BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062197
Article Type:	Protocol
Date Submitted by the Author:	21-Feb-2022
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Keywords:	EPIDEMIOLOGY, MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, PUBLIC HEALTH, THERAPEUTICS, Anxiety disorders <

	PSYCHIATRY

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

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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 2010 in the Embase and MEDLINE databases. 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 or other sociodemographics. 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 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 to international conferences on mental health and pharmacoepidemiology, as well as general public events.

PROSPERO registration details

CRD42021247423

KEYWORDS

Antidepressants; Prevalence; Systematic review; Drug utilization research.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first systematic review to estimate the prevalence of antidepressant utilization among different age groups in the community.
- This review will follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols guidelines.
- Findings from this review will provide better knowledge about antidepressants use in the community and highlight possible inappropriate use.
- Differences in populations, data sources, study designs and antidepressants studied may preclude meta-analysis and thus a pooled estimation of prevalence rates of antidepressant use.

WORD COUNT: 2057 words

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 recognize 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 receptor 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 three 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 of 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 JBI Manual for Evidence Synthesis (39) for its conduct and the PRISMA (40) and MOOSE (41) guidelines for its reporting. The current protocol has been published in the International Prospective Register of Systematic Reviews database (PROSPERO no. CRD42021247423).

We have engaged with a panel of knowledge users (patients, caregivers, clinicians) and researchers in establishing our review question and literature search strategy. We will continue to engage 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., health care 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) and atypical antidepressants.

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 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. We will then download results and eliminated duplicates using EndNote version 9.3.3. (Clarivate). We decided to limit our results to the publication years from 2010 to the present. 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 minimizes the risks of underestimating its prevalence.

Study selection and data extraction

We have developed standardized forms to select eligible studies through title and abstract screening and full-text examination and we will conduct pilot testing of each form across 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 of 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. Version 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 using the Joanna Briggs Institute Critical Appraisal tool: *Checklist for Studies Reporting Prevalence Data*. All the discrepancies between reviewers will be resolved by discussion or arbitration of 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, 42). If relevant, other subgroup analyses will be explored, such as antidepressant class, country, socioeconomic status, or ethnicity. We will undertake a meta-analysis to generate estimates of antidepressant use prevalence across included studies if the data allows it. Subgroup and sensitivity analyses will be performed when possible and appropriate. If a meta-analytic approach is possible, we will use the I^2 statistic to evaluate heterogeneity. In case of heterogeneity (i.e., I^2>50%) across studies, we will use random-effects models. An experienced biostatistician of the group will conduct the meta-analyses.

EXPECTED LIMITATIONS

This systematic review protocol may have a few limitations. First, despite the extensive databases search, we did 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 estimation 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.

ANTICIPATED RESULTS

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 provide evidence on the epidemiology of antidepressant drug utilization over the last decade and differences between age groups and sexes. Variability across countries, databases and health systems will be reported too. We will analyze results on antidepressant use 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 patients subgroups. It may allow for highlighting their possible inappropriate use in terms of drug type, duration of treatment, indication or patient characteristics (i.e., 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.

ETHICS AND DISSEMINATION

This systematic review does not require ethical approval since it will not 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 standardized 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.

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.

AUTHORS CONTRIBUTIONS

CL, EP and JaL initially conceived the study. AL, BS, CL, JaL, JoL, and MD, substantially contributed to the design of the study methods. CL, JoL and MD prepared the PROSPERO submission. AL, BS, CL, JaL, JoL, and MD elaborated the search strategy, and BS will perform the databases searches. AL, CL, CM, DMN, GE, JoL, LJ, MD, MPD, NE, OS, PB, PSA, TS and VC will perform the screening selection by title and abstract. AL, CL, CM, GE, JoL, MD, NE, OS, PB, TS, and VC will perform the screening selection by full-text examination. CL and CM produced the first draft of this manuscript. AL, BS, DMN, EP, GE, JaL, JoL, LJ, MD, MPD, NE, OS, PB, PSA, TS, and VC critically commented on the first draft and substantially contributed to the final version. All the authors approved the final version of this protocol.

FUNDING STATEMENT

This review is funded by the SPOR Evidence Alliance, which is supported by the Canadian Institutes of Health Research (CIHR) under Canada's Strategy for Patient-Oriented Research (SPOR) Initiative (https://sporevidencealliance.ca). CL received institutional grants from the Université du Québec à Rimouski (Fonds Institutionnel de Recherche, 2019 and 2020) for conducting this systematic review. Two knowledge users from the Qualaxia Network (https://qualaxia.org) provided in-kind support. In-kind support will also be provided by the Centre de Recherche du CISSS de Chaudière-Appalaches with the involvement of a statistician from the group.

COMPETING INTEREST STATEMENT

Authors have no conflict of interest to disclose

ACKNOWLEDGMENTS

We thank Kaitryn Campbell, MLIS, MSc (St. Joseph's Healthcare Hamilton/McMaster University), for the MEDLINE search strategy peer review.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1,2
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1,4
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3,4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4,5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5,6

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5,6
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	5,6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	5,6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	4

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062197.R1
Article Type:	Protocol
Date Submitted by the Author:	04-May-2022

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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Epidemiology, Mental health, Public health, General practice / Family practice
Keywords:	EPIDEMIOLOGY, MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, PUBLIC HEALTH, THERAPEUTICS, Anxiety disorders < PSYCHIATRY

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

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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 Jan 1, 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 to international conferences on mental health and pharmacoepidemiology, as well as general public events.

PROSPERO registration number

CRD42021247423.

KEYWORDS

Antidepressants; Prevalence; Systematic review; Drug utilization research.

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 relevant PRISMA and MOOSE guidelines.
- A potential limitation is that differences in populations, data sources, study designs and antidepressants studied may preclude 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.

WORD COUNT: 2404 words

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 recognize 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 receptor 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 three 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 JBI Manual for Evidence Synthesis (39) for its conduct and the PRISMA guidelines (40) and MOOSE recommendations (41) for its reporting. The current protocol has been published in the International Prospective Register of Systematic Reviews database (PROSPERO no. 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., health care 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 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 supplementary file of this protocol. We will then download results and eliminated duplicates using EndNote version 9.3.3. (Clarivate). We decided to limit our results to the publication years from Jan 1, 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 minimizes the risks of underestimating its prevalence.

Study selection and data extraction

We have developed standardized 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. Version 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 (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 (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 sub-groups... 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 standardized 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 summarized in this review, when compared to 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 (i.e., 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 estimation 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. 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. 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.

Contributors

CL, EP and JaL initially conceived the study. AL, BS, CL, JaL, JoL, MD and ST, substantially contributed to the design of the study methods. CL, JoL and MD prepared the PROSPERO submission. AL, BS, CL, JaL, JoL, and MD elaborated the search strategy, and BS will perform the databases searches. AL, CL, CM, DMN, GE, JoL, LJ, MD, MPD, NE, OS, PB, PSA, TS and VC will perform the screening selection by title and abstract. AL, CL, CM, GE, JoL, MD, NE, OS, PB, TS, and VC will perform the screening selection by full-text examination. ST will perform the statistical analyses. CL and CM produced the first draft of this manuscript. AL, BS, DMN, EP, GE, JaL, JoL, LJ, MD, MPD, NE, OS, PB, PSA, ST, TS, and VC critically commented on the first draft and substantially contributed to the final version. All the authors approved the final version of this protocol.

Funding

This review is funded by the SPOR Evidence Alliance, which is supported by the Canadian Institutes of Health Research (CIHR) under Canada's Strategy for Patient-Oriented Research (SPOR) Initiative (https://sporevidencealliance.ca). CL received institutional grants from the Université du Québec à Rimouski (Fonds Institutionnel de Recherche, 2019 and 2020) for conducting this systematic review. Two knowledge users from the Qualaxia Network (https://qualaxia.org) provided in-kind support. In-kind support will also be provided by the Centre de Recherche du CISSS de Chaudière-Appalaches with the involvement of a statistician from the group.

Competing interests

The authors have no conflicts of interest to disclose.

Acknowledgments

We thank Kaitryn Campbell, MLIS, MSc (St. Joseph's Healthcare Hamilton/McMaster University), for the MEDLINE search strategy peer review.

