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Global prevalence of antidepressant drug utilization in the community: protocol for a systematic review

Carlotta Lunghi ,[1,2,3,4] Michèle Dugas,[5] Jacinthe Leclerc ,[6,7,8] Elisabetta Poluzzi,[4] Cathy Martineau,[1] Valérie Carnovale,[5] Théo Stéfan,[5] Patrick Blouin,[5] Johanie Lépine,[5] Laura Jalbert,[5] Nataly R Espinoza Suarez,[5] Olha Svyntozelska,[5] Marie-Pier Dery,[5] Giraud Ekanmian ,[2,3,8] Daniele Maria Nogueira,[9] Pelumi Samuel Akinola,[6,10] Stéphane Turcotte,[3] Becky Skidmore,[11] Annie LeBlanc [5,12]

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For numbered affiliations see end of article.

Correspondence to
Dr Carlotta Lunghi;
Carlotta_Lunghi@uqar.ca

ABSTRACT

Introduction Antidepressant drugs are the most frequently prescribed medication for mental disorders. They are also used off-label and for non-psychiatric indications. Prescriptions of antidepressants have increased in the last decades, but no systematic review exists on the extent of their use in the community.

Methods and analysis We will conduct a systematic review to estimate the prevalence of antidepressant use in the community. We will search for studies published from 1 January 2010 in the Embase and MEDLINE databases using a combination of controlled vocabulary and keywords adjusted for each database without any language restriction. The main inclusion criterion is the presence of prevalence data of antidepressant utilization. Thus, we will include all studies with a descriptive observational design reporting the prevalence of antidepressant use in the community. Study selection (by title/abstract and full-text screening) and data extraction for included studies will be independently conducted by pairs of reviewers. We will then synthesize the data on the prevalence of antidepressant use in individuals living in the community. If possible, we will perform a meta-analysis to generate prevalence-pooled estimates. If the data allows it, we will conduct subgroup analyses by antidepressant class, age, sex, country and other sociodemographic categories. We will evaluate the risk of bias for each included study through a quality assessment using the Joanna Briggs Institute Critical Appraisal tool: Checklist for Studies Reporting Prevalence Data. DistillerSR software will be used for the management of this review.

Ethics and dissemination Ethical approval is not required for this review as it will not directly involve human or animal subjects. The findings of our systematic review will be disseminated through publications in peer-reviewed journals, the Qualaxia Network (https://qualaxia.org), presentations at international conferences on mental health and pharmacoepidemiology, as well as general public events.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this will be the first systematic review to summarize epidemiological data on antidepressant utilization in the community.
⇒ It will also estimate the prevalence of antidepressant use by sex and among different age groups.
⇒ This review protocol has been built, and the review will be reported, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.
⇒ A potential limitation is that differences in populations, data sources, study designs and antidepressants studied may preclude the meta-analysis and thus a pooled estimation of prevalence rates of antidepressant use.
⇒ Another limitation is the exclusion of grey literature in the search strategy.

INTRODUCTION

Of the roughly 800 million people worldwide with a mental disorder, depression and anxiety are the most frequent, and both have a significant burden of disability.[1] Antidepressants are first-line medications to treat current mental disorders, such as depression and anxiety,[2–4] and these indications are those driving the number of prescriptions.[5] Nevertheless, these medications are also prescribed for other in-label and off-label indications such as insomnia, pain, fibromyalgia, eating disorders, smoking cessation, migraine and attention-deficit/hyperactivity disorders.[5–10]

In the last two decades, various epidemiological studies have shown an increased prevalence of antidepressant prescriptions in industrialized countries.[11–17] This could be due to an increased prevalence of current mental disorders,[18 19] which may also be due to primary care physicians' improved ability to recognise these disorders and promptly begin pharmacological treatment. Conversely, other studies suggest a relatively stable prevalence

of mental disorders or under-recognition and undertreatment.[20 21] Other facilitating factors possibly contributing to the rise in antidepressant prescriptions and use are the availability of new medications with a better risk–benefit profile (e.g., selective serotonin reuptake inhibitors (SSRIs)),[22] the introduction of generics on the market,[23] experience or fear of withdrawal symptoms,[24] other socioeconomic and cultural factors (e.g, stigma mental health well-being campaigns)[25 26] or increased duration of treatment.[27 28]

