has been any increment in efficacy and tolerability with newer agents, and also whether methodological techniques and study design has impacted outcome from clinical trials. I would suggest however the authors do consider, when writing their final paper, the inclusion of some critique regarding both the commercial pressures to develop new methodologies and the fact that many methodologies are not comparable and are specifically geared to compensate for the rising effect of placebo. If the editors thought it appropriate, the authors could include this in this particular paper, though I understand that it is specifically outlining a methodology and protocol, rather than findings.

REVIEWER	Juan Undurraga, MD, PhD 1. Department of Psychiatry, Faculty of Medicine, Clínica Alemana Universidad del Desarrollo. Santiago, Chile. 2. Early Intervention Program, J. Horwitz Psychiatric Institute. Santiago, Chile.
REVIEW RETURNED	26-Apr-2016

GENERAL COMMENTS	Title: “Comparative Efficacy and Acceptability of First and Second-

	Generation Antidepressants in the Acute Treatment of Major Depression: Protocol for a Network Meta-analysis" The authors (a solid team of experts in the field) present a protocol for a systematic review and network metaanalysis of first and second generation antidepressants (ADs) in the acute treatment of major depression. It will be based on a previously published network metaanalysis by the same group (Cipriani et al. 2009), but will add more ADs and will include ADs vs placebo comparisons as well. Main outcomes: 1. Efficacy: Response, defined as reduction of 50% or more in the total score between baseline and week 8. 2. Acceptability, defined as proportion of dropouts in the first 8 weeks. Methods are very cared for and of high quality standards Inclusion: Double blind RCTs using monotherapy. Participants: adults, unipolar mayor depression as primary diagnosis, excluded >20% bipolars/psychotic, serious medical illness, post-partum, resistant depression in all participants. Search strategy and data extraction is exhaustive. Missing outcome data management is appropriate. Risk of bias will be evaluated systematically by two raters using a standardized tool and will be classified accordingly for further analyses. Random effects model will be used for pairwise meta-analyses. Comments: A. Methods: 1. It is not clear why the authors decided to exclude imipramine from their analysis. It is frequently used as comparator in antidepressant trials, moreover, it is an agent of proven efficacy and still widely used in some clinical settings. 2. Transitivity assumption will be assessed for variables that could influence primary outcomes (age, depressive severity, dosing). Perhaps could be pertinent to include gender? 3. Selection bias. Network meta-regression models will be run to detect associations between study size and effect size. I suggest other variables that could bias the effect size should be considered such as year of publication and number of centers participating (Undurraga & Baldessarini, 2012; Kahn & Brown, 2015). B. Figure1. The figure includes Hypericum as one of the possible agents for pairwise comparisons. This agent is not included in the list of active agents that will be included in the methods section (2.1.3 Types of interventions). Please amend. References. 1.Khan, A., & Brown, W. A. (2015). Antidepressants versus placebo in major depression: an overview. World Psychiatry, 14(3), 294-300. 2.Undurraga, J., & Baldessarini, R. J. (2012). Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. Neuropsychopharmacology, 37(4), 851-864.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

This brief paper outlines a protocol for a systematic review and network analysis that will focus on second generation as well as first generation antidepressants. The group aims to look at efficacy and acceptability in the acute treatment of major depression and involves a number of key people who have extensive experience in this type of analyses. The methods and analysis are sound and the topic is of particular interest given the expansion in the number of new antidepressants available and the ongoing discussion as to whether there has been any increment in efficacy and tolerability with newer agents, and also whether methodological techniques and study design has impacted outcome from clinical trials.

Authors' response
Thank you, no comment needed

I would suggest however the authors do consider, when writing their final paper, the inclusion of some critique regarding both the commercial pressures to develop new methodologies and the fact that many methodologies are not comparable and are specifically geared to compensate for the rising effect of placebo. If the editors thought it appropriate, the authors could include this in this particular paper, though I understand that it is specifically outlining a methodology and protocol, rather than findings.

Authors' response
This is an interesting point and in the full text review we will discuss about commercial pressure and the development of new methodologies. We agree with Prof Malhi and think it is better to elaborate on these issues when writing the final paper and presenting real data, in order to base our discussion on data/figures and not on abstract reasoning.

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Reviewer #2

The authors (a solid team of experts in the field) present a protocol for a systematic review and network metaanalysis of first and second generation antidepressants (ADs) in the acute treatment of major depression. It will be based on a previously published network metaanalysis by the same group (Cipriani et al. 2009), but will add more ADs and will include ADs vs placebo comparisons as well.
Main outcomes:
1. Efficacy: Response, defined as reduction of 50% or more in the total score between baseline and week 8.
2. Acceptability, defined as proportion of dropouts in the first 8 weeks.
Methods are very cared for and of high quality standards

Authors' response
Thank you, no comment needed

Inclusion: Double blind RCTs using monotherapy.
Participants: adults, unipolar mayor depression as primary diagnosis, excluded >20% bipolars/psychotic, serious medical illness, post-partum, resistant depression in all participants.
Search strategy and data extraction is exhaustive.
Missing outcome data management is appropriate.

Authors' response
Thank you, no comment needed

Risk of bias will be evaluated systematically by two raters using a standardized tool and will be classified accordingly for further analyses.
Random effects model will be used for pairwise meta-analyses.
Comments:
1. It is not clear why the authors decided to exclude imipramine from their analysis. It is frequently used as comparator in antidepressant trials, moreover, it is an agent of proven efficacy and still widely used in some clinical settings.

Authors' response
Among tricyclic antidepressants, we decided to include only amitryptiline and clomipramine because they are included in the WHO model list of essential medicines (http://www.who.int/selection_medicines/committees/expert/20/EML_2015_FINAL_amended_AUG2015.pdf?ua=1)

2. Transitivity assumption will be assessed for variables that could influence primary outcomes (age, depressive severity, dosing). Perhaps could be pertinent to include gender?

Authors' response
This is an interesting issue and possibly a clinically relevant question, however split data about gender distribution are often not reported in summary data from primary studies. The only reliable way to use such information would be an individual patient data (IPD) meta-analysis, but unfortunately we are still far from having IPD from an adequate number of randomised studies in depression.

3. Selection bias. Network meta-regression models will be run to detect associations between study size and effect size. I suggest other variables that could bias the effect size should be considered such as year of publication and number of centers participating (Undurraga & Baldessarini, 2012; Kahn & Brown, 2015).

Authors' response
Yes, as reported on page 12 (paragraph 2.5.6) we will include study year as one of the variables in our meta-regression analysis. Moreover, following Prof Undurraga's advice, we have now included also the number of recruiting centres as one of the variables to explore in the meta-regression analysis.

B. Figure1. The figure includes Hypericum as one of the possible agents for pairwise comparisons. This agent is not included in the list of active agents that will be included in the methods section (2.1.3 Types of interventions). Please amend.

Authors' response
Sorry for the typo, we have amended Figure 1 accordingly.

VERSION 2 – REVIEW

REVIEWER	Juan Undurraga, MD, PhD 1. Department of Psychiatry, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo. Santiago, Chile. 2. Early Intervention Program, J. Horwitz Psychiatric Institute, Santiago, Chile.

REVIEW RETURNED	11-May-2016

GENERAL COMMENTS	Thank you