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Supplementary file 1 – Full search strategies

Ovid Multifile

Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>, Embase Classic+Embase <1947 to 2021 April 29>
Search Strategy:
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1 Antidepressive Agents/ (139870)
2 (antidepressant* or anti-depressant* or antidepressive* or anti-depressive* or neurothymoleptic* or neuro-thymoleptic* or psychoenergi#er* or psycho-energi#er* or thymoanaleptic* or thymoleptic* or thymolytic*).tw,kf. (177266)
3 ((antidepression or anti-depression) adj (agent? or drug? or medication? or pharmaceutic* or prescription?)).tw,kf. (133)
4 Serotonin Uptake Inhibitors/ (65207)
5 ((5 ht or 5ht or 5-hydroxytryptamine or serotonin) adj2 ((uptake or reuptake or re-uptake) adj inhibitor?)).tw,kf. (42043)
6 (SSRI or SSRIs).tw,kf. (27705)
7 "Serotonin and Noradrenaline Reuptake Inhibitors"/ (6522)
8 ((dual monoamine or triple monoamine or noradrenaline or nor-adrenaline or norepinephrine or nor-epinephrine) adj2 ((uptake or reuptake or re-uptake) adj inhibitor?)).tw,kf. (8884)
9 ((dual uptake or dual reuptake or dual re-uptake or triple uptake or triple reuptake or triple re-uptake) adj inhibitor?).tw,kf. (509)
10 (SNRI or SNRIs or SSNRI or SSNRIs or NRI or NRIs or SNDRI or SNDRIs).tw,kf. (9161)
11 Monoamine Oxidase Inhibitors/ (29352)
12 ((amine oxidase or MAO or monoamine or mono amine or monoamino* or mono amino* or tyraminase) adj2 inhibitor?).tw,kf. (19974)
13 MAO inhibit*.tw,kf. (5338)
14 (MAOI or MAOIs).tw,kf. (2485)
15 (RIMA or RIMAs).tw,kf. (1203)
16 Antidepressive Agents, Tricyclic/ (44259)
17 ((tricyclic* or tri-cyclic*) adj2 (antidepress* or anti-depress*)).tw,kf. (24286)
18 ((TCA or TCAs) and (antidepress* or anti-depress*)).tw,kf. (4650)
19 Antidepressive Agents, Second-Generation/ (99918)
20 ((atypical or 2nd generation or second generation) adj2 (antidepress* or anti-depress*)).tw,kf. (2177)
21 Citalopram/ (28532)
22 (citalopram$2 or escitalopram$2 or lexapro$2 or 59729-33-8 or 0DHU5B8D6V).tw,kf,rn. (39430)
23 (acelopam$2 or adeprenal$2 or apo-cital$2 or aurex$2 or ceform$2 or celexa$2 or cilopress$2 or cinavol$2 or ciprager$2 or cipram$2 or cipramil$2 or cipraned$2 or ciprotan$2 or ciral$2 or citabex$2 or citacip$2 or citagen$2 or cital$2 or citalec$2 or citalich$2 or citalon$2 or citalonte$2 or citalostad$2 or citalox$2 or citalver$2 or citapram$2 or citaxin$2 or citesint$2 or citopam$2 or citrol$2 or citronil$2 or cytalopram$2 or dalsan$2 or elopram$2 or exenadil$2 or frimaind$2 or futuril$2 or galapran$2 or humorap$2 or kaidor$2 or kitapram$2 or linisan$2 or lopracil$2 or lopraxer$2 or loxopgram$2 or "lu 10 171" or "lu 10171" or "lu10 171" or lu10171 or lupram$2 or malicon$2 or nitalapram$2 or oropgram$2 or percitale$2 or pralotam$2 or pramital$2 or prefucet$2 or pricital$2 or prisdal$2 or psiconor$2 or renevil$2 or ricap$2 or ropramin$2 or selon$2 or sepram$2 or seralgan$2 or seregra$2 or serital$2 or seropram$2 or seror$2 or sintopram$2 or sotovon$2 or talam$2 or talosin$2 or varom$2 or vesema$2

or xadorek$2 or zanipram$2 or "zd 211" or zd211 or zeclicid$2 or zentius$2 or zitolex$2 or zyloram$2).tw,kf,rn. (4564)
24 (escitalopram$2 or cipralex$2 or enlift$2 or entact$2 or esciprex$2 or "lu 26054 0" or "lu 260540" or lu260540 or premalex$2 or prilect$2 or seroplex$2 or sipralexa$2 or zecidec$2 or zocital$2 or 128196-01-0 or 4O4S742ANY).tw,kf,rn. (16548)
25 Fluoxetine/ (57704)
26 (fluoxetine$2 or actan$2 or adofen$2 or afeksin$2 or "alzac 20" or andep$2 or andepin$2 or ansilan$2 or "atd 20" or auroken$2 or auscap$2 or bioxetin$2 or captaton$2 or daforin$2 or dagrilan$2 or depren$2 or deprex$2 or deprexetin$2 or deprexin$2 or deprizac$2 or deproxin$2 or diesan$2 or digassim$2 or elizac$2 or exostrept$2 or felicium$2 or fldiss$2 or flotinal$2 or floxet$2 or fluctin$2 or fluctine$2 or fludac$2 or flufran$2 or fluketin$2 or flunil$2 or flunirin$2 or fluohexal$2 or fluoksetin$2 or fluoksetyna$2 or fluox$2 or fluoxac$2 or fluoxeren$2 or fluoxetin$2 or fluoxetina$2 or fluoxifar$2 or fluoxil$2 or fluoxone$2 or fluoxtab$2 or fluronin$2 or flusac$2 or flustad$2 or flutin$2 or flutine$2 or fluxemed$2 or fluxen$2 or fluxet$2 or fluxetil$2 or fluxil$2 or fluxomed$2 or fluzac$2 or fokeston$2 or fontex$2 or foxetin$2 or foxtin$2 or fropine$2 or fuloren$2 or gerozac$2 or ladose$2 or lanclic$2 or "lilly 110140" or lilly110140 or lorien$2 or lovan$2 or luramon$2 or "ly 110140" or ly110140 or magrilan$2 or margrilan$2 or meropan$2 or modipran$2 or mutan$2 or nopres$2 or nuzak$2 or olena$2 or oxactin$2 or oxedep$2 or plazeron$2 or plinzene$2 or pragmaten$2 or prizma$2 or proctin$2 or prodep$2 or prosac$2 or prozac$2 or prozamel$2 or prozamin$2 or prozep$2 or prozit$2 or psipax$2 or qualisac$2 or rapiflux$2 or reneuron$2 or rowexetina$2 or salipax$2 or sanzur$2 or sarafem$2 or sartuzin$2 or selfemra$2 or seromex$2 or seronil$2 or sinzac$2 or sofelin$2 or stephadilat-s$2 or xeredien$2 or zactin$2 or zepax$2 or zinovat$2 or 54910-89-3 or 01K63SUP8D).tw,kf,rn. (1078328)
27 Fluvoxamine/ (15400)
28 (fluvoxamine$2 or DU-23000 or desiflu$2 or dumirox$2 or faverin$2 or fevarin$2 or floxyfral$2 or fluvoxadura$2 or fluvoxamin$2 or fluvoxamina$2 or luvox$2 or 54739-18-3 or O4L1XPO44W).tw,kf,rn. (17458)
29 (nefazodone$2 or "bmy 13754" or "bmy 13754 1" or bmy13754 or "bmy13754 1" or bmy137541 or dutonin$2 or "mj 13754" or "mj 13754 1" or mj13754 or "mj13754-1" or mj137541 or menfazona$2 or nefadar$2 or nefazadone$2 or reseril$2 or rulivan$2 or serzone$2 or serzonil$2 or 83366-66-9 or 59H4FCV1TF).tw,kf,rn. (6243)
30 Paroxetine/ (32492)
31 (paroxetine$2 or arketis$2 or aropax$2 or aroxat$2 or brisdelle$2 or "brl 29060" or "brl 29060a" or brl29060 or brl29060a or daparox$2 or deroxat$2 or dexorat$2 or divarius$2 or dropax$2 or euplix$2 or eutimil$2 or "fg 7051" or fg7051 or frosinor$2 or motivan$2 or optipar$2 or paluxetil$2 or paluxon$2 or paroc$2 or parogen$2 or paroxedura$2 or paroxet$2 or paroxetin$2 or paroxetina$2 or paroxia$2 or paxan$2 or paxil$2 or paxtine$2 or paxxet$2 or paxxet$2 or sereupin$2 or seroxat$2 or setine$2 or si 211103 or si211103 or solben$2 or syntopar$2 or tagonis$2 or 61869-08-7 or 41VRH5220H).tw,kf,rn. (35895)
32 Sertraline/ (30357)
33 (sertraline$2 or adjuvin$2 or altruline$2 or aremis$2 or atruline$2 or besitran$2 or "cp 51974" or cp51974 or "cp 519741" or cp519741 or dominum$2 or doxime$2 or fatral$2 or fridep$2 or gladem$2 or lesefer$2 or lustral$2 or nudep$2 or sealdin$2 or seltra$2 or serad$2 or sercerin$2 or serlain$2 or serlift$2 or sertralin$2 or sertranex$2 or sertranquil$2 or sosser$2 or tatig$2 or tresleen$2 or zolof$2 or zoloft$2 or zosert$2 or 79617-96-2 or QUC7NX6WMB).tw,kf,rn. (33443)
34 Trazodone/ (13945)
35 (trazodone$2 or af-1161 or azonz$2 or beneficat$2 or bimaran$2 or deprax$2 or depresil$2 or depyrel$2 or desirel$2 or desyrel$2 or "kb 831" or manegan$2 or molipaxin$2 or oleptro$2 or pesyrel$2