A Canadian study on the surveillance of antidepressant drug prescription patterns showed an increased prevalence between 2006 and 2012, from 9% to 13%.[29] Nevertheless, the incidence rate remained approximately stable in the same period.[29] Similar data on the incidence and prevalence of antidepressant utilization were also reported by other studies in different countries.[11 13 16 27 28] Thus, these results may indicate that the rise in prevalence could be due, at least partially, to an increased mean treatment duration rather than a higher number of patients being prescribed antidepressants. Indeed, a Finnish study estimated that, among antidepressant users in 2000–2001, 43% were long-term users, 32% intermittent and only 26% short-term users. Moreover, only three-quarters of them had a psychiatric condition for which an antidepressant would have been appropriate.[30] A more recent study conducted in Italy showed that almost 30% of patients who started an antidepressant drug treatment in 2013 were still on medication 3 years later.[31] Among them, 10% used more than 180 defined daily doses (DDDs) per year.[31] In addition to these significant changes in prescriptions and use over time, the prevalence in antidepressant drug use also varies according to age,[12 14] sex,[12] country[14 25 32 33] and antidepressant agent or class.[17 32 34]

Despite the extensive utilization of antidepressant drugs worldwide, the increased use over the last decades, and the differences according to relevant sociodemographic factors, no systematic review exists on the prevalence of antidepressant use in the community. To our knowledge, the only systematic reviews on the use of antidepressants focused on specific populations, such as pregnant women[35] or people with particular diseases, such as cancer[36] or acute coronary syndrome.[37] Estimating the prevalence of antidepressant utilization in the general population is essential to inform researchers, clinicians and decision-makers on prescription patterns over time and according to age groups and sex to guide new research, clinical decisions and allocation of health resources. Surveillance of antidepressant use may thus highlight potentially inappropriate prescriptions, such as their use in mild depression.[38] Therefore, this systematic review aims to estimate the prevalence of antidepressant use among children and adolescents, adults and older adults living in the community.

METHODS AND ANALYSIS

We will conduct a systematic review following the Joanna Briggs Institute Manual for Evidence Synthesis[39] for its conduct and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[40] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations[41] for its reporting. The current protocol has been published in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021247423).

We have engaged with a panel of knowledge users (patients, caregivers, clinicians) and researchers to establish our review question and literature search strategy. We will continue to engage with them through the review process (e.g., data extraction, results interpretation and findings dissemination).

Participants

We will include studies on participants living in the community and exposed to antidepressants, independently of age, sex, ethnicity, religion or geographical area. We will exclude all the studies focusing on inpatient populations only (e.g., hospitalized patients, nursing homes) and those focusing on patients with a specific disease (e.g., depression or cancer), condition (e.g., pregnant women) or from a particular social group (e.g., healthcare workers, veterans).

Exposure

We will include studies reporting on antidepressant use independently of class. Thus, all will be included: SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), atypical antidepressants and other antidepressants not elsewhere classified.

Outcomes

The primary outcome will be the prevalence of antidepressant use.

Study design

We will include studies with a descriptive observational design reporting the prevalence of antidepressant use (e.g., cohort studies, cross-sectional studies). Experimental, quasi-experimental, case-series and case-reports studies will be excluded. Case-control studies will be included only if the control group is representative of the general population. We will exclude reviews, commentaries, editorials, letters to the editor, lectures, theses, conference abstracts and grey literature.

Language

No language restriction will be applied.

Search strategy

Search strategies were developed by an experienced medical information specialist (BS) in collaboration with the research team and knowledge users during the protocol phase to ensure feasibility. The MEDLINE strategy was peer-reviewed by a second information specialist following the Peer Review of Electronic Search Strategies (PRESS) checklist. For the search, we used a combination of controlled vocabulary (e.g.,

'Antidepressive Agents', 'Incidence', 'Drug Utilization') and keywords (e.g., 'antidepressants', 'SSRI', 'prevalence'). We will search Embase and MEDLINE (including Epub Ahead of Print and In-Process & Other Non-Indexed Citations) and adjust vocabulary and syntax across databases. The full research strategy is presented as a online supplemental file 1 of this protocol. We will then download results and eliminated duplicates using EndNote V.9.3.3. (Clarivate). We decided to limit our results to the publication years from 1 January 2010 to the date of the final searches. The rationale for this choice was to provide the most up-to-date evidence regarding antidepressant use. Additionally, with antidepressant use increasing in recent years, this strategy minimises the risks of underestimating its prevalence.

Study selection and data extraction

We have developed standardised forms to select eligible studies through title and abstract screening and full-text examination and we will conduct pilot testing of each form with all reviewers. Pairs of reviewers will independently undertake title, abstract and full-text screening and data extraction. Discrepancies between reviewers will be resolved by discussion or arbitration by a third senior reviewer. Extracted data will include (1) study identification (e.g., title, journal, year of publication); (2) study characteristics (e.g., country, study design, source of data); (3) population characteristics (e.g., age, gender, ethnicity) and (4) outcomes (e.g., prevalence, indication/diagnostic, drug prescribed). We will use the DistillerSR software for the management of this review (DistillerSR. V.2.35. Evidence Partners; 2021. Accessed April 2021–February 2022. https://www.evidencepartners.com).

Quality assessment

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.[42] All the discrepancies between reviewers will be resolved by discussion or arbitration by a third senior reviewer.

