

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Global prevalence of antidepressant utilization in the community: protocol for a systematic review
AUTHORS	Lunghi, Carlotta; Dugas, Michèle; Leclerc, Jacinthe; Poluzzi, Elisabetta; Martineau, Cathy; Carnovale, Valérie; Stéfan, Théo; Blouin, Patrick; Lépine, Johanie; Jalbert, Laura; Espinoza Suarez, Nataly R; Svyntozelska, Olha; Dery, Marie-Pier; Ekanmian, Giraud; Nogueira, Daniele Maria; Akinola, Pelumi Samuel; Turcotte, Stéphane; Skidmore, Becky; LeBlanc, Annie

VERSION 1 – REVIEW

REVIEWER	Foulds, James A Department of Psychological Medicine, University of Otago
REVIEW RETURNED	25-Feb-2022

GENERAL COMMENTS	<p>This is a well-designed review in an important area. Comments:</p> <ol style="list-style-type: none">1. I think some of the papers identified will report antidepressant dispensing data (e.g. from insurers or national medication benefits schemes). These studies should presumably be included, but dispensing data is not quite the same as "antidepressant use": some patients who are dispensed medication may not take it. This is a minor semantic point but might be worth acknowledging in the Study Design.2. In "participants"- presumably all clinical samples (i.e. populations of people seeking medical treatment) will be excluded irrespective of whether they are inpatient or outpatient samples.3. Medline and Embase have good coverage of English language publications, but less thorough coverage of other languages. As the aim is not to restrict publications to English language only, consider including LILACS, which has good coverage of publications in Spanish and Portuguese.
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REVIEWER	Lin, Yen-Kuang Taipei Medical University, Statistics Center
REVIEW RETURNED	06-Mar-2022

GENERAL COMMENTS	<p>The authors indicate no systematic review regarding prescriptions of antidepressants for the general population. However, I believed there are quite a few through systematic review as well as meta-analysis focusing on the topic of prescription patterns for adults with depressive disorder. For example, A Cipriani, TA Furukawa, G Salanti, et al., 2018; As the authors have pointed out, Mercier, A., Auger-Aubin, I., Lebeau, J. P., et al., 2013 is also looking at the</p>
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	<p>prescription of antidepressants for non-psychiatric conditions. This reference should also be properly discussed in the present study.</p> <p>The perspective of critically appraising a meta-analysis is missing. For example, how will the study selection process be conducted systematically? Which of the statistical methods will be used to combine the studies reported? What are the alternatives if the pooled studies are shown to be rather homogenous? Will the publication bias be assessed?</p> <p>There are more frequently prescribed for health conditions other than psychiatric ones based on literature. Thus, a review of evidence from guidelines for an antidepressant prescription for the general population is worth to be investigated. However, this topic would be much more beneficial if the results of the review is presented, rather than a protocol.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr James A Foulds, Department of Psychological Medicine, University of Otago

Comments to the Author:

This is a well-designed review in an important area. Comments:

1. I think some of the papers identified will report antidepressant dispensing data (e.g. from insurers or national medication benefits schemes). These studies should presumably be included, but dispensing data is not quite the same as “antidepressant use”: some patients who are dispensed medication may not take it. This is a minor semantic point but might be worth acknowledging in the Study Design.

We thank the reviewer for highlighting this important point which is not only semantic. We anticipate that some studies will use dispensing data, and we are aware that a prescription claim is not synonymous with current use. We thus added this as a limitation of the review results in the Discussion section.

Moreover, despite the aim of this review being to estimate the prevalence of antidepressant utilization, it is possible that some studies that will be identified and included report antidepressant dispensing data (e.g., from medico-administrative data) rather than actual utilization data. Dispensing data differ from actual antidepressant use, even if many pharmacoepidemiologic studies use dispensing data as a proxy for drug use. To overcome this possible limitation, results will be presented according to the data type, and prevalence will be estimated separately for dispensing data.

2. In “participants”, - presumably all clinical samples (i.e. populations of people seeking medical treatment) will be excluded irrespective of whether they are inpatient or outpatient samples.

As this review aimed to estimate the prevalence of antidepressant use in the community rather than in patients with specific diseases, our inclusion criteria were established so that participants using antidepressants with an associated diagnosis would be excluded. Thus, as mentioned by Dr Foulds, clinical samples would likely be excluded regardless of the settings. However, as many studies compared the prevalence of antidepressant use in specific populations (e.g., depressed individuals) to a control population, the information regarding the study setting would still be relevant to our review for the control group. Therefore, these papers would be included. Additionally, we will further categorize the outpatient settings to document our findings better when summarizing the information.

3. Medline and Embase have good coverage of English language publications, but less thorough coverage of other languages. As the aim is not to restrict publications to English language only, consider including LILACS, which has good coverage of publications in Spanish and Portuguese. We thank the reviewer for this comment. Although we chose not to restrict publications to English only, we did not specifically actively seek to include publications in other languages by searching specific databases covering publications in other languages. We are aware that this may be a limiting factor to our review and acknowledge it in the limitation section:

“Even if we did not put restrictions on publication search by language, we did not actively seek to include publications in other languages by searching specific databases covering publications in other languages. This could thus limit the number of studies included in the review.”