or pragazone$2 or pragmarel$2 or pragmazone$2 or reslin$2 or taxagon$2 or thombran$2 or thromban$2 or thrombran$2 or tombran$2 or tradozone$2 or trasodon$2 or trasodone$2 or trazodil$2 or trazodon$2 or trazolan$2 or trazon$2 or trialodine$2 or trittico$2 or 19794-93-5 or YBK48BXK30).tw,kf,rn. (14995)

36 Vilazodone Hydrochloride/ (774)

37 (vilazodone$2 or "emd 68843" or emd68843 or "sb 659746" or "sb 659746a" or sb659746 or sb659746a or viibryd$2 or 163521-12-8 or S239O2OOV3).tw,kf,rn. (873)

38 Vortioxetine/ (1494)

39 (vortioxetine$2 or brintellix$2 or "lu aa21004" or luaa21004 or trintellix$2 or 508233-74-7 or 3O2K1S3WQV).tw,kf,rn. (1752)

40 Amitriptyline/ (47860)

41 (amitriptyline$2 or adepress$2 or adepril$2 or ambivalon$2 or amilit$2 or amineurin$2 or amiplin$2 or amiprin$2 or amirol$2 or amitid$2 or amitril$2 or amitrip$2 or amitriptylene$2 or amitriptylin$2 or amitriptylinumhydrochloride$2 or amitryptiline$2 or amitryptilline$2 or amitryptine$2 or amitryptyline$2 or amyline$2 or amytril$2 or amytriptiline$2 or amytriptyline$2 or amytryptiline$2 or amyzol$2 or anapsique$2 or "anp 3548" or antalin$2 or antitriptyline$2 or damilen$2 or damilene$2 or damitriptyline$2 or damylene$2 or deprelio$2 or domical$2 or elatrol$2 or elatrolet$2 or elavil$2 or enafon$2 or endep$2 or enovil$2 or etafon$2 or etafron$2 or euplit$2 or lantron$2 or laroxal$2 or lentizol$2 or miketorin$2 or "mk 230" or "n 750" or novoprotect$2 or ormal$2 or pinsaun$2 or proheptadien$2 or qualitriptine$2 or redomex$2 or "ro 4 1575" or sarboten retard$2 or sarotard$2 or saroten$2 or sarotena$2 or sarotex$2 or stelminal$2 or sylvemid$2 or syneudon$2 or syneydon$2 or teperin$2 or terepin$2 or trepiline$2 or tridep$2 or tripta or triptaR or triptaTM or triptanol$2 or triptizol$2 or triptyl$2 or triptyline$2 or trynol$2 or tryptanol$2 or tryptizol$2 or trytomer$2 or uxen or uxenR or uxenTM or vanatrip$2 or 50-48-6 or 1806D8D52K).tw,kf,rn. (52240)

42 Clomipramine/ (20960)

43 (clomipramine$2 or anafranil$2 or anafranilin$2 or anafranyl$2 or chlomipramine$2 or chlorimipramine$2 or chloroimipramine$2 or clofranil$2 or clomicalm$2 or clomipramin$2 or clomipramine$2 or clopress$2 or domipramine$2 or equinorm$2 or "g 34586" or g34586 or gromin$2 or hydiphen$2 or monochlor imipramine$2 or monochlorimipramine$2 or monochloroimipramine$2 or placil$2 or zoiral$2 or 303-49-1 or NUV44L116D).tw,kf,rn. (22928)

44 Desvenlafaxine Succinate/ (2093)

45 (desvenlafaxine$2 or "dvs 233" or dvs233 or ellefore$2 or khedezla$2 or pristiq$2 or pristiqs$2 or "wy 45233" or wy45233 or 93413-62-8 or NG99554ANW).tw,kf,rn. (2124)

46 Doxepin/ (10595)

47 (doxepin$2 or adapin$2 or anten or antenR or antenTM or aponal$2 or co dox$2 or curatin$2 or deptran$2 or desidox$2 or doneurin$2 or doxal$2 or doxepine$2 or expan or expanR or expanTM or gilex$2 or mareen$2 or "nsc 108160" or "p 3693a" or prudoxin$2 or quitaxon$2 or silenor$2 or sinequan$2 or sinquan$2 or sinquane$2 or zonalon$2 or 1668-19-5 or 5ASJ6HUZ7D).tw,kf,rn. (12898)

48 Duloxetine Hydrochloride/ (13292)

49 (duloxetine$2 or ariclaim$2 or cymbalta$2 or drizalma$2 or dulane$2 or duzela$2 or irenka$2 or "ly 227942" or ly227942 or "ly 248686" or ly248686 or xeristar$2 or yentreve$2 or 116539-59-4 or O5TNM5N07U).tw,kf,rn. (14584)

50 Imipramine/ (47078)

51 (imipramine$2 or antidep$2 or antideprin$2 or berkomin$2 or chrytemin$2 or daypress$2 or deprinol$2 or depsol$2 or depsonil$2 or ethipramine$2 or fronil$2 or "g 22150" or g22150 or "g 22355" or g22355 or ia pram$2 or imavate$2 or imidol$2 or imipramide$2 or imipramin$2 or imiprin$2 or imizin$2 or imizine$2 or janimine$2 or melipramin$2 or melipramine$2 or norchlorimipramine$2 or norpramine$2 or novopramine$2 or pramine$2 or presamine$2 or primonil$2 or pryleugan$2 or