Data synthesis and analysis

We will synthesize the data on the prevalence of antidepressant drug utilization. Where possible, we will conduct subgroup analyses according to different relevant variables reported in the selected studies. Particular attention will be placed on age groups (children and adolescents; young adults; adults and older adults) and sex differences since antidepressant use (and diseases for which antidepressants are prescribed) varies significantly according to these characteristics.[12 14 43] If relevant, other subgroup analyses will be explored, such as antidepressant class, country or socioeconomic status. 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*.[44] 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 (CIs) 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.[45] 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.[46] 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 heterogenicity, the global estimate will not be interpreted, and the emphasis will be placed on the individual studies. Random-effects meta-regression analyses will thus 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.

Patient and public involvement

Preliminary results of this systematic review will be presented to the patient partner and knowledge users (Qualaxia Network representatives) to involve them in interpreting and understanding the potential implications of the results and getting their feedback.

ETHICS AND DISSEMINATION

This systematic review does not require ethical approval since it will not directly involve human or animal subjects. We will produce a dissemination report for the knowledge users and share the results on social media platforms and through webinars for researchers and healthcare professionals of Quebec. A special issue on the Qualaxia Network Website will cover the results of this systematic review. In addition, a short and standardised policy brief will be shared through the SPOR Evidence Alliance Website. We will further disseminate results through presentations at scientific conferences, research webinars and manuscripts submitted to scientific, peer-reviewed journals for publication.

DISCUSSION

Drug utilization studies are essential to highlight prescription practices and uses of drugs in a real-world context. Nevertheless, systematic reviews of drug utilization studies are missing, except for a few specific populations or diseases. This review will be the first to synthesize information on the global extent of antidepressant use in the community. We will summarize the existing evidence on the epidemiology of antidepressant drug utilization over the last decade and the differences between age groups and sexes. Variability across countries, databases and health systems will be reported and discussed. Results

on antidepressant use globally and across subgroups will be analyzed in light of current clinical guidelines for antidepressant primary indications (e.g., depression and anxiety). Clinical practice guidelines are essential for clinicians to decide when to start an antidepressant, which drug to prescribe and how long to continue the treatment, all depending on patient characteristics. Thus, this systematic review will contribute to the knowledge on antidepressant use among different patient subgroups. Epidemiological data summarised in this review, when compared with guidelines, may indicate a possible over or underuse and a potentially inappropriate use in terms of drug type, duration of treatment, indication or patient characteristics (ie, frailty elders), according to the availability of the information. The evidence will guide clinicians when prescribing these drugs, improving the quality of care offered to people with mental disorders. The results may also guide governments when designing public health policies in mental health, especially to promote, prevent or treat common mental disorders, such as depression and anxiety.

This systematic review protocol may have a few limitations. First, despite the extensive database searches, we will not include grey literature in the search strategy. Moreover, we may not be able to perform a meta-analysis, depending on the available data. In fact, a pooled estimate of the prevalence of antidepressant drug use will be valid only if the heterogeneity among studies is not too large. Differences in populations, data sources, study designs and antidepressants studied may thus preclude a meta-analysis. Although we did not restrict our publication searches by language, we did not actively seek to include publications in other languages than English by searching specific databases covering publications in different languages, such as Spanish or Portuguese. This could thus limit the number of studies included in the review. Moreover, despite the aim of this review being to estimate the prevalence of antidepressant utilization, it is possible that some identified and included studies will 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.

Author affiliations
[1]Department of Health Sciences, Université du Québec à Rimouski, Lévis, Quebec, Canada
[2]Population Heath and Optimal Health Practices Axis, CHU de Québec-Université Laval Research Center, Quebec, Quebec City, Canada
[3]CISSS de Chaudière-Appalaches Research Center, Lévis, Quebec, Canada
[4]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[5]VITAM Research Center on Sustainable Health, Quebec Integrated University Health and Social Services Center, Quebec City, Quebec, Canada
[6]Department of Nursing, Université du Québec à Trois-Rivières, Trois-Rivières, Quebec, Canada
[7]Quebec Heart and Lung Institute Research Centre – Université Laval, Quebec City, Quebec, Canada
[8]Faculty of Pharmacy, Université Laval, Quebec City, Quebec, Canada
[9]Nursing College of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil
[10]Department of Nursing, University of Pecs, Pecs, Hungary
[11]Independent Specialist, Ottawa, Ottawa, Canada
[12]Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada

Twitter Carlotta Lunghi @Carlotta_Lunghi and Jacinthe Leclerc @jacinthelec

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Competing interests None declared.

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ORCID iDs
Carlotta Lunghi http://orcid.org/0000-0001-7636-6285
Jacinthe Leclerc http://orcid.org/0000-0001-5261-2648
Giraud Ekanmian http://orcid.org/0000-0003-2670-3524
Annie LeBlanc http://orcid.org/0000-0002-5377-8102

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