Reviewer: 2

Dr Yen-Kuang Lin, Taipei Medical University

Comments to the Author:

The authors indicate no systematic review regarding prescriptions of antidepressants for the general population. However, I believed there are quite a few through systematic review as well as meta-analysis focusing on the topic of prescription patterns for adults with depressive disorder. For example, A Cipriani, TA Furukawa, G Salanti, et al., 2018; As the authors have pointed out, Mercier, A., Auger-Aubin, I., Lebeau, J. P., et al., 2013 is also looking at the prescription of antidepressants for non-psychiatric conditions. This reference should also be properly discussed in the present study. We appreciate the time Dr Lin took to find other reviews regarding antidepressant patterns in adults with depressive disorders. However, our review entirely differs from those mentioned above. Cipriani et al.'s systematic review and network analysis aimed to rank 21 antidepressants for the acute treatment of unipolar major depressive disorders in adults. It did so by analyzing randomized controlled trials examining the efficacy and tolerability of antidepressant medications. We have chosen to study antidepressants differently. We thus did not include randomized clinical trials but only observational studies, as our focus is not on the efficacy or effectiveness of antidepressant drugs but their prevalence of use in the community. The review by Mercier et al. aimed to analyze clinical guidelines to give evidence for the prescription of antidepressants for non-psychiatric conditions in primary care. The purpose was thus not to estimate the prevalence of use but to identify evidence-based indications for the benefit of antidepressants for non-psychiatric conditions. Despite the methodological differences with our review, we believe that the Mercier et al. review will undoubtedly be of great relevance for discussing the results of our review once accomplished. We will certainly cite it and discuss our results in light of the guideline evidence Mercier et al. reported. Thus, we believe that discussing Mercier et al.'s review will be more suitable for the future publication of our review results than this protocol.

The perspective of critically appraising a meta-analysis is missing. For example, how will the study selection process be conducted systematically? Which of the statistical methods will be used to combine the studies reported? What are the alternatives if the pooled studies are shown to be rather homogenous? Will the publication bias be assessed?

We thank the reviewer for highlighting this missing point. We have added in the text specific information on the meta-analysis process we aim to perform:

“We will undertake a meta-analysis to generate estimates of antidepressant use prevalence across included studies if the data allows it. We plan on following the method of Barendregt et al. (Barendregt et al. 2013) for the meta-analysis of prevalence. If a meta-analytic approach is possible, we will calculate the aggregate point prevalence estimate of antidepressant use with 95% confidence intervals (CI) and perform subgroup analyses according to sex, age group, period, country, or other appropriate variables. We will use the I^2 statistic to evaluate heterogeneity across studies (Higgins et al. 2002). An I^2 value above 50% will indicate substantial heterogeneity, while an I^2 value between 25% and 50% will indicate moderate heterogeneity and finally, an I^2 value lower than 25% will

indicate a low heterogeneity. In case of low heterogeneity, we will compute prevalence estimates with the Mantel-Haenszel fixed-effects method (Leonard et al. 2002). Otherwise, we will use random-effects methods and perform sensitivity and subgroup analyses based on the pre-established subgroups. In case subgroup analyses do not permit understanding the heterogeneity, the global estimate will not be interpreted, and the emphasis will be placed on the individual studies. Random-effects meta-regression analyses will be used to evaluate whether the prevalence of antidepressant use differs according to the period, region, or population. We will assess publication bias using funnel plots. P-values less than 0.05 will be considered statistically significant. An experienced biostatistician of the group (ST) will conduct the meta-analyses.”

Moreover, we added a reference for the analysis of the risk of bias in the included studies. We will thus use the Checklist for Prevalence Studies tool from the Joanna Briggs Institute Critical Appraisal tools for use in JBI systematic reviews.

“Pairs of reviewers will independently assess the methodological quality of the included articles and will evaluate the risk of bias by using the Joanna Briggs Institute Critical Appraisal tool: Checklist for Studies Reporting Prevalence Data (Munn Z et al. 2015).”

There are more frequently prescribed for health conditions other than psychiatric ones based on literature. Thus, a review of evidence from guidelines for an antidepressant prescription for the general population is worth to be investigated. However, this topic would be much more beneficial if the results of the review is presented, rather than a protocol.

We thank the reviewer for acknowledging the importance of the topic. Based on the present protocol, our review will thus present results on the prevalence of antidepressant use in the community. We look forward to delivering our results in a future publication.

VERSION 2 – REVIEW

REVIEWER	Foulds, James A Department of Psychological Medicine, University of Otago
REVIEW RETURNED	04-May-2022

GENERAL COMMENTS	Authors have responded constructively to my previous comments.
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REVIEWER	Lin, Yen-Kuang Taipei Medical University, Statistics Center
REVIEW RETURNED	08-May-2022

GENERAL COMMENTS	Thanks for addressing my concerns. I have no further questions.
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