psychoforin$2 or psychoforine$2 or sermonil$2 or servipramine$2 or sk pramine$2 or talpramin$2 or tofranil$2 or trofanil$2 or venefon$2 or 50-49-7 or OGG85SX4E4).tw,kf,rn. (51712)
52 Milnacipran/ (3157)
53 (milnacipran$2 or "f 2207" or f2207 or "f 2695" or f2695 or fetzima$2 or impulsor$2 or ixel$2 or levomilnacipran$2 or midalcipran$2 or savella$2 or "tn 912" or tn912 or toledomin$2 or 92623-85-3 or G56VK1HF36).tw,kf,rn. (3601)
54 Venlafaxine Hydrochloride/ (24848)
55 (venlafaxine$2 or apclaven$2 or dobupal$2 or duofaxin$2 or efectin$2 or efexor$2 or effexor$2 or elafax$2 or faxiprol$2 or genexin$2 or pracet$2 or serosmine$2 or sunveniz$2 or trevilor$2 or trewilor$2 or vandral$2 or vaxor$2 or venix-xr$2 or venla$2 or venlabrain$2 or venlafaxin$2 or venlafaxina$2 or venlalic$2 or venlaneo$2 or venlax$2 or venlaxin$2 or venlazid$2 or venxin$2 or venzip$2 or viepax$2 or "wy 45030" or wy45030 or zarelis$2 or 93413-69-5 or GRZ5RCB1QG).tw,kf,rn. (26911)
56 (bifemelane$2 or alnert$2 or celeport$2 or "mci 2016" or mci2016 or 90293-01-9 or Z4501GN13G).tw,kf,rn. (365)
57 Isocarboxazid/ (1949)
58 (isocarboxazid$2 or bmih$2 or enerzer$2 or isocarboazide$2 or isocarboxacid$2 or isocarboxazide$2 or marplan$2 or "ro 5 0831" or "ro 50831" or "u 10387 59-63-2" or 34237V843T).tw,kf,rn. (2074)
59 Moclobemide/ (5385)
60 (moclobemide$2 or arima$2 or aurorex$2 or aurorix$2 or deprenorm$2 or feraken$2 or manerix$2 or meclobemide$2 or moclaime$2 or moclamide$2 or moclamine$2 or moclix$2 or moclobamide$2 or moclobamid$2 or moclobeta$2 or moclodura$2 or moclonorm$2 or rimoc$2 or "ro 11 1163" or "ro 111163" or zorix$2 or 71320-77-9 or PJ0Y7AZB63).tw,kf,rn. (8446)
61 MAO A inhibitor?.tw,kf,rn. (1346)
62 Phenelzine/ (7359)
63 (phenelzine$2 or benzylmethylhydrazine$2 or beta phenethylhydrazine$2 or beta phenylethylhydrazine$2 or fenelzin$2 or fenelzine$2 or fenizin$2 or mao rem$2 or nardelzine$2 or nardil$2 or phenalzine$2 or phenelzin$2 or phenethylhydrazine$2 or phenylethylhydrazine$2 or stinerval$2 or "w 1544" or w1544 or 51-71-8 or O408N561GF).tw,kf,rn. (7780)
64 (toloxatone$2 or humoryl$2 or perenum$2 or 29218-27-7 or 5T206015T5).tw,kf,rn. (408)
65 Tranylcypromine/ (8284)
66 (tranylcypromine$2 or jatrosom$2 or parmodalin$2 or parnate$2 or parnitene$2 or parnitine$2 or "sk and f 385" or "skf 385" or "skf trans 385" or trancilpromine$2 or trancylpromine$2 or trancylprominesulfate$2 or trancylprominesulphate$2 or tranilacipromina$2 or transamine$2 or tranylcypomia$2 or tranylcypromide$2 or tranylcypromin$2 or tranylcypromine$2 or tylciprine$2 or 155-09-9 or 3E3V44J4Z9).tw,kf,rn. (9057)
67 Mazindol/ (2493)
68 (mazindol$2 or "AN-448" or dasten$2 or degonan$2 or diestet$2 or drinamyl$2 or fagolipo$2 or liofindol$2 or mazanor$2 or manzindol$2 or mazindole$2 or pento adiparthrol$2 or sanjorex$2 or sanorex$2 or slankosan$2 or solucaps$2 or teronac$2 or teronak$2 or 22232-71-9 or C56709M5NH).tw,kf,rn. (2983)
69 (amitriptyline$2 or amioxid-neuraxpharm$2 or amitriptyline n oxide$2 or dano or danoR or danoTM or equilibrin$2 or 4317-14-0 or TYR2U59WMA).tw,kf,rn. (52583)
70 Amoxapine/ (2733)
71 (amoxapine$2 or adisen$2 or amoxan$2 or amoxapin$2 or asendin$2 or asendis$2 or "cl 67,772" or "cl 67772" or "cl67,772" or "cl67772" or defanyl$2 or demolox$2 or desmethylloxapine$2 or moxadil$2 or 14028-44-5 or R63VQ857OT).tw,kf,rn. (2960)

72 (demexiptiline$2 or demexiptyline$2 or deparon$2 or tinoran$2 or 24701-51-7 or EYX738UZ5P).tw,kf,rn. (41)
73 Desipramine/ (28138)
74 (desipramine$2 or "aw 1151129" or aw1151129 or demethylimipramine$2 or deprexan$2 or desimipramine$2 or desipramin$2 or desipramine$2 or desmethyl imipramin$2 or desmethyl imipramine$2 or desmethylimipramin$2 or desmethylimipramine$2 or despiramine$2 or "ex 4355" or ex4355 or "g 15020" or "g 35020" or g15020 or g35020 or "jb 8181" or jb8181 or n demethylimipramine$2 or nebril$2 or norimipramine$2 or norpramin$2 or norpramine$2 or nortimil$2 or "nsc 114901" or nsc114901 or pentrofane$2 or pertofran$2 or pertofrane$2 or pertofrin$2 or pertrofran$2 or petrofran$2 or petrofrane$2 or petylyl$2 or "rmi 9,384a" or "rmi 9384a" or "rmi9,384a" or rmi9384a or sertofren$2 or 50-47-5 or 58-28-6 or TG537D343B).tw,kf,rn. (31505)
75 (dibenzepin$2 or bibenzepin$2 or deprex$2 or dibenzepine$2 or dibenzepinum$2 or dibenzoazepine$2 or ecatril$2 or "hf 1927" or hf1927 or "l.w. 1927" or neodalit$2 or neodil$2 or noveril$2 or 4498-32-2 or 510SJZ1Y6L).tw,kf,rn. (1188)
76 (dimetacrin$2 or dimetacrine$2 or dimethacin$2 or dimethacine$2 or dimethacrin$2 or dimethacrine$2 or istonil$2 or miroistonil$2 or "sd 709" or 3759-07-7 or 4757-55-5 or O341NY501N).tw,kf,rn. (249)
77 Dothiepin/ (2786)
78 (dothiepin$2 or altapin$2 or depresym$2 or dosulepin$2 or dosulepine$2 or dothapax$2 or dothiepin$2 or idom or idomR or idomTM or prepadine$2 or prothiaden$2 or prothiadene$2 or prothiadiene$2 or prothiadine$2 or protiaden$2 or 113-53-1 or 897-15-4 or W13O82Z7HL).tw,kf,rn. (3028)
79 (imipraminoxide$2 or elepsin$2 or imipramine$2 or imiprex$2 or 6829-98-7 or 8MKS280XJW).tw,kf,rn. (51507)
80 Lofepramine/ (1221)
81 (lofepramine$2 or amplit$2 or deftan$2 or feprapax$2 or gam#nil$2 or "leo 640" or lomont$2 or tymelyt$2 or "whr 2908a" or 23047-25-8 or 26786-32-3 or OCA4JT7PAW).tw,kf,rn. (1696)
82 (melitracen$2 or dixeran$2 ormelitracene$2 or melixeran$2 or metrisil$2 or 5118-29-6 or 10563-70-9 or Q7T0Y1109Z).tw,kf,rn. (553)
83 (metapramine$2 or "19560 rp" or "rp 19560" or timaxel$2 or 21730-16-5 or 303954M7YF).tw,kf,rn. (172)
84 (nitroxazepine$2 or "233-go" or "2330 go" or "c 2330 go" or "c2330 go" or c2330go or sintamil$2 or 16398-39-3 or CNU9GY55SI).tw,kf,rn. (74)
85 (nordoxepin$2 or demethyldoxepin$2 or desmethyldoxepin$2 or "doxepin,nor$2" or 1225-56-5 or F498JSH8R).tw,kf,rn. (440)
86 Nortriptyline/ (17647)
87 (nortriptyline$2 or acetexa$2 or allegron$2 or altile$2 or ateben$2 or atilev$2 or avantyl$2 or aventyl$2 or desitriptyline$2 or desmethylamitriptylin$2 or desmethylamitriptyline$2 or "l 38489" or martimil$2 or noramitriptyline$2 or norfenazin$2 or noritren$2 or norline$2 or norpress$2 or nortrilen$2 or nortrilene$2 or nortriptylin$2 or nortriptyline$2 or nortrix$2 or nortryptilin$2 or nortryptiline$2 or nortryptyline$2 or nortyline$2 or norventyl$2 or ortrip$2 or pamelor$2 or paxtibi$2 or psychostyl$2 or sensaval$2 or sensival$2 or vividyl$2 or 72-69-5 or BL03SY4LXB).tw,kf,rn. (18938)
88 (noxiptiline$2 or agedal$2 or "bay 1521" or bay1521 or "bayer 1521" or dibenzoxin$2 or elronon$2 or nogedal$2 or noxiphylin$2 or noxiptilin$2 or noxiptiline$2 or noxiptillin$2 or noxiptilline$2 or noxiptylin$2 or noxiptyline$2 or noxyptiline$2 or 24573-06-6 or 3362-45-6 or DF7D3NY7EL).tw,kf,rn. (314)
89 Opipramol/ (1287)

90 (opipramol$2 or dinsidon$2 or ensidon$2 or eusidon$2 or "g 33040" or g33040 or insidon$2 or nisidan$2 or opipramole$2 or pramolan$2 or "rp 8307" or rp8307 or 315-72-0 or D23ZXO613C).tw,kf,rn. (1386)
91 (propizepin$2 or propizepine$2 or pyridobenzodiazepine$2 or "up 106" or vagran$2 or 10321-12-7 or 09B57945V9).tw,kf,rn. (1017)
92 Protriptyline/ (2889)
93 (protriptyline$2 or amimetilina$2 or concordin$2 or maximed$2 or "mk 240" or mk240 or protriphyline$2 or protryptyline$2 or triptil$2 or vivactil$2 or 438-60-8 or 4NDU154T12).tw,kf,rn. (3302)
94 (quinupramine$2 or kevopril$2 or kinupril$2 or "lm 208" or 31721-17-2 or 29O61HFF4L).tw,kf,rn. (137)
95 (tianeptine$2 or coaxil$2 or "s 1574" or s1574 or stablon$2 or 72797-41-2 or 0T493YFU8).tw,kf,rn. (2295)
96 Trimipramine/ (4133)
97 (trimipramine$2 or apo-trimip$2 or eldoral$2 or herphonal$2 or "il 6001" or rhotrimine$2 or "rp 7162" or sapilent$2 or stangyl$2 or sumontil$2 or surmontil$2 or trimepramine$2 or trimeprimin$2 or trimeprimine$2 or trimepropimine$2 or trimidura$2 or trimineurin$2 or trimipramine$2 or trimoprimine$2 or tripress$2 or tydamine$2 or 739-71-9 or 6S082C9NDT).tw,kf,rn. (4438)
98 or/1-97 [DRUG CLASSES/DRUGS OF INTEREST] (1492537)
99 Data Collection/ (312402)
100 Incidence/ (733335)
101 incidenc*.tw,kf. (2052347)
102 Prevalence/ (1097648)
103 prevalen*.tw,kf. (1987884)
104 Databases, Factual/ (109779)
105 ((admin* or billing* or claim? or factual or insurance or utili#ation) adj3 (data or database* or data-base* or databank* or data-bank* or dataset? or data-set? or statistic*)).tw,kf. (146575)
106 exp Drug Prescriptions/sn [statistics & numerical data, trends] (9243)
107 Drug Utilization/ (42374)
108 Practice Patterns, Physicians'/sn, td [statistics & numerical data, trends] (24160)
109 or/99-108 [EPI FILTER] (4785817)
110 98 and 109 [DRUG CLASSES OF INTEREST - EPI FILTER] (77826)
111 exp Animals/ not Humans/ (16979954)
112 110 not 111 [ANIMAL-ONLY REMOVED] (56366)
113 (comment or editorial or letter or newspaper article or news).pt. (4064318)
114 112 not 113 [OPINION PIECES REMOVED] (55375)
115 limit 114 to yr="2010-current" (28582)
116 115 use ppez [MEDLINE RECORDS] (12995)
117 antidepressant agent/ (104014)
118 (antidepressant* or anti-depressant* or antidepressive* or anti-depressive* or neurothymoleptic* or neuro-thymoleptic* or psychoenergi#er* or psycho-energi#er* or thymoanaleptic* or thymoleptic* or thymolytic*).tw,kw. (180736)
119 ((antidepression or anti-depression) adj (agent? or drug? or medication? or pharmaceutic* or prescription?)).tw,kw. (133)
120 serotonin uptake inhibitor/ (68901)
121 ((5 ht or 5ht or 5-hydroxytryptamine or serotonin) adj2 ((uptake or reuptake or re-uptake) adj inhibitor?)).tw,kw. (42788)
122 (SSRI or SSRIs).tw,kw. (28796)
123 serotonin noradrenalin reuptake inhibitor/ (6130)

124 triple reuptake inhibitor/ (264)
125 ((dual monoamine or triple monoamine or noradrenaline or nor-adrenaline or norepinephrine or nor-epinephrine) adj2 ((uptake or reuptake or re-uptake) adj inhibitor?)).tw,kw. (8996)
126 ((dual uptake or dual reuptake or dual re-uptake or triple uptake or triple reuptake or triple re-uptake) adj inhibitor?).tw,kw. (524)
127 (SNRI or SNRIs or SSNRI or SSNRIs or NRI or NRIs or SNDRI or SNDRIs).tw,kw. (9343)
128 monoamine oxidase inhibitor/ (29352)
129 ((amine oxidase or MAO or monoamine or mono amine or monoamino* or mono amino* or tyraminase) adj2 inhibitor?).tw,kw. (19729)
130 MAO inhibit*.tw,kw. (5457)
131 (MAOI or MAOIs).tw,kw. (2554)
132 (RIMA or RIMAs).tw,kw. (1233)
133 tricyclic antidepressant agent/ (34650)
134 ((tricyclic* or tri-cyclic*) adj2 (antidepress* or anti-depress*)).tw,kw. (24624)
135 ((TCA or TCAs) and (antidepress* or anti-depress*)).tw,kw. (4725)
136 ((atypical or 2nd generation or second generation) adj2 (antidepress* or anti-depress*)).tw,kw. (2202)
137 citalopram/ (28532)
138 (citalopram$2 or escitalopram$2 or lexapro$2 or 59729-33-8 or 0DHU5B8D6V).tw,kw,rn. (39455)
139 (acelopam$2 or adeprenal$2 or apo-cital$2 or aurex$2 or ceform$2 or celexa$2 or cilopress$2 or cinavol$2 or ciprager$2 or cipram$2 or cipramil$2 or cipraned$2 or ciprotan$2 or ciral$2 or citabex$2 or citacip$2 or citagen$2 or cital$2 or citalec$2 or citalich$2 or citalon$2 or citalonte$2 or citalostad$2 or citalox$2 or citalver$2 or citapram$2 or citaxin$2 or citesint$2 or citopam$2 or citrol$2 or citronil$2 or cytalopram$2 or dalsan$2 or elopram$2 or exenadil$2 or frimaind$2 or futuril$2 or galapran$2 or humorap$2 or kaidor$2 or kitapram$2 or linisan$2 or lopracil$2 or lopraxer$2 or loxopgram$2 or "lu 10 171" or "lu 10171" or "lu10 171" or lu10171 or lupram$2 or malicon$2 or nitalapram$2 or oropgram$2 or percitale$2 or pralotam$2 or pramital$2 or prefucet$2 or pricital$2 or prisdal$2 or psiconor$2 or renevil$2 or ricap$2 or ropramin$2 or selon$2 or sepram$2 or seralgan$2 or seregra$2 or serital$2 or seropram$2 or seror$2 or sintopram$2 or sotovon$2 or talam$2 or talosin$2 or varom$2 or vesema$2 or xadorek$2 or zanipram$2 or "zd 211" or zd211 or zeclicid$2 or zentius$2 or zitolex$2 or zyloram$2).tw,kw,rn. (4569)
140 escitalopram/ (17738)
141 (escitalopram$2 or cipralex$2 or enlift$2 or entact$2 or esciprex$2 or "lu 26054 0" or "lu 260540" or lu260540 or premalex$2 or prilect$2 or seroplex$2 or sipralexa$2 or zecidec$2 or zocital$2 or 128196-01-0 or 4O4S742ANY).tw,kw,rn. (16569)
142 fluoxetine/ (57704)
143 (fluoxetine$2 or actan$2 or adofen$2 or afeksin$2 or "alzac 20" or andep$2 or andepin$2 or ansilan$2 or "atd 20" or auroken$2 or auscap$2 or bioxetin$2 or captaton$2 or daforin$2 or dagrilan$2 or depren$2 or deprex$2 or deprexetin$2 or deprexin$2 or deprizac$2 or deproxin$2 or diesan$2 or digassim$2 or elizac$2 or exostrept$2 or felicium$2 or fldiss$2 or flotinal$2 or floxet$2 or fluctin$2 or fluctine$2 or fludac$2 or flufran$2 or fluketin$2 or flunil$2 or flunirin$2 or fluohexal$2 or fluoksetin$2 or fluoksetyna$2 or fluox$2 or fluoxac$2 or fluoxeren$2 or fluoxetin$2 or fluoxetina$2 or fluoxifar$2 or fluoxil$2 or fluoxone$2 or fluoxtab$2 or fluronin$2 or flusac$2 or flustad$2 or flutin$2 or flutine$2 or fluxemed$2 or fluxen$2 or fluxet$2 or fluxetil$2 or fluxil$2 or fluxomed$2 or fluzac$2 or fokeston$2 or fontex$2 or foxetin$2 or foxtin$2 or fropine$2 or fuloren$2 or gerozac$2 or ladose$2 or lanclic$2 or "lilly 110140" or lilly110140 or lorien$2 or lovan$2 or luramon$2 or "ly 110140" or ly110140 or magrilan$2 or margrilan$2 or meropan$2 or modipran$2 or mutan$2 or nopres$2 or nuzak$2 or olena$2 or oxactin$2 or oxedep$2 or plazeron$2 or plinzene$2 or pragmaten$2 or prizma$2 or

proctin$2 or prodep$2 or prosac$2 or prozac$2 or prozamel$2 or prozamin$2 or prozep$2 or prozit$2 or psipax$2 or qualisac$2 or rapiflux$2 or reneuron$2 or rowexetina$2 or salipax$2 or sanzur$2 or sarafem$2 or sartuzin$2 or selfemra$2 or seromex$2 or seronil$2 or sinzac$2 or sofelin$2 or stephadilat-s$2 or xeredien$2 or zactin$2 or zepax$2 or zinovat$2 or 54910-89-3 or 01K63SUP8D).tw,kw,rn. (1080237)
144 fluvoxamine/ (15400)
145 (fluvoxamine$2 or DU-23000 or desiflu$2 or dumirox$2 or faverin$2 or fevarin$2 or floxyfral$2 or fluvoxadura$2 or fluvoxamin$2 or fluvoxamina$2 or luvox$2 or 54739-18-3 or O4L1XPO44W).tw,kw,rn. (17468)
146 nefazodone/ (5387)
147 (nefazodone$2 or "bmy 13754" or "bmy 13754 1" or bmy13754 or "bmy13754 1" or bmy137541 or dutonin$2 or "mj 13754" or "mj 13754 1" or mj13754 or "mj13754-1" or mj137541 or menfazona$2 or nefadar$2 or nefazadone$2 or reseril$2 or rulivan$2 or serzone$2 or serzonil$2 or 83366-66-9 or 59H4FCV1TF).tw,kw,rn. (6246)
148 paroxetine/ (32492)
149 (paroxetine$2 or arketis$2 or aropax$2 or aroxat$2 or brisdelle$2 or "brl 29060" or "brl 29060a" or brl29060 or brl29060a or daparox$2 or deroxat$2 or dexorat$2 or divarius$2 or dropax$2 or euplix$2 or eutimil$2 or "fg 7051" or fg7051 or frosinor$2 or motivan$2 or optipar$2 or paluxetil$2 or paluxon$2 or paroc$2 or parogen$2 or paroxedura$2 or paroxet$2 or paroxetin$2 or paroxetina$2 or paroxia$2 or paxan$2 or paxil$2 or paxtine$2 or paxxet$2 or paxxet$2 or sereupin$2 or seroxat$2 or setine$2 or si 211103 or si211103 or solben$2 or syntopar$2 or tagonis$2 or 61869-08-7 or 41VRH5220H).tw,kw,rn. (35932)
150 sertraline/ (30357)
151 (sertraline$2 or adjuvin$2 or altruline$2 or aremis$2 or atruline$2 or besitran$2 or "cp 51974" or cp51974 or "cp 519741" or cp519741 or dominum$2 or doxime$2 or fatral$2 or fridep$2 or gladem$2 or lesefer$2 or lustral$2 or nudep$2 or sealdin$2 or seltra$2 or serad$2 or sercerin$2 or serlain$2 or serlift$2 or sertralin$2 or sertranex$2 or sertranquil$2 or sosser$2 or tatig$2 or tresleen$2 or zolof$2 or zoloft$2 or zosert$2 or 79617-96-2 or QUC7NX6WMB).tw,kw,rn. (33468)
152 trazodone/ (13945)
153 (trazodone$2 or af-1161 or azonz$2 or beneficat$2 or bimaran$2 or deprax$2 or depresil$2 or depyrel$2 or desirel$2 or desyrel$2 or "kb 831" or manegan$2 or molipaxin$2 or oleptro$2 or pesyrel$2 or pragazone$2 or pragmarel$2 or pragmazone$2 or reslin$2 or taxagon$2 or thombran$2 or thromban$2 or thrombran$2 or tombran$2 or tradozone$2 or trasodon$2 or trasodone$2 or trazodil$2 or trazodon$2 or trazolan$2 or trazon$2 or trialodine$2 or trittico$2 or 19794-93-5 or YBK48BXK30).tw,kw,rn. (15008)
154 vilazodone/ (774)
155 (vilazodone$2 or "emd 68843" or emd68843 or "sb 659746" or "sb 659746a" or sb659746 or sb659746a or viibryd$2 or 163521-12-8 or S239O2OOV3).tw,kw,rn. (879)
156 vortioxetine/ (1494)
157 (vortioxetine$2 or brintellix$2 or "lu aa21004" or luaa21004 or trintellix$2 or 508233-74-7 or 3O2K1S3WQV).tw,kw,rn. (1762)
158 amitriptyline/ (47860)
159 (amitriptyline$2 or adepress$2 or adepril$2 or ambivalon$2 or amilit$2 or amineurin$2 or amiplin$2 or amiprin$2 or amirol$2 or amitid$2 or amitril$2 or amitrip$2 or amitriptylene$2 or amitriptylin$2 or amitriptylinumhydrochloride$2 or amitryptiline$2 or amitryptilline$2 or amitryptine$2 or amitryptyline$2 or amyline$2 or amytril$2 or amytriptiline$2 or amytriptyline$2 or amytryptiline$2 or amyzol$2 or anapsique$2 or "anp 3548" or antalin$2 or antitriptyline$2 or damilen$2 or damilene$2 or damitriptyline$2 or damylene$2 or deprelio$2 or domical$2 or elatrol$2 or elatrolet$2 or elavil$2 or

enafon$2 or endep$2 or enovil$2 or etafon$2 or etafron$2 or euplit$2 or lantron$2 or laroxal$2 or lentizol$2 or miketorin$2 or "mk 230" or "n 750" or novoprotect$2 or ormal$2 or pinsaun$2 or proheptadien$2 or qualitriptine$2 or redomex$2 or "ro 4 1575" or sarboten retard$2 or sarotard$2 or saroten$2 or sarotena$2 or sarotex$2 or stelminal$2 or sylvemid$2 or syneudon$2 or syneydon$2 or teperin$2 or terepin$2 or trepiline$2 or tridep$2 or tripta or triptaR or triptaTM or triptanol$2 or triptizol$2 or triptyl$2 or triptyline$2 or trynol$2 or tryptanol$2 or tryptizol$2 or trytomer$2 or uxen or uxenR or uxenTM or vanatrip$2 or 50-48-6 or 1806D8D52K).tw,kw,rn. (52262)

160 clomipramine/ (20960)

161 (clomipramine$2 or anafranil$2 or anafranilin$2 or anafranyl$2 or chlomipramine$2 or chlorimipramine$2 or chloroimipramine$2 or clofranil$2 or clomicalm$2 or clomipramin$2 or clomipramine$2 or clopress$2 or domipramine$2 or equinorm$2 or "g 34586" or g34586 or gromin$2 or hydiphen$2 or monochlor imipramine$2 or monochlorimipramine$2 or monochloroimipramine$2 or placil$2 or zoiral$2 or 303-49-1 or NUV44L116D).tw,kw,rn. (22936)

162 desvenlafaxine/ (2093)

163 (desvenlafaxine$2 or "dvs 233" or dvs233 or ellefore$2 or khedezla$2 or pristiq$2 or pristiqs$2 or "wy 45233" or wy45233 or 93413-62-8 or NG99554ANW).tw,kw,rn. (2126)

164 doxepin/ (10595)

165 (doxepin$2 or adapin$2 or anten or antenR or antenTM or aponal$2 or co dox$2 or curatin$2 or deptran$2 or desidox$2 or doneurin$2 or doxal$2 or doxepine$2 or expan or expanR or expanTM or gilex$2 or mareen$2 or "nsc 108160" or "p 3693a" or prudoxin$2 or quitaxon$2 or silenor$2 or sinequan$2 or sinquan$2 or sinquane$2 or zonalon$2 or 1668-19-5 or 5ASJ6HUZ7D).tw,kw,rn. (12904)

166 duloxetine/ (13292)

167 (duloxetine$2 or ariclaim$2 or cymbalta$2 or drizalma$2 or dulane$2 or duzela$2 or irenka$2 or "ly 227942" or ly227942 or "ly 248686" or ly248686 or xeristar$2 or yentreve$2 or 116539-59-4 or O5TNM5N07U).tw,kw,rn. (14606)

168 imipramine/ (47078)

169 (imipramine$2 or antidep$2 or antideprin$2 or berkomin$2 or chrytemin$2 or daypress$2 or deprinol$2 or depsol$2 or depsonil$2 or ethipramine$2 or fronil$2 or "g 22150" or g22150 or "g 22355" or g22355 or ia pram$2 or imavate$2 or imidol$2 or imipramide$2 or imipramin$2 or imiprin$2 or imizin$2 or imizine$2 or janimine$2 or melipramin$2 or melipramine$2 or norchlorimipramine$2 or norpramine$2 or novopramine$2 or pramine$2 or presamine$2 or primonil$2 or pryleugan$2 or psychoforin$2 or psychoforine$2 or sermonil$2 or servipramine$2 or sk pramine$2 or talpramin$2 or tofranil$2 or trofanil$2 or venefon$2 or 50-49-7 or OGG85SX4E4).tw,kw,rn. (51728)

170 milnacipran/ (3157)

171 (milnacipran$2 or "f 2207" or f2207 or "f 2695" or f2695 or fetzima$2 or impulsor$2 or ixel$2 or levomilnacipran$2 or midalcipran$2 or savella$2 or "tn 912" or tn912 or toledomin$2 or 92623-85-3 or G56VK1HF36).tw,kw,rn. (3606)

172 venlafaxine/ (24848)

173 (venlafaxine$2 or apclaven$2 or dobupal$2 or duofaxin$2 or efectin$2 or efexor$2 or effexor$2 or elafax$2 or faxiprol$2 or genexin$2 or pracet$2 or serosmine$2 or sunveniz$2 or trevilor$2 or trewilor$2 or vandral$2 or vaxor$2 or venix-xr$2 or venla$2 or venlabrain$2 or venlafaxin$2 or venlafaxina$2 or venlalic$2 or venlaneo$2 or venlax$2 or venlaxin$2 or venlazid$2 or venxin$2 or venzip$2 or viepax$2 or "wy 45030" or wy45030 or zarelis$2 or 93413-69-5 or GRZ5RCB1QG).tw,kw,rn. (26929)

174 bifemelane/ (240)

175 (bifemelane$2 or alnert$2 or celeport$2 or "mci 2016" or mci2016 or 90293-01-9 or Z4501GN13G).tw,kw,rn. (365)

176 isocarboxazid/ (1949)

177 (isocarboxazid$2 or bmih$2 or enerzer$2 or isocarboazide$2 or isocarboxacid$2 or isocarboxazide$2 or marplan$2 or "ro 5 0831" or "ro 50831" or "u 10387 59-63-2" or 34237V843T).tw,kw,rn. (2075)
178 moclobemide/ (5385)
179 (moclobemide$2 or arima$2 or aurorex$2 or aurorix$2 or deprenorm$2 or feraken$2 or manerix$2 or meclobemide$2 or moclaime$2 or moclamide$2 or moclamine$2 or moclix$2 or moclobamide$2 or moclobamid$2 or moclobeta$2 or moclodura$2 or moclonorm$2 or rimoc$2 or "ro 11 1163" or "ro 111163" or zorix$2 or 71320-77-9 or PJ0Y7AZB63).tw,kw,rn. (8494)
180 monoamine oxidase A inhibitor/ (821)
181 MAO A inhibitor?.tw,kw,rn. (1367)
182 phenelzine/ (7359)
183 (phenelzine$2 or benzylmethylhydrazine$2 or beta phenethylhydrazine$2 or beta phenylethylhydrazine$2 or fenelzin$2 or fenelzine$2 or fenizin$2 or mao rem$2 or nardelzine$2 or nardil$2 or phenalzine$2 or phenelzin$2 or phenethylhydrazine$2 or phenylethylhydrazine$2 or stinerval$2 or "w 1544" or w1544 or 51-71-8 or O408N561GF).tw,kw,rn. (7782)
184 toloxatone/ (316)
185 (toloxatone$2 or humoryl$2 or perenum$2 or 29218-27-7 or 5T206015T5).tw,kw,rn. (408)
186 tranylcypromine/ (8284)
187 (tranylcypromine$2 or jatrosom$2 or parmodalin$2 or parnate$2 or parnitene$2 or parnitine$2 or "sk and f 385" or "skf 385" or "skf trans 385" or trancilpromine$2 or trancylpromine$2 or trancylprominesulfate$2 or trancylprominesulphate$2 or tranilacipromina$2 or transamine$2 or tranylcypomia$2 or tranylcypromide$2 or tranylcypromin$2 or tranylcypromine$2 or tylciprine$2 or 155-09-9 or 3E3V44J4Z9).tw,kw,rn. (9054)
188 mazindol/ (2493)
189 (mazindol$2 or "AN-448" or dasten$2 or degonan$2 or diestet$2 or drinamyl$2 or fagolipo$2 or liofindol$2 or mazanor$2 or manzindol$2 or mazindole$2 or pento adiparthrol$2 or sanjorex$2 or sanorex$2 or slankosan$2 or solucaps$2 or teronac$2 or teronak$2 or 22232-71-9 or C56709M5NH).tw,kw,rn. (2989)
190 amitriptylinoxide/ (239)
191 (amitriptyline$2 or amioxid-neuraxpharm$2 or amitriptyline n oxide$2 or dano or danoR or danoTM or equilibrin$2 or 4317-14-0 or TYR2U59WMA).tw,kw,rn. (52554)
192 amoxapine/ (2733)
193 (amoxapine$2 or adisen$2 or amoxan$2 or amoxapin$2 or asendin$2 or asendis$2 or "cl 67,772" or "cl 67772" or "cl67,772" or "cl67772" or defanyl$2 or demolox$2 or desmethylloxapine$2 or moxadil$2 or 14028-44-5 or R63VQ857OT).tw,kw,rn. (2961)
194 demexiptiline/ (39)
195 (demexiptiline$2 or demexiptyline$2 or deparon$2 or tinoran$2 or 24701-51-7 or EYX738UZ5P).tw,kw,rn. (41)
196 desipramine/ (28138)
197 (desipramine$2 or "aw 1151129" or aw1151129 or demethylimipramine$2 or deprexan$2 or desimipramine$2 or desipramin$2 or desipramine$2 or desmethyl imipramin$2 or desmethyl imipramine$2 or desmethylimipramin$2 or desmethylimipramine$2 or despiramine$2 or "ex 4355" or ex4355 or "g 15020" or "g 35020" or g15020 or g35020 or "jb 8181" or jb8181 or n demethylimipramine$2 or nebril$2 or norimipramine$2 or norpramin$2 or norpramine$2 or nortimil$2 or "nsc 114901" or nsc114901 or pentrofane$2 or pertofran$2 or pertofrane$2 or pertofrin$2 or pertrofran$2 or petrofran$2 or petrofrane$2 or petylyl$2 or "rmi 9,384a" or "rmi 9384a" or "rmi9,384a" or rmi9384a or sertofren$2 or 50-47-5 or 58-28-6 or TG537D343B).tw,kw,rn. (31523)
198 dibenzepin/ (765)

199 (dibenzepin$2 or bibenzepin$2 or deprex$2 or dibenzepine$2 or dibenzepinum$2 or dibenzoazepine$2 or ecatril$2 or "hf 1927" or hf1927 or "l.w. 1927" or neodalit$2 or neodil$2 or noveril$2 or 4498-32-2 or 510SJZ1Y6L).tw,kw,rn. (1190)
200 dimetacrin/ (113)
201 (dimetacrin$2 or dimetacrine$2 or dimethacin$2 or dimethacine$2 or dimethacrin$2 or dimethacrine$2 or istonil$2 or miroistonil$2 or "sd 709" or 3759-07-7 or 4757-55-5 or O341NY501N).tw,kw,rn. (249)
202 dosulepin/ (2786)
203 (dothiepin$2 or altapin$2 or depresym$2 or dosulepin$2 or dosulepine$2 or dothapax$2 or dothiepin$2 or idom or idomR or idomTM or prepadine$2 or prothiaden$2 or prothiadene$2 or prothiadiene$2 or prothiadine$2 or protiaden$2 or 113-53-1 or 897-15-4 or W13O82Z7HL).tw,kw,rn. (3030)
204 imipraminoxide/ (106)
205 (imipraminoxide$2 or elepsin$2 or imipramine$2 or imiprex$2 or 6829-98-7 or 8MKS280XJW).tw,kw,rn. (51521)
206 lofepramine/ (1221)
207 (lofepramine$2 or amplit$2 or deftan$2 or feprapax$2 or gam#nil$2 or "leo 640" or lomont$2 or tymelyt$2 or "whr 2908a" or 23047-25-8 or 26786-32-3 or OCA4JT7PAW).tw,kw,rn. (1694)
208 melitracen/ (433)
209 (melitracen$2 or dixeran$2 ormelitracene$2 or melixeran$2 or metrisil$2 or 5118-29-6 or 10563-70-9 or Q7T0Y1109Z).tw,kw,rn. (553)
210 metapramine/ (124)
211 (metapramine$2 or "19560 rp" or "rp 19560" or timaxel$2 or 21730-16-5 or 303954M7YF).tw,kw,rn. (172)
212 nitroxazepine/ (44)
213 (nitroxazepine$2 or "233-go" or "2330 go" or "c 2330 go" or "c2330 go" or c2330go or sintamil$2 or 16398-39-3 or CNU9GY55SI).tw,kw,rn. (74)
214 nordoxepin/ (291)
215 (nordoxepin$2 or demethyldoxepin$2 or desmethyldoxepin$2 or "doxepin,nor$2" or 1225-56-5 or F498JSH8R).tw,kw,rn. (440)
216 nortriptyline/ (17647)
217 (nortriptyline$2 or acetexa$2 or allegron$2 or altile$2 or ateben$2 or atilev$2 or avantyl$2 or aventyl$2 or desitriptyline$2 or desmethylamitriptylin$2 or desmethylamitriptyline$2 or "l 38489" or martimil$2 or noramitriptyline$2 or norfenazin$2 or noritren$2 or norline$2 or norpress$2 or nortrilen$2 or nortrilene$2 or nortriptylin$2 or nortriptyline$2 or nortrix$2 or nortryptilin$2 or nortryptiline$2 or nortryptyline$2 or nortyline$2 or norventyl$2 or ortrip$2 or pamelor$2 or paxtibi$2 or psychostyl$2 or sensaval$2 or sensival$2 or vividyl$2 or 72-69-5 or BL03SY4LXB).tw,kw,rn. (18953)
218 noxiptiline/ (222)
219 (noxiptiline$2 or agedal$2 or "bay 1521" or bay1521 or "bayer 1521" or dibenzoxin$2 or elronon$2 or nogedal$2 or noxiphylin$2 or noxiptilin$2 or noxiptiline$2 or noxiptillin$2 or noxiptilline$2 or noxiptylin$2 or noxiptyline$2 or noxyptiline$2 or 24573-06-6 or 3362-45-6 or DF7D3NY7EL).tw,kw,rn. (315)
220 opipramol/ (1287)
221 (opipramol$2 or dinsidon$2 or ensidon$2 or eusidon$2 or "g 33040" or g33040 or insidon$2 or nisidan$2 or opipramole$2 or pramolan$2 or "rp 8307" or rp8307 or 315-72-0 or D23ZXO613C).tw,kw,rn. (1386)
222 propizepine/ (88)

223 (propizepin$2 or propizepine$2 or pyridobenzodiazepine$2 or "up 106" or vagran$2 or 10321-12-7 or 09B57945V9).tw,kw,rn. (1027)
224 protriptyline/ (2889)
225 (protriptyline$2 or amimetilina$2 or concordin$2 or maximed$2 or "mk 240" or mk240 or protriphyline$2 or protryptyline$2 or triptil$2 or vivactil$2 or 438-60-8 or 4NDU154T12).tw,kw,rn. (3304)
226 quinupramine/ (112)
227 (quinupramine$2 or kevopril$2 or kinupril$2 or "lm 208" or 31721-17-2 or 29O61HFF4L).tw,kw,rn. (137)
228 tianeptine/ (1640)
229 (tianeptine$2 or coaxil$2 or "s 1574" or s1574 or stablon$2 or 72797-41-2 or 0T493YFU8).tw,kw,rn. (2295)
230 trimipramine/ (4133)
231 (trimipramine$2 or apo-trimip$2 or eldoral$2 or herphonal$2 or "il 6001" or rhotrimine$2 or "rp 7162" or sapilent$2 or stangyl$2 or sumontil$2 or surmontil$2 or trimepramine$2 or trimeprimin$2 or trimeprimine$2 or trimepropimine$2 or trimidura$2 or trimineurin$2 or trimipramine$2 or trimoprimine$2 or tripress$2 or tydamine$2 or 739-71-9 or 6S082C9NDT).tw,kw,rn. (4438)
232 or/117-231 [DRUG CLASSES/DRUGS OF INTEREST] (1483583)
233 incidence/ (733335)
234 incidenc*.tw,kw. (2055546)
235 prevalence/ (1097648)
236 prevalen*.tw,kw. (1992031)
237 factual database/ (112807)
238 ((admin* or billing* or claim? or factual or insurance or utili#ation) adj3 (data or database* or data-base* or databank* or data-bank* or dataset? or data-set? or statistic*)).tw,kw. (147089)
239 drug utilization/ (42374)
240 or/233-239 [EPI FILTER] (4490422)
241 232 and 240 [DRUG CLASSES OF INTEREST - EPI FILTER] (75145)
242 exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (55421554)
243 exp human/ or exp human experimentation/ or exp human experiment/ (43048494)
244 242 not 243 (12374929)
245 241 not 244 [ANIMAL-ONLY REMOVED] (67735)
246 (comment or editorial or letter or newspaper article or news).pt. (4064318)
247 245 not 246 [OPINION PIECES REMOVED] (66685)
248 conference abstract.pt. (4080457)
249 247 not 248 [CONFERENCE ABSTRACT REMOVED] (57454)
250 limit 249 to yr="2010-current" (31564)
251 250 use emczd [EMBASE RECORDS] (19401)
252 116 or 251 [BOTH DATABASES] (32396)
253 limit 252 to yr="2020-current" (4877)
254 remove duplicates from 253 (3418)
255 limit 252 to yr="2019" (3170)
256 remove duplicates from 255 (2252)
257 limit 252 to yr="2017-2018" (5693)
258 remove duplicates from 257 (4036)
259 limit 252 to yr="2015-2016" (5659)
260 remove duplicates from 259 (3933)

261 limit 252 to yr="2013-2014" (5722)
262 remove duplicates from 261 (3960)
263 limit 252 to yr="2011-2012" (4978)
264 remove duplicates from 263 (3552)
265 limit 252 to yr="2010" (2297)
266 remove duplicates from 265 (1668)
267 254 or 256 or 258 or 260 or 262 or 264 or 266 [TOTAL UNIQUE RECORDS] (22819)
268 267 use ppez [MEDLINE UNIQUE RECORDS] (12968)
269 267 use emczd [EMBASE UNIQUE RECORDS] (9851)

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1,2
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1,4
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	8
Sponsor	#5b	Provide name for the review funder and / or sponsor	8
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	8
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3,4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4,5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4,5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5, supplementary file
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5,6

Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5,6
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5,6
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	5,6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	5,6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5,6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5,6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	4